Clinical evidence review

Familial breast cancer:

Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.

Update of clinical guideline 14 and 41

Clinical evidence reviews, 2004, 2006 & 2013

Developed for NICE by the National Collaborating Centre for Cancer

Contents

1 The Clinical Significance of a Family History of Breast Cancer

1.1 Accuracy of Family History Taking

1.1.1 Evidence Summary

A number of studies have been identified which relate to the recording and assessment of family history in women with a family history of breast cancer, although generally, study design lacks rigour.

Four studies have assessed the accuracy of the family histories provided by women with and without breast cancer and have found that reporting of breast cancer family histories is generally reliable (Theis et al, 1994; Parent et al, 1997; Eerola et al, 2000; Husson et al, 2000). Case studies have shown, however, the importance of verifying family histories as a false family history has serious implications for patient management (Kerr et al, 1998). Another study found poor communication amongst families can impede the collection of family history information (Green et al, 1997).

Two studies have evaluated methods of identifying patients at increased genetic risk of breast and other cancers suitable for referral for genetic screening (a postal questionnaire and a family history assessment tool), both of which appeared to be useful instruments (Leggatt et al, 1999 and Gilpin et al, 2000, respectively). A computer support programme for interpreting family histories of breast and ovarian cancer was found to produce more accurate pedigrees, more appropriate management decisions and was preferred by doctors, in comparison to other methods (Emery et al, 2000); doctors found, however that it affected their control of the consultation (Emery et al, 1999).

In terms of evidence relating to psychosocial aspects of recording and assessing family history of breast cancer, 2 surveys have found that collecting family histories and notifying family members about their cancer risk does not appear to cause anxiety (Winter et al, 1996; Leggatt et al, 2000). An RCT, however, found that completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist (Qureshi et al, 2001).

1.1.2 Evidence statements (2004)

- Reporting of breast cancer family histories, by women with and without breast cancer, is generally valid. (III)
- Completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist. (Ib)
- Poor communication amongst families can impede the collection of family history information. (III)
- Postal questionnaires and family history assessment tools are useful instruments to support the identification of women at increased risk of breast cancer. (III)
- GPs have been found to prefer computerised programs to collect family history information compared to pen-and-paper methods. (III)

- Computer support programmes have been found to produce more accurate pedigrees and more appropriate management decisions. (III)

1.1.3 Studies

Emery et al (2000)
In a crossover experiment involving a random sample of 36 UK general practitioners, the potential impact of computer support for interpreting family histories of familial breast and ovarian cancer and the effectiveness of two different types of computer programme were evaluated. Eighteen hypothetical cases designed to cover a range of risk levels were managed by each doctor, six each with the following methods of support: RAGS, a computerised decision support system; Cyrillic, an established family history drawing programme designed for clinical geneticists; and pen and paper. Results showed that RAGS produced significantly more appropriate management decisions (median 6) compared to either Cyrillic (median 3) or pen and paper (median 3), with a median difference between RAGS and Cyrillic of 2.5 (95% CI, 2.0-3.0; P<0.0001). Significantly more accurate pedigrees were also taken using RAGS compared to Cyrillic and pen and paper, with a median difference between RAGS and Cyrillic of 1.5 (95% CI, 1.0-2.0; P<0.0001). RAGS took longer to use per case than pen and paper, but was quicker than Cyrillic (P=0.02). Thirty-three doctors (92%) preferred using RAGS overall.

Gilpin et al (2000)
A family history assessment tool (FHAT) for use by clinicians in selecting individuals for genetic counselling underwent a preliminary validation in this Canadian study involving 184 unrelated families at risk of breast and ovarian cancer. Women who were either selected or excluded by the tool were compared to how those same individuals would be assessed using a doubling (22%) of the lifetime risk as estimated by Claus and by BRCAPRO. The number of women who tested positive for BRCA1/2 mutations who would have been selected or excluded by each of the methods was also assessed. The FHAT performed well in selecting patients for referral as compared to using the Claus or BRCAPRO methods. Both positive and negative predictive values for the FHAT were better than the Claus tables (0.31 and 0.97 v 0.28 and 0.90, respectively). BRCAPRO was more effective in reducing the number of referrals for genetics but would have missed some women selected by the FHAT and found to be mutation-positive.

Husson et al (2000)
The reliability of maternal history of cancer information was assessed as part of a US case-control study by comparing the medical records of 214 women with breast cancer and of their controls aged 26-59 years and diagnosed between 1974-1995, with the records of their mothers. In the sample of women, 30% of cases and 17% of controls had a maternal cancer history. For any type of cancer, the proportion documented in the daughter's medical record was only 56% among cases and 32% among controls, although for breast cancer, the percentage was higher (79% among cases and 57% among controls).

Eerola et al (2000)
The validity of the family history of breast cancer as reported by the patient was evaluated in a Finnish survey of 288 women with breast cancer. Family history of breast or ovarian cancer was reported by approximately 30% of the patients, with 7-9% classified as breast cancer families. The information reported by the patients proved to be quite accurate, with only about 5-7% of all reported diagnoses among breast cancer families found to be incorrect.

Emery et al (1999)

General practitioners' attitudes towards and use of a computer programme for assessing genetic risk of cancer were explored in a UK qualitative study, using interviews and video recordings of simulated consultations. A purposive sample of 15 general practitioners took part, with each doctor using the Risk Assessment in Genetics (RAGS) programme in 2 consultations in which an actor played a women concerned about her family history of cancer. Results indicated that most of the doctors found the programme easy to use and an appropriate application of information technology, but it affected their control of the consultation, in that they wanted to share the computer screen with the patient but were concerned about the risk of premature disclosure of bad news.

Leggatt et al (1999)
In a UK survey in general practice, the feasibility of using a postal questionnaire to identify patients at increased genetic risk of breast or colorectal cancer was assessed. 960 patients aged 35-65 years registered at one practice took part and were sent a questionnaire requesting details of first degree, second degree and more distant relatives known to have had cancer; of these 666 returned the questionnaire. The majority of patients were assessed to be at lower risk (not at sufficiently increased risk of breast or colorectal cancer to be offered surveillance). Twenty-nine patients were assessed to be at higher risk; of these, 14 had previously received genetic advice, although 12 of the remaining 15 patients had never previously discussed their family history with their general practitioner. The authors conclude that a self-completed questionnaire was a useful instrument to identify patients at increased genetic risk.

Kerr et al (1998)
Case studies are presented of 5 individuals attending UK and North American family cancer or genetic counselling clinics whose factitious family or personal history resulted in inaccurate risk estimations. Factors which may indicate a false history are a history of benign breast disease, poor communication within families, long survival with early onset or bilateral disease, a lack of detailed knowledge of the illness and treatment in close relatives, and inconsistencies in the history in repeated consultations. The authors note the importance of verifying family histories because a false family or personal history of breast cancer is not a rare occurrence and has serious implications for risk assessment and management.

Parent et al (1997)
Pathology records were compared with reports of breast cancer events among 125 first-degree relatives provided by 68 women with breast cancer and 37 women without the disease in a Canadian study. Sixty-seven (90.5%) of the reports of the occurrence of breast cancer in relatives by affected women and 32 (97.0%) of those by unaffected women were accurate. Women reporting several affected relatives often over-reported the presence of breast cancer events. The authors conclude that reliance on reports by patients should not critically affect the assessment of breast cancer risks for family members.

Green et al (1997)
Forty-six women attending a UK genetics clinic for familial breast/ovarian cancer took part in interviews as part of a longitudinal qualitative study which assessed the process of communicating family history between family members. Nearly all the women reported affected maternal, rather than paternal, relatives which may indicate lack of awareness. Thirty-six (78%) of the 46 women approached at least one relative for information before going to the clinic, with mothers, if they were still alive, being the key figures in supplying family information. Although most women contacted at least one relative regarding counselling, most named a relative with whom they did not feel able to communicate on this subject. The communication process was impeded by factors such as divorce, adoption, family rifts and large age groups between siblings.

Theis et al (1994)
The validity of information relating to family histories of cancers reported by 165 Canadian women with breast cancer was assessed using questionnaires and interviews. Results showed that questionnaire and interview reports agreed with records for 82-96% of reports on first-degree and 48-80% on second-degree relatives. In terms of reported cancer sites, these were generally accurate in first-degree relatives (breast 99%, ovary 100%, prostate 85% and colon 93%). Reports for second-degree relatives were accurate for prostate cancer but only for 85% of breast and 72% of colon cancers. The authors conclude that in a similar population, use of the questionnaire alone should provide adequate data for identifying families which need to undergo further genetic investigation.

Lalloo et al (2003)
Lalloo et al examined the correlation between frequency and penetrance of BRCA1, BRCA2 and TP53 mutations in young women (30 and under) with a diagnosis of breast cancer and family history. They found that 17 of 36 familial cases had a BRCA1, BRCA2 or TP53 mutation compared with three of 63 non-familial cases. They also found that TP53 accounted for 4% of patients diagnosed with breast cancer at a young age, rather than the usual reported rate of 1%. Their conclusions were that family history was important to ensure that those women who need altered management (eg TP53 carriers with the high risk of radiation induced tumours) were identified.

Family history taking: (psychosocial outcomes)

Qureshi et al (2001)
A UK randomised controlled trial was conducted to assess the psychological impact of a family history-screening questionnaire used in general practice. Individuals who had not had a health check within the previous 2 years were randomised to an intervention (receiving a health check and a self-administered family history questionnaire; n=50) or to a control group (health check only; n=50). Of the 100 patients, 76 of them were followed through to the 3-month end point. Results showed that at both 1 and 2 weeks after the health check, anxiety was higher in the intervention group than the control group (F=6.4; df=1,73; P=0.014), but at 3 months, there was no significant difference between the groups. These results would suggest that the family history questionnaire led to short-term psychological distress, but this did not persist.

Leggatt et al (2000)
The psychological impact of completing a cancer family history questionnaire and receiving an assessment of personal genetic risk of breast or colorectal cancer was evaluated in this UK survey. A total of 604 patients registered with a single general practice returned baseline (before completion of the questionnaire) and follow-up (4-6 weeks after receipt of their risk assessment) measures of anxiety and cancer worry. Patients were assessed to be either not at significantly increased risk (lower risk group; n=568) or at potentially increased risk; of the latter group, 25 patients were subsequently confirmed to be at significantly increased risk (higher risk group) and 11 deemed not to be at significantly increased risk (false positive group). There were no differences between the 2 time points for any of the groups except for the lower risk group, where perceptions of personal risk of developing cancer showed a small reduction (P<0.001). For both the higher risk group and the false positive group, baseline responses showed that their pre-existing breast cancer risk perception was higher than that of the lower risk group (P<0.001 and P=0.003, respectively). The authors conclude that completion of a cancer family history questionnaire and receipt of risk assessment does not make patients more anxious or worried about cancer.

Winter et al (1996)
To determine the impact of breast cancer risk notification on family members, 376 male and female relatives of 160 breast cancer patients were contacted as part of a US epidemiological follow-up

study. Participants were surveyed to assess prior knowledge of family history of cancer, issues relating to study participation and concerns regarding developing cancer. Results showed that 24% of blood relatives were not aware of their family history of breast cancer, and more blood relatives (76%) than non-blood relatives (62%; P<0.01) were aware of their family history. Forty-three (12%) of participants expressed concerns about taking part in a large genetic follow-up study. Level of concern about developing cancer was high across all participants (range 50-78%), with males being as concerned as females and non-blood relatives only slightly less concerned than blood relatives. The authors conclude, however, that risk notification does not appear to have a significant detrimental impact on family members**.**

1.1.4 Evidence Tables

Table 1.1: Recording and assessing family history

Study	Design	Aim(s)	Population	Results
Theis et al (1994)	Survey/qualitative interviews	To assess the validity of information relating to family history of cancer	165 Canadian women with breast cancer	Questionnaire and interview reports agreed with records for 82-96% of reports on 1st-degree and 48-80% on 2nd-degree relatives. Reported cancer sites generally accurate in 1st-degree relatives (breast 99%, ovary 100%, prostate 85%, colon 93%), though only accurate for 85% of breast and 72% of colon cancers in 2nd-degree relatives. Conclusion: use of questionnaire should provide adequate data for identifying families for genetic investigation.
Green et al (1997)	Qualitative study	To assess the process of communicating family history of breast/ovarian cancer among family members	46 UK women with family history of breast/ovarian cancer attending genetics clinic	Most women reported affected maternal, rather than paternal, relatives which may indicate lack of awareness of paternal history. 36/46 of women (78%) approached at least 1 relative for information prior to clinic visit. Mothers (if alive) were key figures in supplying information. Communication process was impeded by divorce, remarriage, adoption, family rifts and large age differences between siblings.
Parent et al (1997)	Survey/review of pathology records	To assess the accuracy of reports of breast cancer events in relatives	68 women with and 37 women without breast cancer (Canadian) providing reports on 125 1st-degree relatives	67 (90.5%) of reports of breast cancer in relatives by affected women and 32 (97.0%) of those by unaffected women were accurate. There was some over- reporting in women with several affected relatives. Conclusion: family histories reported by patients are generally reliable.

Study	Design	Aim(s)	Population	Results
Kerr et al (1998)	Case studies	To describe cases where factitious family/personal histories of cancer resulted in inaccurate risk estimations	5 individuals attending UK and North American family cancer or genetic counselling clinics	Factors which indicate a false history are history of benign breast disease, poor communication within families, long survival with early onset or bilateral disease, a lack of detailed knowledge of the illness and treatment in close relatives, and inconsistencies in the history in repeated consultations. Conclusion: it is important to verify family histories because false histories are not rare and have serious implications for risk assessment and management.
Emery et al (1999)	Qualitative study	To explore general practitioners' attitudes towards and use of a computer programme for assessing genetic risk of cancer (RAGS)	15 UK general practitioners	Most doctors found the computer programme easy to use and an appropriate application of information technology. However, they felt it affected their control of the consultation; they wanted to share the computer screen with the patient but were concerned about potential risk of disclosing bad news prematurely.
Leggatt et al (1999)	Survey	To assess the feasibility of using a postal questionnaire to identify patients at increased genetic risk of breast or colorectal cancer	960 patients aged 35-65 registered at one UK general practice.	Most patients assessed to be at lower risk (no genetic screening necessary). 29 patients were identified at higher risk; of these, 12 had never discussed family history with GP. Conclusion: a self-completed questionnaire was a useful instrument to identify patients at increased genetic risk.
Eerola et al (2000)	Survey	To evaluate the validity of the family history of breast cancer as reported by the patient	288 Finnish women with breast cancer	Family history of breast/ovarian cancer reported by about 30% of patients; 7-9% were classified as breast cancer families. Information reported by patients was quite accurate, with only 5-7% reported diagnoses found to be incorrect.

Study	Design	Aim(s)	Population	Results
Emery et al (2000)	Crossover experimental study	To evaluate the potential impact of computer support for interpreting family histories of familial breast/ovarian cancer, and to evaluate the effectiveness of 2 computer programmes (RAGS and Cyrillic) using hypothetical cases	36 UK general practitioners	RAGS gave significantly more appropriate management decisions (median 6) compared to either Cyrillic (median 3) or pen and paper (median 3); median difference between RAGS and Cyrillic was 2.5 (95% CI, 2.0-3.0; P<0.0001). Significantly more accurate pedigrees taken using RAGS compared to Cyrillic and pen and paper; median difference between RAGS and Cyrillic was 1.5 (95% CI, 1.0-2.0; P<0.0001). RAGS took longer to use per case than pen and paper, but was quicker than Cyrillic (P=0.02). 92% of GPs preferred using RAGS.
Gilpin et al (2000)	Preliminary validation study	To evaluate a family history assessment tool (FHAT) in selecting individuals for genetic counselling/BRCA1/2 mutation status compared to assessment by Claus	184 unrelated Canadian families at risk of breast/ovarian cancer	FHAT performed well in selecting patients for referral compared to using Claus or BRCAPRO (0.31 and 0.97 vs 0.28 and 0.90, respectively). BRCAPRO more effective in reducing number of referrals for genetics, but missed some women selected by FHAT found to be mutation carriers.
Husson et al (2000)	Part of case-control study	To assess the reliability of maternal history of cancer information	Medical records of 189 US women with breast cancer (cases) and 201 women without the disease (controls) aged 26-59 and diagnosed between 1974-1995; medical records of their mothers	30% of cases and 17% of controls had maternal cancer history. For any type of cancer, only 56% of cases and 32% of controls had mother's history documented in the medical record; however, for breast cancer, percentage was higher (79% of cases and 57% of controls).

Table 1.2: Psychosocial aspects of recording and assessing family history

Study	Design	Aim(s)	Population	Results
Winter et al (1996)	Survey (part of epidemiological follow-up study)	To determine the impact of breast cancer risk notification on family members	376 US male and female relatives of 160 breast cancer patients	24% of blood relatives not aware of family history of breast cancer; more blood relatives than non-blood relatives (76% vs 62%; P<0.01) were aware of family history. 12% concerned about taking part in genetic follow-up study. Concern about developing cancer high across all participants (range 50-78%), with males as concerned as females and non-blood relatives only slightly less concerned than blood relatives. Conclusion: risk notification does not appear to have a significant detrimental impact on family members.
Leggatt et al (2000)	Survey	To evaluate the psychological impact of completing a cancer family history questionnaire and receiving an assessment of personal genetic risk of breast/colorectal cancer	604 UK patients registered with one general practice	568 patients assessed as lower risk group. 36 assessed as potentially increased risk; of these 25 were confirmed at significantly increased risk (higher risk group) and 11 not at increased risk (false positive group). No differences between baseline and follow-up (4-6 weeks after risk assessment), except in lower risk group who had small reduction in risk perception of developing cancer (P<0.001). Baseline responses for higher risk and false positive groups showed higher risk perception than lower risk group (P<0.001 and P=0.003, respectively). Conclusion: family history questionnaire/risk assessment does not make patients more anxious about cancer.
Qureshi et al (2001)	RCT	To assess the psychological impact of a family history-screening questionnaire in general practice	50 patients receiving health check and family history questionnaire (cases) and 50 patients	Of 100 patients, 76 were followed through to 3-month end point. At both 1 and 2 weeks after the health check, anxiety was higher in the intervention group than control group (*F*=6.4; df=1,73; P=0.014), but at 3 months, no

			receiving health check only (controls) registered at one UK general practice	significant difference between groups. Conclusion: family history questionnaire led to short-term psychological distress, but this did not persist.

1.2 Risk Assessment Tools

1.2.1 Evidence Statements

- Existing computer models (Gail, Claus, BRCAPRO) underestimate in a family history setting in terms of breast cancer risk prediction, although the manual Claus tables produce risks close to those seen in a screened familial risk population. (III)
- One US study found that BRCAPRO predicted BRCA 1 & 2 mutation status better than genetic counsellors. (III)
- The degree of correlation between different risk models is relatively poor. (III)

Evidence has been identified from the literature concerning methods of predicting individual risk of developing breast cancer in women with a family history of breast cancer. The evidence relates to a number of risk assessment models and a number of studies, which have reviewed or compared these models. The models can be divide into those that predict

a) Breast cancer risk over time
b) The chances of an individual or family carrying a BRCA1 or BRCA2 mutation
c) Both the above

Four guidelines have also been identified for genetic risk assessment and management of women with a family history of breast cancer.

1.2.2 Breast cancer risk assessment models

BRCAPRO (Berry et al 1997)

BRCAPRO is a mathematical model, which has been developed to calculate the probability that a woman with a family history of breast and/or ovarian cancer carries a BRCA1 or BRCA2 gene mutation. The model applies Bayes' theorem to predict risk, using estimates of BRCA1 mutation frequencies in the general population and age-specific incidence rates of breast and ovarian cancers in mutation carriers and non-carriers, with probability based on the cancer statuses of all 1st- and 2nd-degree relatives.

Claus et al 1994

The Claus model uses a mathematical approach to model the likely inheritance of breast cancer genes in the population studied (known as segregation analysis). The genetic model that best fitted the data was that of a rare allele (or alleles) associated with high penetrance. Non genetic factors are not taken into account in this model.

This statistical model uses data from the Cancer and Steroid Hormone Study (CASH), which was a US population-based case-control study of 4,730 white breast cancer cases and 4,688 age-matched controls aged 20-54 years. Data on breast cancer occurrence in 1st-degree relatives and age at onset were obtained from participants, with an aim of determining whether these data supported the existence of an inherited breast cancer susceptibility gene. The data supported the existence of a rare autosomal dominant allele which increased predisposition to breast cancer. The Claus model provides breast cancer risk estimates in tabular form at 10-year increments between the ages of 29 and 79 years, based on which relatives were affected with the disease and age at diagnosis.

Gail et al 1989

The Gail model is a risk assessment model which focuses on non-genetic risk factors, with limited information on family history.

Data from 2,852 white breast cancer cases and 3,146 white controls aged between 35 and 79 years who took part in the Breast Cancer Detection Demonstration Project (BCDDP) are used in this statistical model. The model estimates the probability of a woman of a given age and set of risk factors developing breast cancer over a specified time interval, the risk factors being age at menarche, age at 1st live birth, number of affected 1st-degree relatives, and number of previous breast biopsies. The Gail model has been evaluated in 3 populations and has been adapted for use in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-BCPT).

Further risk assessment models/estimations which have not been identified by our searches are mentioned by McTiernan et al (1997) and Tischkowitz et al (2000). These papers are not presented in the review but are listed in references (Ottman et al (1983), Anderson et al (1985), Taplin et al (1990), Houlston et al (1992), Murday (1994), National Surgical Adjuvant Breast and Bowel Project (1992)).

1.2.3 Reviews/comparisons of risk assessment models

Amir et al (2003)

Amir et al assessed the goodness of fit and discriminatory value of the Tyrer-Cuzick, Gail, Claus and Ford models. This was assessed using data from 1933 women taking part in a family history evaluation and screening programme. The observed/expected ratios (for breast cancer) were: Gail 0.48 (0.37-0.64); Claus 0.56 (0.43-0.75); Ford 0.49 (0.37-0.65) and Tyrer-Cuzick 0.81 (0.62-1.08). ROC curves were calculated and showed: Gail 0.735; Claus 0.716; Ford 0.737 and Tyrer-Cuzick 0.762. The authors concluded that the Tyrer-Cuzick model is the most consistently accurate for prediction of breast cancer, and the others all underestimate risk.

Euhus et al (2002)

This study looked at the relative performance of eight cancer risk counsellors compared with BRCAPRO in identifying likely to carry a BRCA gene mutation. Pedigrees with a proband affected by breast or ovarian cancer having a gene sequence that was unequivocal were used (148 pedigrees). The study found that the counsellors and BRCAPRO had similar results in terms of sensitivity (counsellors 94% [range 81-98%], BRCAPRO 92% [range 91-92%]). BRCAPRO had better findings in terms of specificities (counsellors 16% [range 6-34%], BRCAPRO 32% [range 30-34%]). It was also found that BRCAPRO had better results in terms of ROC curves (counsellors 0.671 [range 0.620-0.717], BRCAPRO 0.712 [range 0.706-0.720]). The better findings in terms of specificities meant that BRCAPRO was thought to have slightly better overall discrimination.

McTiernan et al (2001)

The lifetime and 5-year breast cancer risk estimates of the Gail and Claus models were compared in this US study of 491 women aged 18-74 years with a family history of breast cancer. Women were recruited between 1996-1997 from the general population, with additional samples of Ashkenazi Jewish, African-American and lesbian women. About one-quarter of women were assigned the 'high' risk category according to the Gail model (>1.7% risk of developing breast cancer in the next 5 years). Estimation of average lifetime risk was 13.2% using the Gail model and 11.2% using the Claus model. Estimates of the 2 models were moderately correlated (r=0.55) with the Gail model producing higher estimation than the Claus model for most women. The authors conclude that in women with a family history of breast cancer, it may be preferable to present both Claus and Gail estimates.

Tischkowitz et al (2000)
This study compared lifetime risk estimations of developing breast cancer in 200 women attending a UK breast cancer genetic assessment clinic, using 3 different risk assessment methods which are currently being used in the UK; the Claus model, the 'Houlston/Murday' method and a qualitative method. Women were assigned a 'high' (>20%) or 'low/moderate' (<20%) lifetime risk according to each method. Comparison of the 3 models found significant differences in terms of women's allocation to the moderate or high risk categories (chi-squared=73.3, 2 df, P<0.00001). Only 108 (54%) of women were allocated the same risk category with all 3 methods. The authors conclude that these 3 methods provide inconsistent risk estimations for breast cancer.

McTiernan et al (1997)
This review compared the breast cancer risk assessment models of Ottman et al, Anderson et al, Taplin et al, Claus, Gail, and the NSABP-BCPT adaptation of the Gail model in terms of populations used for estimates, risk factors included, estimation methods, and applications of the method. Each method was also tested with particular ranges of patient characteristics to compare estimates of breast cancer probability across the different methods. The authors note that a direct comparison of the different risk assessment methods is difficult because the models include different sets of risk factors; some do not specify the total number of 1st-degree relatives with breast cancer; some are derived from small sample sizes and have wide confidence intervals; and some do not account for competing causes of death. McTiernan et al concluded:

- the validity of risk estimation from any of the methods is questionable, with each having particular strengths and weaknesses:
- the Gail model may be a valid predictor for postmenopausal women attending regular mammographic surveillance, although it overestimates breast cancer risk by 30-50% in premenopausal women.
- the Taplin method may be useful for a qualitative classification of populations.
- the Gail and NSABP-BCPT models may provide the best available risk estimates in women without a family history of breast cancer, or for women with a history of atypical benign breast disease.
- no models have been developed for other racial or ethnic groups than white women, apart from the NSABP-BCPT model, which can predict risk in African-American women, although it has not been tested for validity.

1.2.4 Evidence Tables

Table 1.3: Comparison of methods for risk estimates

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Amir et al (2003)	Evaluation of different risk assessment models	All models discussed applied to women attending a programme Gail, Claus, Ford, Tyrer-Cuzick – computerised models (Claus and Ford were in form of BRCAPRO). Claus tables with adjustment (manual model). Data analysis was carried out on both the full population that had ever visited the Family History clinic and again among women still enrolled in the 12-18 monthly mammography programme.	Family history clinic, University Hospital of South Manchester. Participants attended the family history evaluation and screening programme	3170 women had all elements of hormonal, reproductive and computerised pedigree available. Of these, 1933 women were followed in regular 12-18 month mammography. 1217 discharged to routine care. 1366 women had missing elements to dataset.	Sample was limited to women for whom breast cancer risk estimation could be derived by all models.	***Population*** Age: Median 44 years (range 21-73 years) Ethnic origin (available for 2398/3150 [76%]) 95.7% White Northern European 2.6% Jewish 1.7% other (including Afro- Caribbean and Asian)	***Population*** Mean 5.27 years (range 0.10-15.00 years) 55% of population had a follow up of more than 5 years. ***Screening population*** Mean 6.39 years (range 0.28-15.00 years) 70% had follow- up of more than 5 years.	***Screening population*** Age: Median 46 years (range 25-73 years) Predicted risk compared against observed numbers of breast cancers (Receiver operating characteristic curves generated)

Results

O/E ratios (95% CI)

Gail 0.48 (0.37-0.64)

Claus 0.56 (0.43-0.75)

Ford 0.49 (0.37-0.65)

Tyrer-Cuzick 0.81 (0.62-1.08)

Area under the ROC curve values and confidence intervals for the Gail, Claus, Ford (BRCAPRO), Tyrer-Cuzick, and the Manual models

		Asymptotic 95% confidence interval	
Risk assessment model	Area	Lower bound	Upper bound
Gail	0.735	0.666	0.803
Claus	0.716	0.648	0.784
Ford	0.737	0.671	0.803
Tyrer-Cuzick	0.762	0.700	0.824
Manual	0.727	0.656	0.798

Comparison of expected and observed cancers for categories defined by breast cancer risk factors for the women enrolled in the screening programme

			Gail			**Claus**			**Ford**			**Tyrer-Cuzick**			**Manual**		
Variable	N	O	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI
Family history	686	18	6.98	0.39	0.25 to 0.65	5.79	0.32	0.20 to 0.54	5.36	0.30	0.19 to 0.50	10.05	0.56	0.35 to 0.94	12.14	0.67	0.43 to 1.14
1FDR	137	3	3.56	1.19	0.41 to 5.75	2.45	0.82	0.28 to 3.96	1.88	0.63	0.21 to 3.04	3.51	1.17	0.40 to 5.67	3.45	1.15	
2FDRs	405	13	6.87	0.53	0.31 to 0.99	10.51	0.81	0.47 to 1.52	7.82	0.60	0.35 to 1.13	11.41	0.88	0.51 to 1.65	12.74	0.98	0.39 to 5.58
1FDR+2 other																	0.57 to 1.84
Relatives	128	8	1.64	0.21	0.10 to 0.47	2.27	0.28	0.14 to 0.66	3.74	0.47	0.24 to 1.08	4.83	0.60	0.31 to 1.40	3.88	0.49	
Ca Ovary	577	10	5.98	0.60	0.33 to 1.25	8.13	0.81	0.44 to 1.70	6.60	0.66	0.36 to 1.38	12.25	1.23	0.67 to 2.55	14.20	1.42	
Other history																	0.25 to 1.12
Menarche	840	21	11.12	0.53	0.35 to 0.86	11.82	0.56	0.37 to 0.91	10.34	0.49	0.32 to 0.80	17.49	0.83	0.54 to 1.35	20.12	0.96	
≤12 years	1093	31	13.91	0.45	0.32 to 0.66	17.33	0.56	0.39 to 0.82	15.06	0.49	0.34 to 0.71	24.56	0.79	0.56 to 1.17	26.31	0.85	0.77 to 2.96
>12 years																	
First live birth	1292	28	18.00	0.64	0.44 to 0.97	19.95	0.71	0.49 to 1.07	17.16	0.61	0.42 to 0.92	25.87	0.92	0.64 to 1.39	29.28	1.05	
≤30 years	641	24	7.03	0.29	0.20 to 0.46	9.20	0.38	0.26 to 0.60	8.24	0.34	0.23 to 0.54	16.17	0.67	0.45 to 1.05	17.14	0.71	
>30 years																	

Comparison of expected and observed cancers for categories defined by breast cancer risk factors for the full study population

				Gail			Claus			Ford			Tyrer-Cuzick			Manual		
Variable	N	O	Prevalent Cancers	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI	E	E/O	95% CI
Family history																		
1 FDR	1224	25	4	13.69	0.55	0.37 to 0.85	10.93	0.44	0.30 to 0.68	10.29	0.41	0.28 to 0.64	18.78	0.75	0.51 to 1.16	22.56	0.90	0.61 to 1.39
2 FDRs	204	4	2	6.56	1.64	0.64 to 6.02	4.08	1.02	0.40 to 3.74	3.16	0.79	0.31 to 2.90	6.28	1.57	0.61 to 5.76	5.41	1.35	0.53 to 4.96
1 FDR+2 other	555	14	6	11.02	0.79	0.47 to 1.44	16.73	1.20	0.71 to 2.19	12.36	0.88	0.53 to 1.61	17.90	1.28	0.76 to 2.34	19.94	1.42	0.85 to 2.61
Relatives																		
OC	196	9	2	2.75	0.31	0.16 to 0.67	3.40	0.38	0.20 to 0.83	5.53	0.61	0.32 to 1.34	6.83	0.76	0.40 to 1.66	6.07	0.67	0.36 to 1.47
Other history	971	12	6	10.28	0.86	0.49 to 1.66	13.41	0.76	0.64 to 2.16	10.95	0.91	0.52 to 1.77	19.76	1.65	0.94 to 3.19	23.95	2.00	1.14 to 3.86
Menarche																		
≤12 years	1391	26	5	19.49	0.75	0.51 to 1.15	19.79	0.76	0.52 to 1.17	17.30	0.67	0.45 to 1.02	29.43	1.13	0.77 to 1.73	33.90	1.30	0.89 to 2.00
>12 years	1759	38	15	24.81	0.65	0.48 to 0.92	28.76	0.76	0.55 to 1.07	24.98	0.66	0.48 to 0.93	40.13	1.06	0.77 to 1.49	44.02	1.16	0.84 to 1.64
First live birth																		
≤30 years	2026	38	13	32.31	0.85	0.62 to 1.20	33.81	0.89	0.65 to 1.26	29.34	0.77	0.56 to 1.09	43.92	1.16	0.84 to 1.63	48.35	1.27	0.93 to 1.80
>30 years or nulliparous	1124	26	7	12.00	0.46	0.31 to 0.71	14.75	0.57	0.39 to 0.87	12.94	0.50	0.34 to 0.76	25.65	0.99	0.67 to 1.61	29.58	1.14	0.78 to 1.74

OC, ovarian cancer

Author's conclusions:

Tyrer-Cuzick showed better overall agreement between expected and observed counts of breast cancer amonth the total study population.

Manual model was stronger among the screening population.

Gail, Claus and Ford models all significantly underestimated risk – although some comparisons by risk factor categories did not reach statistical significance – they particularly underestimated risk in women with a single first degree relative.

Table 3 (contd.): Comparison of methods for risk estimates

Author	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Euhus et al (2002)	Comparison of risk estimation by risk counsellors and computer model BRCAPRO	8 cancer risk counsellors BRCAPRO computer model 148 pedigrees (final sample limited to pedigrees with a proband affected by breast or ovarian cancer and BRCA1 or BRCA2 gene sequencing unequivocally reported as negative or positive for a deleterious mutation).	Risk counsellors from university based cancer genetics clinics that employ interdisciplinary teams for identifying and managing people at high risk. 3 clinics counselled >30 families (breast and ovarian cancer risk) per month 3 clinics counsel 11-30 families per month 2 clinics counsel 6-10 families per month			95% or more of counsellors' practice was devoted to clinical cancer genetics. Six of the eight counsellors spent >90% devoted to counselling. Each counsellor had a Master's degree. 4 counsellors certified by American Board of Genetic Counsellors		Each counsellor assigned a BRCA gene mutation probability to each of the 148 pedigrees using a five-point scale. Sensitivity and specifically calculated and ROC curves plotted.

Results

Using greater than 10% mutation probability threshold (American Society of Clinical Oncology threshold for testing).

Median sensitivity (range):
risk counsellors 94% (81-
98%) BRCAPRO 92% (91-
92%)

Median specificity
(range): risk counsellors
16% (6-34%) BRCAPRO
32% (30-34%)

Median area under ROC curves
(range): risk counsellors 0.671
(0.620-0.717) BRCAPRO 0.712
(0.706-0.720)
(stat sig, p=0.04)

Author's conclusions:

sensitivity for identifying BRCA mutation cameis is similar for experienced risk counsellors and BRCAPRO. BRCAPRO had better specificity.
Overall disamination therefore was slightly better for BRCAPRO.

1.3 The optimal methods for assessing the carrier probability of a patient at different thresholds for genetic testing in women and men at risk of familial breast cancer?

1.3.1 Review Question

What are the optimal methods for assessing the carrier probability of a patient at different thresholds for genetic testing in women and men at risk of familial breast cancer?

1.3.2 Background

Genetic counselling and testing for the breast and ovarian cancer susceptibility genes BRCA1 and BRCA2 is an important element of healthcare services for Familial Breast Cancer. Genetic testing has potentially life-changing implications for people who carry gene mutations associated with high lifetime risks of cancer. But less than 5% of all newly diagnosed breast cancers are attributable to mutations in BRCA1 or BRCA2, so the majority of families with significant breast cancer clustering do not harbour inherited deleterious single gene mutations. Evidence suggests practices to reduce the risk of breast cancer and other cancers in families with high risk gene mutations are clinically effective. Identifying the disease-causing mutation in a family facilitates follow-up (presymptomatic) genetic testing for unaffected at risk relatives, which greatly assists establishing personalised healthcare for cancer risk management, such as surveillance, prophylactic surgery, pharmacological intervention and lifestyle adjustments. Deciding how best to configure genetic testing services in clinical practice for the optimum benefit of familial breast cancer families requires careful consideration of some important issues.

Although the cost and rapidity of mutation screening with current technologies - mostly through Sanger DNA sequencing - has substantially reduced in recent years it is still relatively expensive and is a protracted process. The sensitivity of testing has improved as a result of technical developments. Also, the so called Next Generation Sequencing technology currently being introduced in Regional Genetics Laboratories will lead to further cost efficiencies and substantially reduced turnaround times. In principal this could extend the scope of genetic testing to families with much lower mutation carrier probabilities. However, genetic testing for familial cancer has the potential for substantial psychosocial effects, so genetic testing arguably should be targeted only at those who would most likely benefit with a view to optimising both the sensitivity of testing and the cost efficiency of the service provided, which may be conflicting issues.

The current NICE Guideline (CG14) recommends genetic testing should be offered to families defined as High Risk by family history assessment. In the first instance diagnostic genetic testing for BRCA1 and BRCA2 (and very rarely for TP53 or other syndromic conditions conferring variably increased risks of breast cancer) is offered to an affected individual (women with breast or ovarian cancer, and men with breast cancer or perhaps prostate cancer) where the probability of a BRCA1 or BRCA2 mutation in the family is at least 20%. This testing threshold comprises one component of the definition of High Risk for the purpose of referring to Tertiary Care for genetic counselling. Testing unaffected people is currently not covered in the current Guideline.

Topic A addresses the question, what is the optimal threshold for offering genetic testing for hereditary breast cancer. It has implicit health economics issues, but also should address concerns over the potential for psychosocial harms due to inappropriate testing, that is where a single high risk mutation is very unlikely to be present in the familial. Topic B addresses the question of how

best to assess the probability of a mutation in BRCA1 or BRCA2 being present in families with a history of breast cancer.

The existing Guideline does not specify how genetic mutation probability should be estimated. Several cancer risk and mutation probability assessment tools have been published and are widely but variably used in clinical practice and in conjunction with criterion-based rules and manual statistical estimations. Most of the assessment tools were designed for the purpose of estimating the risk of breast cancer for unaffected family members and have proved helpful in formulating screening advice by categorising lifetime and interval (10 year) risks into average (near population), moderately increased, or highly increased according to definitions established in CG14.

Some assessment tools have been developed to estimate the likelihood of detecting BRCA1/BRCA2 mutations in affected individuals. Some of these make no assumptions about underlying genetic risks such as how frequent are mutations of BRCA1/BRCA2 in the population and how penetrant are their risks. Other models incorporate this more detailed information and use computerised pedigree analysis rather than tabular scoring systems. But these tools may be limited by the validity of the assumptions they make about the overall genetic component of familial breast cancer. For example mutations in other genes, including CHEK2, ATM, NBS1, RAD50, BRIP1 and PALB2 contribute weakly or moderately to risk in the population and other common gene variations with minor risks are likely to be reported over time. These models do however simultaneously compute both lifetime and interval cancer risks and mutation probabilities in readily useable formats and have been validated to some extent. To be effective in clinical practice, there is a requirement for assessment tools to be relative straightforward in use as well as being accurate. For example, the Manchester Scoring System (Evans et al 2004) is a manual approach (with an automated option linked to computerised genetic pedigrees), offering a practical alternative to complex computer-based models, but is only for mutation probability estimation, not cancer risk assessment.

There is considerable variability between the different mathematical models for cancer risk assessment and mutation probability. Some of the inconsistency is due to differences in the types and combinations of families used in model design. Another concern is more recently introduced models may not have been extensively evaluated using the types of family cancer clusters seen in clinical practice. Various attempts at comparative evaluation of mutation risk prediction have given different results with no one model being consistently the best. Moreover, some models are not able to assess more complex family structures such as consanguineous relationships (although less significant in terms of dominant gene mutation prediction). Some family structures cannot be usefully interrogated with every assessment model, including the ability to include cancers in relatives other than first or second degree to the assessed individual. Importantly, some reports suggest underestimation of mutation probabilities is likely in families with weaker breast cancer histories. This has significant implications if the probability threshold for offering genetic testing is reduced, necessitating probability estimates on much weaker family histories. Some models, e.g. Penn II are reportedly more sensitive at mutation prediction when the threshold for genetic testing is lowered to 10%, as practiced in North America and most of Northern Europe.

Key issues for this Topic are: i) is there an optimal mutation probability assessment tool or tools with sufficient utility to be widely adopted in clinical genetics and which may simultaneously be used to assess lifetime and interval cancer risks for the purpose of screening advice; ii) is such a tool(s) capable of estimating mutation risk across a range of family histories indicated by the threshold at which BRCA genetic testing might be set in future; iii) are all of the potentially useful models widely available or are there licensing restrictions; iv) is there an alternative to mathematical modelling, e.g. an existing set of diagnostic criteria based on family history pattern (there are no other identifiable

phenotypes in non-syndromic (i.e. BRCA1/BRCA2) hereditary breast cancer families); and v) what are the risks of using under-evaluated assessment tools in clinical practice?

1.3.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women and men at risk of familial breast cancer	Any method of assessing risk threshold: • Computer Models (BRCAPRO, BOADICEA, Tyrer-Cuzick) • Genetic Counsellors • Manual • Manchester Score	Each Other As compared to the reference standard (genetic testing)	• Discrimination/Calibration (ROC curves) • Accuracy • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value

1.3.4 Relative Importance of Outcomes

All outcomes were considered to be of equal importance for this topic.

1.3.5 Search strategy

Searches:	
Date limits	Yes, from the date of publication of the earliest risk estimation tools
Study design filters	Unlikely to be addressed by RCT's therefore no filters used
Useful search terms.	breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, risk, risk assessment, mutation, probability, sensitivity and specificity, positive and negative predictive value, receiver operating characteristic (ROC) curves, validation, BRCA1, BRCA2, penetrance, mutation frequency, inheritance, empirical models, pedigree, founder mutations, population isolates, founder mutations, polygenic models, tumour histology, triple negative breast cancer (TNBC).

1.3.6 Search Results

Table 1.4: Literature search details and **Update Search detail**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-11/2011	2009	152	06/12/2011
Update Search	11/2011-7/2012	381	33	04/07/2012
Premedline	All-11/2011	81	5	09/12/2011
Update Search	11/2011-7/2012	97	18	04/07/2012
Embase	All-11/2011	5606	118	07/12/2011
Update Search	11/2011-7/2012	754	40	04/07/2012
Cochrane Library	All-11/2011	197	9	09/12/2011
Update Search	11/2011-7/2012	81	0	04/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-11/2011	320	63	09/12/2011
Update Search	11/2011-7/2012	504	10	04/07/2012
PsyInfo	All-11/2011	169	5	09/12/2011
Update Search	11/2011-7/2012	25	0	04/07/2012

Total References retrieved (after de-duplication): 232
Total References retrieved for Update search (after de-duplication): 87

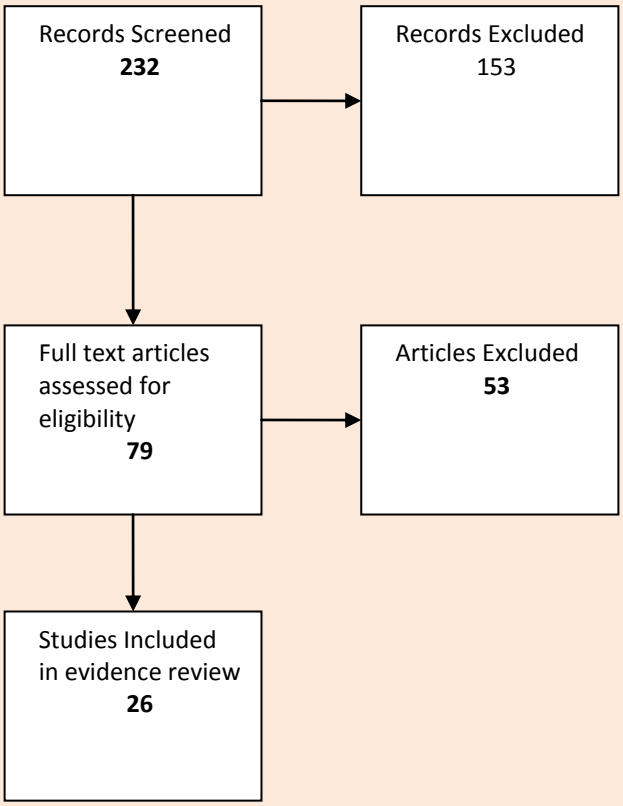
Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. 1 or 2 or 3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetic Predisposition to Disease/
12. (mutation adj1 risk*).tw.
13. lifetime breast cancer risk*.tw.

14. (mutation adj carrier*).tw.
15. (inherited adj mutation*).tw.
16. predictive genetic test*.tw.
17. (probability adj1 threshold*).tw.
18. lifetime risk*.tw.
19. interval risk*.tw.
20. assessment tool*.tw.
21. mutation probability*.tw.
22. cancer risk assessment*.tw.
23. risk estimation tool*.tw.
24. mutation frequenc*.tw.
25. BRCAPRO*.tw.
26. BOADICEA*.tw.
27. Tyrer-Cuzick*.tw.
28. exp Risk Assessment/mt [Methods]
29. exp Genetic Testing/mt [Methods]
30. exp "Predictive Value of Tests"/
31. exp Models, Statistical/
32. 9 or 10 or 11
33. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
34. 8 and 32
35. 33 and 34

There was no filter applied to the search.

1.3.7 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Observational study (n=26)
Case Series Studies (n=0)
Qualitative Study (n=0)

1.3.8 Study quality

Evidence came from 26 studies of carrier probability models (BOADICEA, BRCAPRO, IBIS, MYRIAD, MANCHESTER, PENN, PENN II and FHAT) or risk counsellors (Antoniou et al., 2006, 2008; Barcenas et al., 2006; Berry et al., 2002; Bodmer et al., 2006; Capalbo et al., 2006; de la Hoya et al., 2003; Euhus et al., 2002; Evans et al., 2004, 2009; Fasching et al, 2007; James et al., 2006; Kang et al., 2006; Kurian et al., 2009; Lindor et al., 2010; Oros et al, 2006; Ottini et al., 2003; Panchal et al., 2008; Parmigiani et al., 2007; Rao et al., 2009; Rosati et al., 2004; Roudgari et al., 2008; Simard et al., 2007; Teller et al., 2010; Vogel et al, 2007 and Zanna et al., 2010). The participants in these studies were people tested for BRCA1 and/or BRCA2 mutations identified from the records of clinical genetics services. Referral for these genetic tests would depend on an initial assessment of carrier probability, so these studies excluded people whose carrier probability was judged too low for them to have genetic tests. This limits the applicability of this evidence in patients with low carrier probability.

There were some differences between studies in the way the carrier probability models had been used. Some studies estimated missing values (such ages and or years of death), whilst others excluded these cases. Some did not state the model version used: many of the models have been

updated over time to improve accuracy or modified to better reflect local populations. The sensitivity of the reference standard (genetic tests for BRCA1 and BRCA2 mutations) is likely to have improved over the study periods (2002 to 2010), which in turn could affect the accuracy of the carrier probability models.

1.3.9 Evidence statements

The area under the ROC curve (AUROC) measures the discrimination of a carrier probability model (its ability to separate mutation carriers from non carriers): where 1 is perfect discrimination and 0.5 is no better than chance. There was moderate quality but consistent evidence that carrier prediction models performed significantly better than chance with typical AUROC values between 0.7 and 0.8 for the BOADICEA, BRCAPRO, IBIS, MYRIAD, MANCHESTER, PENN, PENN II and FHAT models. The estimated AUROC for risk counsellors ranged from 0.69 to 0.70 (Table 2.2).

Calibration refers to how well a model's predicted carrier probability relates to the true carrier probability within a group of patients. Antoniou et al (2008) compared the calibration of the BOADICEA, BRCAPRO, IBIS, MANCHESTER and MYRIAD models using data from six UK cancer genetic clinics. . Calibration was tested by comparing predicted and observed mutations within groups defined by their predicted carrier probability. BOADICEA was the best calibrated model – being the only one of the five models in which the total number of observed mutations was not significantly different to the total number of predicted mutations

Table 1.5: Area under the ROC curve (95% confidence interval) of carrier probability models for BRCA1 or BRCA2 mutation

Study	Prevalence	BOADICEA	BRCAPRO	IBIS	MYRIAD	MANCHESTER	PENN	PENN II	FHAT	Risk Counselor
Antoniou et al 2006	0.18	0.81 (0.73 – 0.90)	0.83 (0.75 –0.91)							
Antoniou et al 2008	0.19	0.77 (0.74 – 0.80)	0.76 (0.73 – 0.79)	0.74 (0.71 - 0.77)	0.72 (0.69 – 0.75)	0.75 (0.72 – 0.77)				
Panchal et al 2008	0.33	0.74 (0.67 – 0.80)	0.76 (0.70 – 0.82)	0.47 (0.28 – 0.69)	0.76 (0.71 – 0.82)	0.68 (0.60 – 0.76)		0.74 (0.67 – 0.80)	0.74 (0.66 – 0.80)	
Parmigiani et al 2007 - population based.	0.04		0.85 (0.81 – 0.88)		0.79 (0.72 – 0.86)		0.75 (0.69 – 0.81)		0.79 (073 – 0.85)	
Parmigiani et al 2007 - high risk	0.28		0.76 (0.73 – 0.79)		0.71 (0.68 – 0.74)		0.73 (0.70 – 0.76)		0.71 (0.68 – 0.74)	
Barcenas et al 2006	0.19	0.78 (0.72 – 0.85)	0.80 (0.75 – 0.86)		0.78 (0.72 – 0.84)					
de la Hoya et al 2003	0.34				0.82 (0.73 – 0.89)		0.77 (0.68 – 0.85)			0.69 (0.60 – 0.78)
Euhus et al 2002	0.43		0.71							0.70
Evans et al 2004	0.09		0.60 (0.46 – 0.74)		0.71 (0.60– 0.83)	0.77 (0.67 – 0.88)				
James et al 2006	0.27		0.78 (0.72 – 0.85)		0.74 (0.67 – 0.81)	0.70 (0.62 – 0.77)	0.73 (0.67 – 0.80)		0.68 (0.61 – 0.75)	
Kang et al 2006	0.14		0.74 (0.67 – 0.81)		0.75 (0.68 – 0.83)	0.76 (0.69 – 0.83)	0.76 (0.69 – 0.83)			
Kurian et al 2009 - NHW	0.06	0.83 (0.63 – 0.93)	0.83 (0.63 – 0.93)							
Kurian et al 2009 -Hispanic	0.08	0.56 (0.43 – 0.68)	0.58 (0.45 – 0.70)							
Kurian et al 2009 -African American	0.05	0.75 (0.60 – 0.85)	0.74 (0.59 – 0.85)							
Lindor et al 2010	0.30		0.76 (0.70 – 0.82)		0.71 (0.64 – 0.77)		0.72 (0.64 – 0.78)	0.79 (0.72 – 0.84)		
Oros et al 2006	0.43		0.81		0.74	0.79			0.80	
Rao et al 2009	0.15		0.73 (0.64 – 0.811)		0.74 (0.65 – 0.84)					
Roudgari et al 2008	0.51	0.68		0.73		0.76				
Simard et al 2007	0.29				0.75 (0.66 – 0.83)	0.89 (0.84 – 0.95)				
Teller et al 2010	0.28				0.68			0.72		
Zanna et al 2010	0.10		0.82		0.61				0.72	

Table 1.6: Sensitivity and specificity of models for BRCA1 or BRCA2 mutation at carrier probability thresholds of 10%, 15% and 20%.

Study	Prevalence	BOADICEA						BRCAPRO						IBIS (Tyrer-Cuzick)						MYRIAD (Frank)						MANCHESTER					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20	
		Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
Antoniou et al 2008	0.19	0.90	0.40	0.85	0.50	0.81	0.59	0.88	0.43	0.85	0.52	0.81	0.57	0.80	0.51	0.73	0.59	0.68	0.66	0.79	0.46	0.76	0.53	0.51	0.80	0.87	0.43			0.73	0.61
Panchal et al 2008	0.33	0.70	0.65					0.75	0.62					0.20	0.74					0.71	0.63					0.58	0.71				
Parmigiani et al 2007 - population based.	0.04							0.63	0.85											0.69	0.81										
Parmigiani et al 2007- high risk	0.28							0.82	0.53											0.78	0.48										
Barcenas et al 2006	0.19	0.73	0.71					0.74	0.67											0.81	0.62										
Berry et al 2002	0.56							0.96	0.33																						
Bodmer et al 2006	0.19																						0.84	0.07		0.82	0.54				
Capalbo et al 2006	0.27							0.67	0.57											0.85	0.42										
de la Hoya et al 2003	0.34																														
Euhus et al 2002	0.43							0.92	0.32																						
Evans et al 2004	0.09							0.61	0.44											0.87	0.33					0.87	0.67				
Evans et al 2009	0.18																									0.94	0.52			0.84	0.72
James et al 2006	0.27							0.79	0.61											0.91	0.25					0.72	0.64				
Kang et al 2006	0.14							0.77	0.54			0.65	0.67							0.85	0.51			0.58	0.82	0.88	0.34			0.77	0.56
Kurian et al 2009 -NHW	0.06																														
Kurian et al 2009 -Hispanic	0.08																														
Kurian et al 2009 -African American	0.05																														
Lindor et al 2010	0.30																														
Oros et al 2006	0.4																														

Study	Prevalence	BOADICEA						BRCAPRO						IBIS (Tyrer-Cuzick)						MYRIAD (Frank)						MANCHESTER					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20	
		Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
	3																														
Rao et al 2009a	0.15									0.67	0.68											0.73	0.72								
Roudgari et al 2008	0.51					0.53	0.78									0.62	0.75													0.91	0.43
Simard et al 2007	0.29																														
Teller et al 2010	0.28																			0.85	0.39										

Abbreviations: Sn, sensitivity; Sp, specificity.

Study	Prevalence	PENN (Couch)						PENN II						FHAT						RISK COUNSELLOR					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20	
		Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
Antoniou et al 2008	0.19																								
Panchal et al 2008	0.33							0.93	0.31					0.70	0.63										
Parmigiani et al 2007 - population based.	0.04													0.87	0.59										
Parmigiani et al 2007- high risk	0.28													0.89	0.27										
Barcenas et al 2006	0.19																								
Berry et al 2002	0.56																								
Bodmer et al 2006	0.19															0.80	0.63					0.80	0.63		
Capalbo et al 2006	0.27																								
de la Hoya et al 2003	0.34																								
Euhus et al 2002	0.43																			0.94	0.16				
Evans et al 2004	0.09																								
Evans et al 2009	0.18																								
James et al 2006	0.27	0.72	0.63											0.91	0.15										
Kang et al 2006	0.14	0.69	0.67			0.56	0.74																		
Kurian et al 2009 -NHW	0.06																								
Kurian et al 2009 -Hispanic	0.08																								
Kurian et al 2009 -African American	0.05																								
Lindor et al 2010	0.30																								
Oros et al 2006	0.43																								

Study	Prevalence	PENN (Couch)						PENN II						FHAT						RISK COUNSELLOR					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20	
		Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
Rao et al 2009a	0.15																								
Roudgari et al 2008	0.51																								
Simard et al 2007	0.29																								
Teller et al 2010	0.28							0.92	0.16																

Abbreviations: Sn, sensitivity; Sp, specificity.

Table 1.7: Positive and negative predictive values for BRCA1 or BRCA2 mutation at model carrier probability thresholds of 10%, 15% and 20%.

Study	Prevalence	BOADICEA						BRCAPRO						IBIS (Tyrer-Cuzick)						Myriad (Frank)						MANCHESTER					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15-16		≥0.20		≥0.1		≥0.15		≥0.20	
		PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Antoniou et al 2008	0.19	0.26	0.95	0.28	0.93	0.31	0.93	0.27	0.94	0.29	0.94	0.30	0.93	0.27	0.91	0.29	0.90	0.32	0.90	0.25	0.90	0.27	0.90	0.38	0.88	0.24	0.94				
Panchal et al 2008	0.33	0.50	0.81					0.50	0.83					0.28	0.65					0.49	0.81					0.50	0.77				
Parmigiani et al 2007 - population based.	0.04							0.15	0.98											0.13	0.98										
Parmigiani et al 2007- high risk	0.28							0.40	0.89											0.37	0.85										
Barcenas et al 2006	0.19	0.37	0.92					0.34	0.92											0.33	0.94										
Berry et al 2002	0.56							0.65	0.88																						
Bodmer et al 2006	0.19																					0.27	0.93			0.29	0.93				
Capalbo et al 2006	0.27							0.37	0.82											0.35	0.88										
de la Hoya et al 2003	0.34																														
Euhus et al 2002	0.43							0.50	0.84																						
Evans et al 2004	0.09							0.10	0.92											0.11	0.96					0.21	0.98				
Evans et al 2009	0.18																									0.30	0.97			0.40	0.95
James et al 2006	0.27							0.43	0.89											0.31	0.88					0.43	0.86				
Kang et al 2006	0.14							0.21	0.94	0.24	0.92									0.22	0.95	0.34	0.92								
Kurian et al 2009 -NHW	0.06																														
Kurian et al 2009 -Hispanic	0.08																														
Kurian et al 2009 -African American	0.05																														
Lindor et al 2010	0.30																														
Oros et al 2006	0.4							0.5	0.8																						

Study	Prevalence	BOADICEA						BRCAPRO						IBIS (Tyrer-Cuzick)						Myriad (Frank)						MANCHESTER					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15-16		≥0.20		≥0.1		≥0.15		≥0.20	
		PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
	3							6	6																						
Rao et al 2009a	0.15									0.28	0.92											0.32	0.93							0.62	0.82
Roudgari et al 2008	0.51					0.71	0.62											0.72	0.66												
Simard et al 2007	0.29																														
Teller et al 2010	0.28																			0.35	0.87										

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Study	Prevalence	PENN (COUCH)						PENN II						FHAT						RISK COUNSELLOR					
		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20		≥0.1		≥0.15		≥0.20	
		PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Antoniou et al 2008	0.19													0.49	0.81										
Panchal et al 2008	0.33							0.40	0.90																
Parmigiani et al 2007 - population based.	0.04													0.07	0.99										
Parmigiani et al 2007- high risk	0.28													0.32	0.86										
Barcenas et al 2006	0.19																								
Berry et al 2002	0.56																								
Bodmer et al 2006	0.19													0.33	0.93										
Capalbo et al 2006	0.27																								
de la Hoya et al 2003	0.34																								
Euhus et al 2002	0.43																			0.45	0.78				
Evans et al 2004	0.09																								
Evans et al 2009	0.18																								
James et al 2006	0.27	0.42	0.86											0.29	0.82										
Kang et al 2006	0.14	0.25	0.93	0.23	0.92																				
Kurian et al 2009 -NHW	0.06																								
Kurian et al 2009 -Hispanic	0.08																								
Kurian et al 2009 -African American	0.05																								
Lindor et al 2010	0.30																								
Oros et al 2006	0.43																								
Rao et al 2009a	0.15																								
Roudgari et al 2008	0.51																								
Simard et al 2007	0.29																								
Teller et al 2010	0.28							0.30	0.84																

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Figure 1.1: ROC plot for prediction of BRCA1 or BRCA2 mutation at carrier probability thresholds between 10% and 20%.

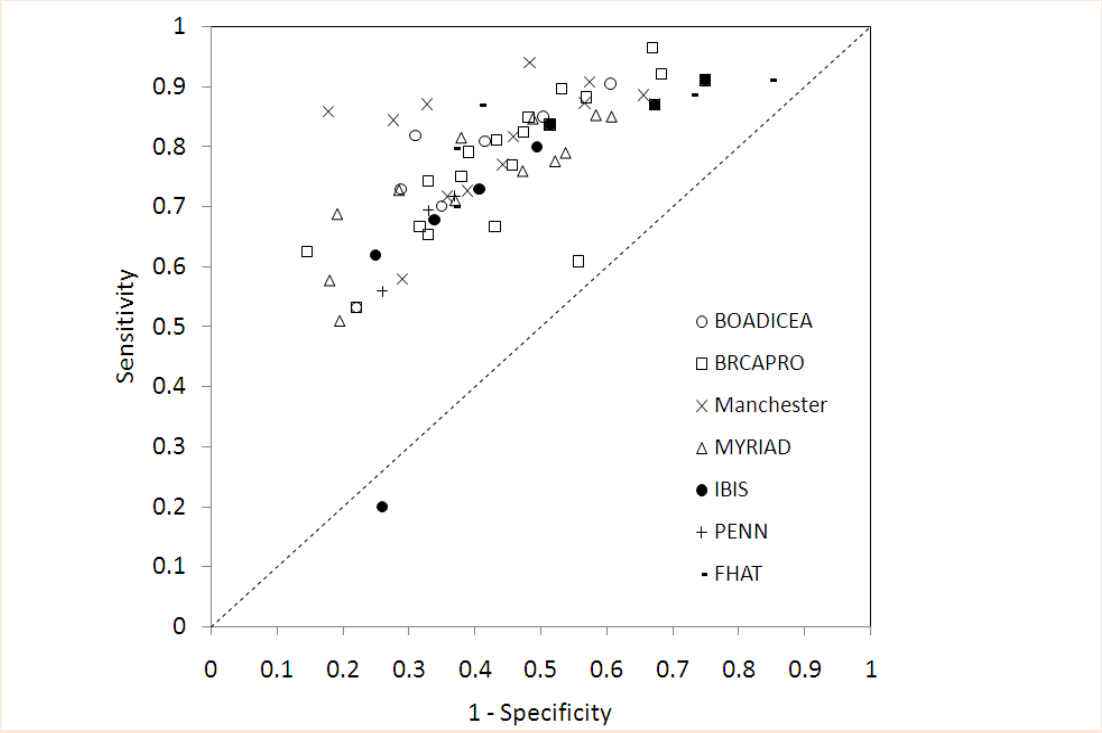


Figure 1.2: Positive predictive value (PPV) of carrier probability thresholds between 10% and 20% versus prevalence of BRCA1 or BRCA2 mutation.

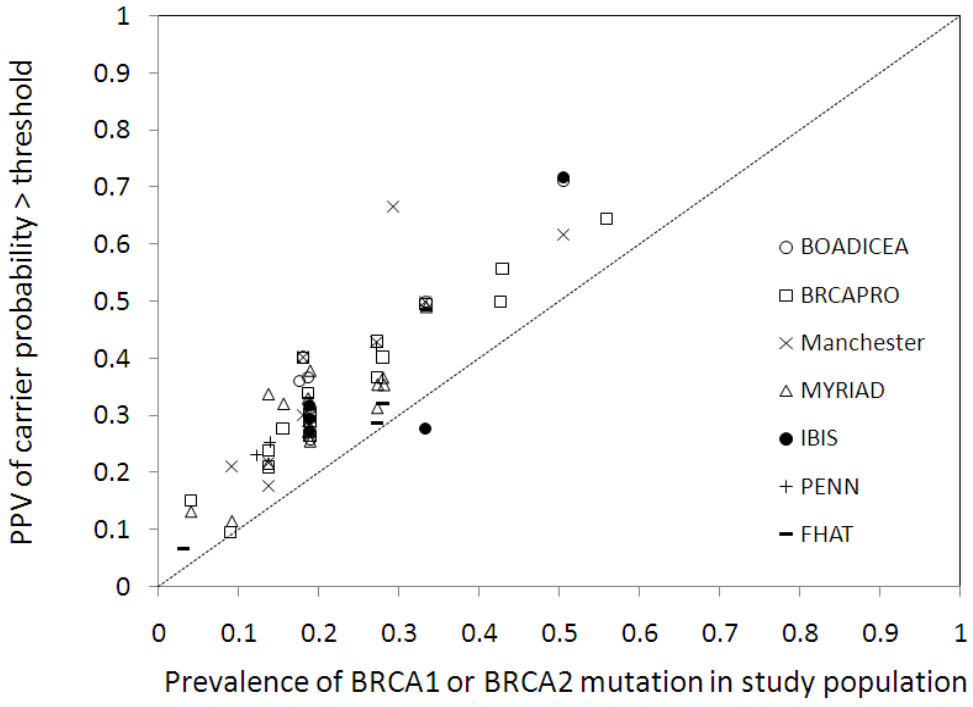


Figure 1.3: Negative predictive value (NPV) of carrier probability thresholds between 10% and 20% versus prevalence of BRCA1 or BRCA2 mutation.

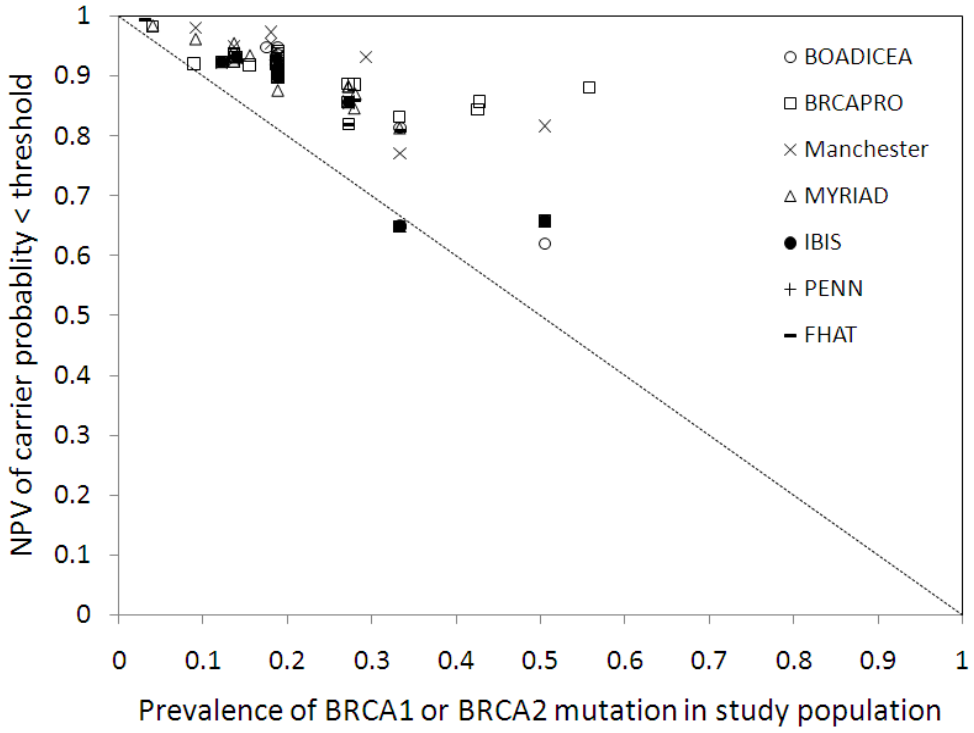
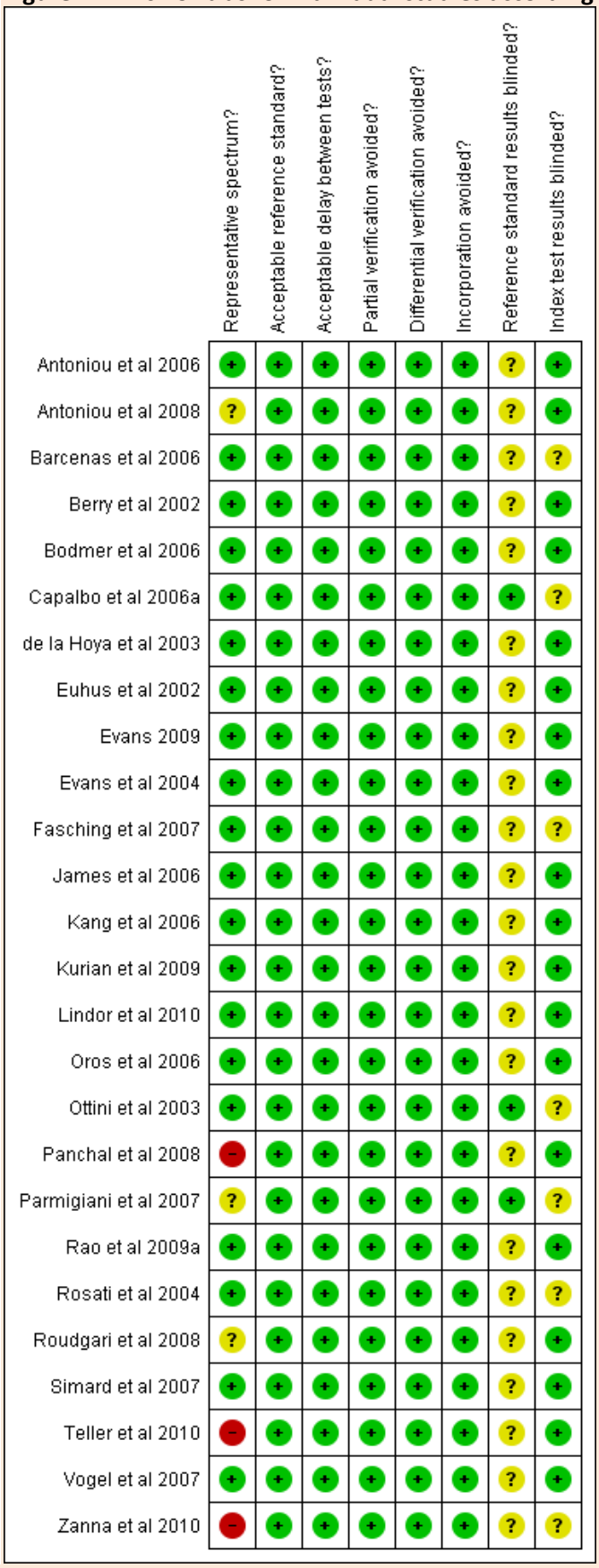


Figure 1.4: Risk of bias for individual studies according to QUADAS criteria



1.3.10 Evidence tables

Citation: Antoniou, A. C., et al. "BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families." Breast Cancer Research 8.1 (2006)

Design: Prospective cohort study
Country: Canada
Aim: To use data from French Canadian families to evaluate the mutation predictions given by the BRCAPRO and BOADICEA models.

Inclusion criteria

Participants were required to meet one or more of the following criteria:

- Four first or second degree relatives diagnosed with breast and/or ovarian cancer at any age.
- Three first degree relatives diagnosed at any age
- Family known to carry a deleterious gene (these individuals excluded from model comparisons)
- Over 18 years of age
- Mentally competent

Population
188 French Canadians at high risk of breast cancer (first family member screened included) recruited between 1996 and 2003

Interventions
BRCAPRO, BOADICEA

Outcomes
Observed and predicted carrier probabilities

Results
BOADICEA

	Mutation carrier	Non-mutation carrier	
≥ 16	27	48	75
< 16	6	107	113
Total	33	155	188

Sensitivity: 82%
Specificity: 69%
Positive predictive value: 36%
Negative predictive value: 95%

BRCAPRO
(only possible to extract 2x2 table for BRCAPRO at cut-off of 25)

	Mutation carrier	Non-mutation carrier	
≥ 25	23	56	79
< 25	10	99	109
Total	33	155	188

Sensitivity: 69%
Specificity: 64%
Positive predictive value: 29%
Negative predictive value: 91%

General comments

- Individuals underwent genetic testing if they had four first or second degree relatives diagnosed with breast and/or ovarian cancer at any age or three first degree relatives diagnosed at any age. The models were

calibrated by comparing the observed and expected numbers of mutations.

- BOADICEA originally developed using data from UK; this study evaluated with French Canadians
- The authors conclude that the BOADICEA model predicts accurately the carrier probabilities in French Canadian families.

References of Included Studies (For systematic reviews): Not applicable

Citation: Antoniou, A. C., et al. "Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics." Journal of Medical Genetics 45.7 (2008): 425-31.

Design: Retrospective cohort study
Country: UK
Aim: The aim of this study was to evaluate the five widely used carrier prediction algorithms: Myriad, BRCAPRO, the Manchester scoring system, BOADICEA and IBIS, using a large cohort of families seen in cancer genetics clinics in the UK and in which an index patient had been screened for BRCA1 and BRCA2 mutations.

Inclusion criteria

- Families with unknown mutation status when genetic testing was initiated
- At least one family member (index case) was screened for BRCA1 and/or BRCA2 mutations using a primary mutation search, and information on the mutation-testing methods used was available.

Exclusion criteria

- Ashkenazi Jewish origin

Population
1934 families who underwent genetic testing in the UK

Interventions
Myriad, BRCAPRO, the Manchester scoring system, BOADICEA and IBIS

Outcomes
Observed and expected mutation probability

Results
BOADICEA

	Mutation carrier	Non-mutation carrier	
≥ 10	330	949	1279
< 10	35	620	655
	365	1569	1934

Sensitivity: 90.4
Specificity: 39.5
Positive predictive value: 25.8
Negative predictive value: 94.6

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	322	893	1215
< 10	43	676	719
Total	365	1569	1934

Sensitivity: 88.2
Specificity: 43.1
Positive predictive value: 26.5
Negative predictive value: 94.0

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 15	337	1045	1382
< 15	28	524	552
Total	365	1569	1934

Sensitivity: 92.3
Specificity: 33.4

Positive predictive value: 24.4
Negative predictive value: 94.9

IBIS

	Mutation carrier	Non-mutation carrier	
≥ 10	285	757	1042
< 10	72	775	847
Total	357	1532	1889

Sensitivity: 79.8
Specificity: 50.6
Positive predictive value: 27.4
Negative predictive value: 91.5

MYRIAD

	Mutation carrier	Non-mutation carrier	
≥ 10	288	843	1131
< 10	77	726	803
Total	365	1569	1934

Sensitivity: 78.9
Specificity: 46.3
Positive predictive value: 25.5
Negative predictive value: 90.4

BOADICEA

	Mutation carrier	Non-mutation carrier	
≥ 20	295	651	946
< 20	70	918	988
Total	365	1569	1934

Sensitivity: 80.8
Specificity: 58.5
Positive predictive value: 31.2
Negative predictive value: 92.9

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 20	296	680	976
< 20	69	889	958
Total	365	1569	1934

Sensitivity: 81.1
Specificity: 56.7
Positive predictive value: 30.3
Negative predictive value: 92.8

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 17	318	888	1206
< 17	47	681	728
Total	365	1569	1934

Sensitivity: 87.1
Specificity: 43.4
Positive predictive value: 26.4
Negative predictive value: 93.6

IBIS

	Mutation carrier	Non-mutation carrier	
≥ 20	242	519	761
< 20	115	1013	1128
Total	357	1532	1889

Sensitivity: 67.8
Specificity: 66.1
Positive predictive value: 31.7
Negative predictive value: 89.8

Myriad

	Mutation carrier	Non-mutation carrier	
≥ 20	186	306	492
< 20	179	1263	1442
Total	365	1569	1934

Sensitivity: 51
Specificity: 80.5
Positive predictive value: 37.8
Negative predictive value: 87.6

General comments

- Date of birth and/or age data were completely missing for approximately 57% of all the individuals submitted.
- The authors concluded that Carrier prediction algorithms provide a rational basis for counselling individuals likely to carry BRCA1 or BRCA2 mutations. Their widespread use would improve equity of access and the cost-effectiveness of genetic testing.

References of Included Studies (For systematic reviews): Not applicable

Citation: Barcenas, C. H., et al. "Assessing BRCA carrier probabilities in extended families." Journal of Clinical Oncology 24.3 (2006): 354-60.

Design: Retrospective cohort study
Country: USA
Aim: To evaluate the accuracy of the BOADICEA model and compare it with that of other models (BRCAPRO, Myriad I and II and Couch)

Inclusion criteria

- Pedigrees of families recruited between 1996 and 2003 at high-risk cancer genetic clinics affiliated with the Texas Cancer Genetics Consortium

Population

- Pedigree data from 472 families

Interventions

- BRCAPRO, Myriad I and II, and Couch

Outcomes

- Sensitivity, specificity, positive and negative predictive values, area under ROC curve for each risk model at the 10% risk threshold

Results

BOADICEA

	Mutation carrier	Non-mutation carrier	
≥ 10	51	88	139
< 10	19	218	237
Total	70	306	376

Sensitivity: 73
Specificity: 71
Positive predictive value: 37
Negative predictive value: 92

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	52	101	153
< 10	18	205	223
Total	70	306	376

Sensitivity: 74
Specificity: 67
Positive predictive value: 34
Negative predictive value: 92

Myriad II

	Mutation carrier	Non-mutation carrier	
≥ 10	57	116	173
< 10	13	190	203
Total	70	306	376

Sensitivity: 81
Specificity: 62
Positive predictive value: 33
Negative predictive value: 94

	Proportion of carriers		Test parameters at 10% threshold (No CIs given)			
	<10%	**≤10%**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
BRCA1						
BOADICEA	Not reported	Not reported	0.86	0.66	0.32	0.96
BRCAPRO	Not reported	Not reported	0.67	0.52	0.20	0.89
Myriad I	Not reported	Not reported	0.67	0.52	0.20	0.89
Couch	Not reported	Not reported	0.80	0.48	0.22	0.93
BRCA2						
BOADICEA	Not reported	Not reported	0.75	0.45	0.11	0.95
BRCAPRO	Not reported	Not reported	0.75	0.46	0.11	0.95

General comments

- A 10% risk threshold was used
- The Manchester scoring system was applied to a Subset of non-Ashkenazi Jewish Pedigrees with a cancer affected proband. It was the most sensitive tool within this sub-group.

References of Included Studies (For systematic reviews): Not applicable

Citation: Bodmer, D., et al. "Optimal selection for BRCA1 and BRCA2 mutation testing using a combination of 'easy to apply' probability models." British Journal of Cancer 95.6 (2006): 757-62.

Design: Retrospective cohort study
Country: The Netherlands
Aim: To compare genetic test results for deleterious mutations of BRCA 1 and 2 with estimated probabilities of carrying such mutations; to assess the relevance of other susceptibility genes in familial breast and ovarian cancer

Inclusion criteria

- Selection for genetic testing based on expert opinion of clinical geneticist

Population
236 families with breast and/or ovarian cancer patients that were tested for BRCA mutations between 1999 and 2001

Interventions
Claus, Frank, Gilpin, Evans

Outcomes
Sensitivity, specificity, PPV and NPV at various cut-off points

Results
Frank

	Mutation carrier	Non-mutation carrier	
≥ 16	41	110	151
< 16	8	104	112
	49	214	263

Sensitivity: 84%
Specificity: 51%
Positive predictive value: 28%
Negative predictive value: 93%

Gilpin

	Mutation carrier	Non-mutation carrier	
≥ 16	39	79	118
< 16	10	135	145
	49	214	263

Sensitivity: 80%
Specificity: 63%
Positive predictive value: 33%
Negative predictive value: 93%

General comments

- Index case was first family member to be tested
- Women had breast/ovarian cancer
- Looked at the sensitivity in models in isolation and in combination

References of Included Studies (For systematic reviews): Not applicable

Citation: Berry, D. A., et al. "BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes." Journal of Clinical Oncology 20.11 (2002): 2701-12.

Design: Retrospective cohort study
Country: USA
Aim: To compare genetic test results for deleterious mutations of BRCA1 and BRCA2 with estimated probabilities of carrying such mutations; to assess sensitivity of genetic testing; and to assess the relevance of other susceptibility genes in familial breast and ovarian cancer.

Inclusion criteria
The criteria used to refer individuals to the cancer genetic counseling services is unclear

Population
301 probands who underwent genetic testing; 216 (71%) were at high risk for carrying mutations on the basis of having three or more cases of having breast or ovarian cancer

Interventions
BRCAPRO

Outcomes
Observed and predicted carrier probabilities

Results
BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	162	89	251
< 10	6	44	50
Total	168	133	301

Sensitivity: 96%
Specificity: 33%
Positive predictive value: 65%
Negative predictive value: 88%

General comments

- All individuals referred to a cancer genetic counseling service appeared eligible for inclusion. Referral criteria are unclear
- Every family for which at least one member had been tested were included, regardless of family history
- The first family member tested was included
- 42% were Ashkenazi Jewish
- Data from 6 cancer genetic counseling centers
- The authors concluded that BRCAPRO is an accurate counseling tool for determining probability of carrying mutations of BRCA1 and BRCA2

References of Included Studies (For systematic reviews): Not applicable

Citation: Capalbo, C., et al. "BRCA1 and BRCA2 genetic testing in Italian breast and/or ovarian cancer families: mutation spectrum and prevalence and analysis of mutation prediction models." Annals of Oncology 17 (2006a): Suppl-40.

Design: Prospective cohort study
Country: Italy
Aim: To assess the prevalence of mutations in the Italian population and to evaluate mutation prediction models.

Inclusion criteria

- Three or more breast cancer cases diagnosed at any age or two first degree relatives affected before 50
- Early onset breast cancer (>35 years)
- Breast and ovarian cancer in the same individual or one breast cancer case and at least one ovarian, or one breast and one ovarian diagnosed before 50 in first degree relatives
- Two or more ovarian cancer cases
- Male breast cancer

Population
99 Italian probands with a family history of breast cancer

Interventions
BRCAPRO, Myriad, IC software

Outcomes
Observed and predicted carrier probabilities

Results
BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	18	31	49
< 10	9	41	50
Total	27	72	99

Sensitivity: 67%
Specificity: 57%
Positive predictive value: 37%
Negative predictive value: 82%

MYRIAD

	Mutation carrier	Non-mutation carrier	
≥ 10	23	42	65
< 10	4	30	34
Total	27	72	99

Sensitivity: 85%
Specificity: 42%
Positive predictive value: 35%
Negative predictive value: 88%

IC

	Mutation carrier	Non-mutation carrier	
≥ 10	24	35	59
< 10	3	37	40
Total	27	72	99

Sensitivity: 89%
Specificity: 51%
Positive predictive value: 41%
Negative predictive value: 93%

General comments

- One proband selected for each family and a priori probability of carrying a mutation calculated
- Everyone meeting the minimal criteria above was tested
- The authors conclude that apparently faulty performances of the prediction models might be at least partially explained by the presence of additional kinds of BRCA1/2 alteration

References of Included Studies (For systematic reviews): Not applicable

Citation: de la Hoya, M., et al. "Pre-test prediction models of BRCA1 or BRCA2 mutation in breast/ovarian families attending familial cancer clinics." Journal of Medical Genetics 40.7 (2003): 503-10.

Design: Retrospective cohort study
Country: Spain
Aim: To test whether statistical models developed to calculate pre-test probability of being a BRCA1/2 carrier can differentiate better between the breast / ovarian families to be referred to the DNA test laboratory.

Inclusion criteria
Pedigrees selected for complete *BRCA* gene sequencing on the basis of cancer family history information suggestive of an inherited breast and ovarian cancer predisposition (all pedigrees included at least three or more first or second degree relatives affected with breast or ovarian cancer in the same lineage). Pedigrees were constructed on the basis of an index case considered to have the highest probability of being a deleterious mutation carrier (generally the youngest affected subject available in each family).

Population
109 Spanish breast/ovarian families previously screened for germline mutations in both the BRCA1 and BRCA2 genes.

Interventions
The Spanish HCSC model, the Dutch LUMC model, the Finnish HUCH model, and the North American U Penn model, Frank

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data presented to allow extraction of a 2x2 table

Model	Area under ROC curve (95% CI)
HCSE	0.82 (0.73 – 0.88)
LUMC	0.80 (0.72 – 0.88)
U-Penn	0.77 (0.68 – 0.85)
HUCH	0.77 (0.69 – 0.84)
Frank	0.82 (0.73 – 0.89)
Counsellor	0.69 (0.60 – 0.78)

No. mutations

	BRCA1 carriers		BRCA2 carriers		Non BRCA1/2 carriers		Total	
	No.	%	No.	%	No.	%	No.	%
No. of patients	19	17	18	17	72	66	109	100

General comments

- Compared models with the performance of a genetic counsellor
- The authors concluded that all models increased the discrimination power of an experienced risk counsellor, suggesting that their use is valuable in the context of clinical counselling and genetic testing to optimise selection of patients for screening and allowing for more focused management. Models developed in different ethnic populations performed similarly well in a Spanish series of families, suggesting that models targeted to specific populations may not be necessary in all cases. Carrier probability as predicted by the models is consistent with actual prevalence, although in general models tend to underestimate it. Our study suggests that these models may perform differently in populations with a high prevalence of BRCA2 mutations.

References of Included Studies (For systematic reviews): Not applicable

Citation: Euhus, D. M., et al. "Pretest prediction of BRCA1 or BRCA2 mutation by risk counselors and the computer model BRCAPRO." Journal of the National Cancer Institute 94.11 (2002): 844-51.

Design: Retrospective cohort study
Country: USA
Aim: To measure the performance of eight cancer risk counsellors and of a computer model, BRCAPRO, at identifying families likely to carry a BRCA gene mutation.

Inclusion criteria

- Pedigrees from families who had obtained BRCA gene mutation testing

Population
148 pedigrees from families who had obtained BRCA gene mutation testing through several different university-based clinical cancer genetics programs.

Interventions

- Risk assessments conducted by eight cancer risk counsellors and BRCAPRO

Outcomes

- Sensitivity, specificity, positive and negative predictive values, and area under ROC curve for each risk model at the 10% risk threshold

Results
BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	58	58	116
< 10	5	27	32
	63	85	148

Sensitivity: 92%
Specificity: 32%
Positive predictive value: 50%
Negative predictive value: 84%

Risk counselor

	Mutation carrier	Non-mutation carrier	
Yes	59	71	130
No	4	14	18
	63	85	148

Sensitivity: 94%
Specificity: 16%
Positive predictive value: 45%
Negative predictive value: 78%

General comments

- The risk counsellors were asked to estimate the probability of BRCA gene mutation for each pedigree by using a five-point scale ((1) ≤ 10%; (2) 11%–30%; (3) 31%–70%; (4) 71%–94%; and (5) ≥ 95%)
- BRCAPRO consistently demonstrated superior specificity over the risk counsellors
- Pedigrees were obtained from a highly pre-screened selection of women attending a cancer genetics clinic who had already been selected for complete BRCA gene sequencing on the basis of family history information suggestive of an inherited breast and ovarian cancer predisposition

References of Included Studies (For systematic reviews): Not applicable

Citation: Evans, D. G., et al. "A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO." Journal of Medical Genetics 41.6 (2004): 474-80.

Design: Retrospective cohort study
Country: United Kingdom
Aim: To develop a simple scoring system for the likelihood of identifying a BRCA1/2 gene

Inclusion criteria

- Affected individuals with breast and/or ovarian cancer, with a family history of breast or ovarian cancer, were ascertained from attendees at cancer genetics clinics in the Manchester region of North West England
- Informed consent for mutation screening of BRCA1 and BRCA2
- Samples were initially prioritised using a clinician's assessment of the likelihood of identifying a mutation: minimal requirement was two close relatives (usually first degree relatives of each other) with breast cancer at 50 years of age, but combinations of male and female breast cancer and breast and ovarian cancer were particularly prioritised for mutation analysis. Exceptions to this were two research projects where population based cases of breast cancer at, 31 years of age 20 and sporadic breast cancer at (35 years of age 21 were screened for mutations in both genes).

Population
258 individuals from the North West of England with a family history of breast cancer

Interventions
Manchester scoring system, BRCAPRO

Outcomes
Sensitivity, specificity, negative and positive predictive values, and areas under receiver operator characteristics (ROC) curves

Results
Manchester

	Mutation carrier	Non-mutation carrier	
≥ 10	4	74	78
< 10	2	178	180
Total	6	252	258

Sensitivity: 67%
Specificity: 71%
Positive predictive value: 5%
Negative predictive value: 98.9%

Frank

	Mutation carrier	Non-mutation carrier	
≥ 10	20	154	174
< 10	3	75	78
Total	23	229	252

Sensitivity: 87%
Specificity: 33%
Positive predictive value: 11.5%
Negative predictive value: 96%

BRCAPRO

	Mutation carrier	Non-mutation carrier	

≥ 10	14	131	145
< 10	9	104	113
Total	23	235	258

Sensitivity: 61%
Specificity: 44%
Positive predictive value: 9.7%
Negative predictive value: 92%

General comments

- This paper describes the development of the Manchester scoring system. DNA samples from affected individuals with a family history of breast and/or ovarian cancer were screened for BRCA1 mutations and a subset of 318 was screened for BRCA2 by whole gene screening techniques. Using a combination of results from screening and the family history of mutation negative and positive kindreds the Manchester scoring system was devised to predict pathogenic mutations and particularly to discriminate at the 10% likelihood level. A second separate dataset of 192 samples was subsequently used to test the model's predictive value. This was further validated on a third set of 258 samples and compared against existing models. The results of this third validation study are considered here.
- The authors concluded that Manchester scoring system is useful in identifying mutations particularly in BRCA2. They also commented that the algorithm may need modifying to include pathological data when calculating whether to screen for BRCA1 mutations. It was aid to be considerably less time-consuming for clinicians than using computer models.

References of Included Studies (For systematic reviews): Not applicable

Citation: Evans, D. G., et al. "Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing." Journal of Medical Genetics 46 (2009): 811-817.

Design: Retrospective case series
Country: United Kingdom
Aim: To investigate whether incorporation of pathology and biomarker information improves accuracy of the Manchester scoring system.

Inclusion criteria
Patients with breast cancer (diagnosed between 1960 and 1990) who were also fully tested for BRCA1/2 and had pathology data, identified from the records of a regional medical genetics service.

Population
2156 patients with breast (N=1918) or ovarian cancer (N=238). Pathology data were available for 1116 patients.

Tests
Manchester scoring system (with and without adjustment for pathology and receptor status data).

Outcomes
Sensitivity, specificity, negative and positive predictive values, and areas under receiver operator characteristics (ROC) curves

Results
Manchester (adjusted for pathology and receptor status)

	BRCA1/2 mutation	No BRCA1/2 mutation	Total
≥ 16 (≥10% carrier prob.)	365	853	1218
< 16 (<10% carrier prob.)	24	914	938
Total	389	1767	2156

Sensitivity: 94%
Specificity: 52%
Positive predictive value: 30%
Negative predictive value: 97.5%

Manchester (adjusted for pathology and receptor status)

	BRCA1/2 mutation	No BRCA1/2 mutation	Total
≥ 20 (≥20% carrier prob.)	328	487	815
< 20 (<20% carrier prob.)	61	1280	1341
Total	389	1767	2156

Sensitivity: 84%
Specificity: 74%
Positive predictive value: 40%
Negative predictive value: 95.5%

Manchester (unadjusted for pathology and receptor status)

	BRCA1/2 mutation	No BRCA1/2 mutation	Total
≥ 16 (≥10% carrier prob.)	361	924	1285
< 16 (<10% carrier prob.)	28	843	871
Total	389	1767	2156

Sensitivity: 93%
Specificity:48%
Positive predictive value: 28%
Negative predictive value: 97%

Manchester (unadjusted for pathology and receptor status)

	BRCA1/2 mutation	No BRCA1/2 mutation	Total

≥ 20 (≥20% carrier prob.)	319	556	875
< 20 (<20% carrier prob.)	70	1211	1281
Total	389	1767	2156

Sensitivity:82 %
Specificity: 70%
Positive predictive value: 36.5%
Negative predictive value: 94.5%

AUC reported separately with/without pathology data and for each threshold level (10% or 20%).

General comments Pathology data were available for less than half of the included patients.

References of Included Studies (For systematic reviews): Not applicable

Citation: Fasching, P. A., et al. "Evaluation of mathematical models for breast cancer risk assessment in routine clinical use." European Journal of Cancer Prevention 16.3 (2007): 216-24.

Design: Prospective cohort study
Country: Germany
Aim: To assess two topics: (1) which model is best able to predict mutation carrier status? and (2) how can lifetime risks be interpreted and used in cancer genetics clinics?

Inclusion criteria

- Two first degree female relatives with a history of invasive breast or ovarian cancer, with one of them at least 50 years old at the onset of disease
- One first-degree female relative with a history of invasive breast or ovarian cancer younger than 30 years old at the onset of disease
- One first degree male relative with a history of invasive breast cancer

Population
111 breast cancer affected patients from 103 kindreds with a family history of breast cancer recruited between 1994 and 2001

Interventions
MENDEL, BRCAPRO, Tyrer-Cuzick

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data presented to allow extraction of a 2x2 table

Model	Area under ROC curve (95% CIs not reported)
Tyrer-Cuzick	0.716
MENDEL	0.714
BRCAPRO	0.699

General comments
Included members of same family (111 breast cancer affected patients from 103 kindreds)

References of Included Studies (For systematic reviews): Not applicable

Citation: James, P. A., et al. "Optimal selection of individuals for BRCA mutation testing: a comparison of available methods." Journal of Clinical Oncology 24.4 (2006): 707-15.

Design: Retrospective cohort study
Country: Australia
Aim: To identify the optimal strategy for selecting individuals for mutation testing in clinical practice

Inclusion criteria

- At least two first or second degree relatives with breast or ovarian cancer
- At least one additional high risk feature (an individual diagnosed with BC before 40, or OC before 50; bilateral breast or breast and ovarian cancer; male breast cancer; or Ashkenazi Jewish decent)

Population
257 families who had completed BRCA1/2 mutation screening

Interventions
Frank, Couch, BRCAPRO, Adelaide, FHAT, Manchester

Outcomes
Sensitivity and specificity at a 10% mutation probability

Results
BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	53	70	123
< 10	14	109	123
Total	67	179	246

Sensitivity: 79%
Specificity: 61%
Positive predictive value: 43%
Negative predictive value: 87%

Frank

	Mutation carrier	Non-mutation carrier	
≥ 10	61	134	195
< 10	6	45	51
	67	179	246

Sensitivity: 91
Specificity: 25
Positive predictive value: 31%
Negative predictive value: 82%

Couch

	Mutation carrier	Non-mutation carrier	
≥ 10	48	66	114
< 10	19	113	132
	67	179	246

Sensitivity: 72%
Specificity: 63%
Positive predictive value: 42%
Negative predictive value: 85%

FHAT

	Mutation carrier	Non-mutation carrier	
≥ 10	61	152	213

< 10	6	27	33
	67	179	246

Sensitivity: 91%
Specificity: 15%
Positive predictive value: 27%
Negative predictive value: 82%

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 10	48	64	112
< 10	19	115	134
	67	179	246

Sensitivity: 72%
Specificity: 64%
Positive predictive value: 43%
Negative predictive value: 86%

General comments

- Testing was also offered to a small number of individuals (n = 15) with one or more high-risk features but without a significant family history.
- The authors conclude that formal probabilistic models provide significantly greater accuracy in the selection of families for gene testing than the use of clinical criteria or scoring methods. The accuracy is further enhanced by incorporating information on the pathology of breast cancers occurring in families.

References of Included Studies (For systematic reviews):

Citation: Kang, H. H., et al. "Evaluation of models to predict BRCA germline mutations." British Journal of Cancer 95.7 (2006): 914-20

Design: Retrospective cohort study
Country: Australia
Aim: To evaluate the performance and the inter-rater reliability of the BRCAPRO, Manchester, Penn and Myriad-Frank risk assessment models.

Inclusion criteria

- At least one affected family member had a life time risk of breast cancer of 1 : 4 or greater as defined by the Australian National Breast Cancer (NBCC) guidelines (NBCC GeneticsWorking Group, 2000). This included individuals with at least two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, together with additional features on the same side of the family. These features included an additional relative with breast or ovarian cancer; breast cancer diagnosed before the age of 40 years, ovarian cancer before 50 years, bilateral breast cancer, breast and ovarian cancer in the same woman, Jewish ancestry or breast cancer in a male relative.

Population

- Pedigrees of 380 families who had undergone BRCA1/2 mutation analysis in the period 1998-2004.

Interventions

- BRCAPRO, Manchester, Penn and Myriad-Frank risk assessment models applied by two investigators.

Outcomes

- Sensitivity, specificity, positive and negative predictive values, area under the ROC curve for each risk model at the 10% risk threshold

Results

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 15	46	215	261
< 15	6	113	119
	52	328	380

Sensitivity: 89%
Specificity: 35%
Positive predictive value: 18%
Negative predictive value: 95%

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 15	40	150	190
< 15	12	178	190
Total	52	328	380

Sensitivity: 77%
Specificity: 54%
Positive predictive value: 21%
Negative predictive value: 94%

Myriad

	Mutation carrier	Non-mutation carrier	
≥ 15	44	160	204
< 15	8	168	176
Total	52	328	380

Sensitivity: 85%

Specificity: 51%
Positive predictive value: 22%
Negative predictive value: 96%

Penn

	Mutation carrier	Non-mutation carrier	
≥ 15	36	106	142
< 15	16	216	232
Total	52	322	374

Sensitivity: 69%
Specificity: 67%
Positive predictive value: 25%
Negative predictive value: 93%

	Proportion of model					
	<10%	**≤10%**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
BRCA1						
Manchester	4/187	30/193	0.88 (0.73-0.95)	0.53 (0.48-0.58)	0.16 (0.11-0.21)	0.98 (0.95-0.99)
BRCAPRO	7/225	27/155	0.79 (0.63-0.90)	0.63 (0.58-0.68)	0.17 (0.12-0.24)	0.97 (0.94-0.99)
Penn	14/281	20/93	0.58 (0.42-0.74)	0.79 (0.74-0.83)	0.22 (0.14-0.31)	0.95 (0.92-0.97)
BRCA2						
Manchester	6/189	12/191	0.67 (0.44-0.84)	0.51 (0.45-0.56)	0.06 (0.04-0.11)	0.97 (0.93-0.99)
BRCAPRO	12/308	6/72	0.33 (0.16-0.56)	0.82 (0.78-0.85)	0.08 (0.04-0.17)	0.96 (0.93-0.98)
Penn	12/348	6/26	0.33 (0.16-0.56)	0.94 (0.92-0.96)	0.23 (0.11-0.42)	0.97 (0.94-0.98)

At the completion of the study, a k score of mutation-risk estimates using the models was determined for 100 randomly selected pedigrees (25 cases for each risk model). Overall, the k score was 0.82 reflecting excellent agreement between observers when calculating the mutation risk for each proband. The measure of agreement differed between models in that perfect agreement was noted for Penn (k¼1.0) and Manchester (k¼0.932), whereas only substantial agreement was found for Myriad (k¼0.714) and for BRCAPRO (k¼0.60). The areas of disagreement in applying the BRCAPRO model were related to clinical judgment on choice of proband, estimation of age of relatives, and inclusion of maternal and paternal relatives.

General comments

- A 10% risk threshold was used
- Families of Ashkenazi Jewish ancestry were not included in this study
- Risk assessment models were applied by two investigators
- Specific issue associated with the models were noted:

(1) The Myriad tables only allowed inclusion of a maximum of three members of the family, including the patient. Breast cancers diagnosed above 50 years were ignored, whereas for those diagnosed before 50 years there was no stratification according to the age at diagnosis. Further deficiencies included the equal weighting given to male and female breast cancers and the inability to input bilateral breast cancer or other tumours associated with BRCA1/2 mutation.

(2) Both the Penn model and BRCAPRO required computer access. In the case of BRCAPRO, the time taken to enter family trees was a major impediment to routine use.

(3) BRCAPRO only incorporates first- and second-degree relatives and therefore cousins of the proband who are affected with cancer will not be used to generate a probability score unless the counselor changes the proband. This scenario was in part responsible for the low k scores associated with the use of BRCAPRO.

(4) The Penn model restricted questions to three generations, and did not include ovarian cancer only families or mother–daughter ovarian–breast cancer inheritance patterns.
References of Included Studies (For systematic reviews): Not applicable

Citation: Kurian, A. W., et al. "Performance of prediction models for BRCA mutation carriage in three racial/ethnic groups: findings from the Northern California Breast Cancer Family Registry." Cancer Epidemiology, Biomarkers & Prevention 18.4 (2009): 1084-91.

Design: Prospective cohort study
Country: USA
Aim: To evaluate the accuracy of BRCAPRO and BOADICEA in three ethnic groups

Inclusion criteria
Category A inclusion criteria (patients whose cancers were likely to be hereditary):

- Breast cancer diagnosis before age 35
- Bilateral breast cancer, with first diagnosis before age 50
- Prior ovarian or childhood cancer
- At least one first-degree relative with breast or ovarian cancer

Category B inclusion criteria (patients whose cancers were less likely to be hereditary)

- All other patients aged < 65 at diagnosis

Population
Patients diagnosed with invasive breast cancer < 65 years between January 1995 and April 2003. Divided into two groups according to likelihood that cancer was genetic.

Interventions
BRCAPRO, BOADICEA

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data presented to allow extraction of a 2x2 table

Model	Area under ROC curve (95% CI)		
	African Americans (with a family history of breast cancer)	Hispanic (with a family history of breast cancer)	Non-Hispanic Whites (with a family history of breast cancer)
BRCAPRO	73.1 (54.7 – 85.9)	68.9 (56.3 – 79.2)	82.3 (71.7 – 89.5)
BOADICEA	73.9 (54.2 – 87.1)	68.5 (54.6 – 79.8)	81.8 (7.06 – 89.4)

General comments

- Participants categorized according to whether or not cancer was likely to be hereditary
- Data reported for sub-groups
- The authors concluded that the poor performance of the model for Hispanics may be due to model misspecification in this racial/ethnic group. However it may also reflect racial/ ethnic differences in the distributions of personal and family histories among breast cancer cases in Northern Carolina

References of Included Studies (For systematic reviews): Not applicable

Citation: Lindor, N. M., et al. "Predicting BRCA1 and BRCA2 gene mutation carriers: comparison of PENN II model to previous study." Familial Cancer 9.4 (2010): 495-502.

Design: Retrospective Cohort Study
Country: USA
Aim: To establish the performance of

Inclusion criteria

- Individuals who underwent clinical genetic testing for mutations in BRCA1 and BRCA2 (criteria for eligibility were unclear)

Population
285 pro-bands seen for genetic risk assessment in a multidisciplinary tertiary care group practice between 1996 and 2005

Interventions
PENN II

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data presented to allow extraction of a 2x2 table

Model	Area under ROC curve (95% CI)
LAMBDA	0.73 (0.66 – 0.79)
BRCAPRO	0.76 (0.70 – 0.82)
Couch 1.5	0.72 (0.64 – 0.78)
Myriad II	0.71 (0.64 – 0.77)
Penn II	0.79 (0.72 – 0.84)

General comments

- Initial consultands from each family
- 27 individuals from Ashkenazi Jewish families
- 277/285 were female

References of Included Studies (For systematic reviews): Not applicable

Citation: Oros, K. K., et al. "Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent." Clinical Genetics 70.4 (2006): 320-29

Design: Retrospective cohort study
Country: Canada
Aim: To evaluate the accuracy of BRCAPRO, Couch, Myriad I and II, Ontario Family History Assessment Tool (FHAT), and Manchester models for their accuracy in classifying 224 French Canadian families for their accuracy in classifying 224 French Canadian families with at least three cases of breast cancer (diagnosed before the age of 65 years)

Inclusion criteria

- Family with at least three cases of female breast cancer diagnosed before the age of 65 years, epithelial ovarian cancer, or male breast cancer
- The index case was a first second or third degree relative of the affected individual. The family member most likely to harbour a BRCA1/2 mutation

Population
224 pro-bands from French Canadian families with at least three cases of breast cancer

Interventions
BRCAPRO, Couch, Myriad I and II, Ontario Family History Assessment Tool (FHAT), and Manchester

Outcomes
Observed and predicted carrier probabilities

Results
BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	86	68	154
< 10	10	60	70
Total	96	128	224

Sensitivity: 90%
Specificity: 47%
Positive predictive value: 56%
Negative predictive value: 86%

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 24	86	67	153
< 24	10	61	71
Total	96	128	224

Sensitivity: 90%
Specificity: 48%
Positive predictive value: 56%
Negative predictive value: 86%

Insufficient data was reported to deduce 2x2 tables for the remaining prediction models.

General comments

- At the recommended BRCAPRO cut-off of 10% for genetic testing, a sensitivity of 90% and specificity of 47% was achieved, where 86 of 96% of mutation positive families were correctly predicted to harbour a mutation in contrast to 61 of 128 mutation negative families
- The authors concluded that while all models were simultaneously efficient at predicting BRCA1/2 mutation status, the distribution of probability and predictive scores suggested that the BRCAPRO model fitted the series of French Canadian cancer families better based on comparison with known cancer status

References of Included Studies (For systematic reviews): Not applicable

DRAFT

Citation: Ottini, L., et al. "BRCA1 and BRCA2 mutation status and tumor characteristics in male breast cancer: a population-based study in Italy." Cancer Research 63.2 (2003): 342-47.

Design: Retrospective cohort study
Country: Italy
Aim: To investigate at the population level, the impact of BRCA1 / BRCA 2 alterations in male breast cancer

Inclusion criteria

- Male diagnosed with breast cancer, alive at the end of 1998
- Residing in the Florence area

Population
25 Italian men diagnosed with breast cancer before 1998

Interventions
BRCAPRO

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data was presented to allow extraction of a 2x2 table. AUROC was not reported. There was said to be good agreement between mutations predicted by BRCAPRO and observed mutations (14% vs. 16%)

General comments

- Very small study
- Included only men diagnosed with breast cancer
- The authors concluded that BRCAPRO showed an agreement between expected and observed mutations (14% versus 16%)

References of Included Studies (For systematic reviews): Not applicable

Citation: Panchal, S. M., et al. "Selecting a BRCA risk assessment model for use in a familial cancer clinic." BMC Medical Genetics 9 (2008): 116.

Design: Retrospective case control study
Country: Canada
Aim: To evaluate the performance of currently used risk models among patients from a large familial programme using the criteria of high sensitivity, simple data collection/entry and BRCA score reporting

Inclusion criteria

- Underwent genetic testing tested between 1995 and 2006

Population
200 non-BRCA mutation and 100 BRCA mutation carriers tested between 1995 and 2006

Interventions
BRCAPRO, Manchester, Penn II, Myriad II, FHAT, IBIS and BOADICEA

Outcomes
Sensitivity and specificity at conventional thresholds

Results
BRCPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	75	76	151
< 10	25	124	149
Total	100	200	300

Sensitivity: 75
Specificity: 62
Positive predictive value: 50
Negative predictive value: 83

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 15	58	58	116
< 15	42	142	184
Total	100	200	300

Sensitivity: 58
Specificity: 71
Positive predictive value: 50
Negative predictive value: 23

Penn II

	Mutation carrier	Non-mutation carrier	
≥ 10	93	138	231
< 10	7	62	69
Total	100	200	300

Sensitivity: 93
Specificity: 31
Positive predictive value: 40
Negative predictive value: 90

Myriad II

	Mutation carrier	Non-mutation carrier	
≥ 10	71	74	145
< 10	29	126	155
Total	100	200	300

Sensitivity: 71
Specificity: 63
Positive predictive value: 49
Negative predictive value: 81

FHAT

	Mutation carrier	Non-mutation carrier	
≥ 10	70	74	144
< 10	30	126	156
Total	100	200	300

Sensitivity: 70
Specificity: 63
Positive predictive value: 49
Negative predictive value: 81

IBIS

	Mutation carrier	Non-mutation carrier	
≥ 10	20	52	72
< 10	80	148	228
Total	100	200	300

Sensitivity: 20
Specificity: 74
Positive predictive value: 28
Negative predictive value: 65

BOADICEA

	Mutation carrier	Non-mutation carrier	
≥ 10	70	70	140
< 10	30	130	160
Total	100	200	300

Sensitivity: 70
Specificity: 65
Positive predictive value: 50
Negative predictive value: 81

General comments

- The authors concluded that the PEN II model closely met the criteria thought most important (high sensitivity, simple data collection/entry, and BRCA score reporting)

References of Included Studies (For systematic reviews): Not applicable

Citation: Parmigiani, G., et al. "Validity of models for predicting BRCA1 and BRCA2 mutations.[Summary for patients in Ann Intern Med. 2007 Oct 2;147(7):I38; PMID: 17909202]." Annals of Internal Medicine 147.7 (2007): 441-50.

Design: Cross sectional multicentre analysis
Country: USA
Aim: To systematically quantify the accuracy of the following publicly available tools to

Inclusion criteria

- Unclear (3 population based samples of participants in research studies and 8 samples from genetic counselling clinics)

Population
3324 families who underwent genetic testing

Interventions
BRCAPRO, Yale, Myriad, NCI, Penn, FHAT, Finnish

Outcomes

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	352	522	874
< 10	75	579	654
Total	427	1101	1528

Sensitivity: 82.4
Specificity: 52.6
Positive predictive value: 40.2
Negative predictive value: 88.5

Yale

	Mutation carrier	Non-mutation carrier	
≥ 10	273	469	742
< 10	154	632	786
Total	427	1101	1528

Sensitivity: 63.9
Specificity: 57.4
Positive predictive value: 36.7
Negative predictive value: 80.4

Myriad

	Mutation carrier	Non-mutation carrier	
≥ 10	331	574	905
< 10	96	527	623
Total	427	1101	1528

Sensitivity: 77.5
Specificity: 47.9
Positive predictive value: 36.6
Negative predictive value: 84.6

NCI

	Mutation carrier	Non-mutation carrier	
≥ 10	75	101	176
< 10	45	192	237
Total	120	293	413

Sensitivity: 62.5

Specificity: 65.5
Positive predictive value: 42.6
Negative predictive value: 81.0

FHAT

	Mutation carrier	Non-mutation carrier	
≥ 10	378	803	1181
< 10	49	298	347
Total	427	1101	1528

Sensitivity: 88.5
Specificity: 27.1
Positive predictive value: 32.0
Negative predictive value: 85.9

Finnish

	Mutation carrier	Non-mutation carrier	
≥ 10	284	358	642
< 10	106	673	779
Total	390	1031	1421

Sensitivity: 72.8
Specificity: 65.3
Positive predictive value: 44.2
Negative predictive value: 86.4

Results
Sensitivity, specificity and c-statistic of model predictions

General comments

- 3 population based samples of participants in research studies and 8 samples from genetic counselling clinics
- The authors concluded that the PEN II model closely met the criteria thought most important (high sensitivity, simple data collection/entry, and BRCA score reporting)

References of Included Studies (For systematic reviews): Not applicable

Citation: Rao, N. Y., et al. "Evaluating the performance of models for predicting the BRCA germline mutations in Han Chinese familial breast cancer patients." Breast Cancer Research & Treatment 116.3 (2009a): 563-70

Design: Retrospective cohort study
Country: China
Aim: To evaluate the risk assessment models Penn II, Myriad and BRCAPRO in a Chinese population

Inclusion criteria
Unclear (reported in an earlier study)

Exclusion criteria
Unclear (reported in an earlier study)

Population
212 Han Chinese women from families with more than three affected breast or ovarian cancer cases who had undergone BRCA1/2 mutation analysis

Interventions

- Penn II, Myriad and BRCAPRO

Outcomes

- Sensitivity, specificity, positive and negative predictive values, area under ROC curve for each risk model at the 10% risk threshold

Results

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 15	22	57	79
< 15	11	123	134
Total	33	180	213

Sensitivity: 67
Specificity: 68
Positive predictive value: 28
Negative predictive value: 92

MYRIADII

	Mutation carrier	Non-mutation carrier	
≥ 15	24	51	75
< 15	9	128	137
Total	33	179	212

Sensitivity: 73
Specificity: 72
Positive predictive value: 32
Negative predictive value: 93

	Proportion of carriers		**Test parameters at 10% threshold (95% CI)**			
	<10%	**≤10%**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
BRCA1						
BRCAPRO	5/148	10/64	0.67 (0.40-0.94)	0.84 (0.75-0.94)	0.27 (0.21-0.31)	0.97 (0.94-0.99)
Penn	13/201	2/11	0.13 (0.00-0.26)	0.82 (0.66-0.98)	0.05 (0.02-0.08)	0.94 (0.97-0.99)
Myriad I	9/185	6/27	0.40 (0.12-	0.78 (0.61-	0.11 (0.06-	0.95 (0.92-

			0.68)	0.95)	0.15)	0.98)
BRCA2						
BRCAPRO	12/156	6/56	0.26 (0.20-0.32)	0.40 (0.20-0.60)	0.33 (0.09-0.57)	0.92 (0.88-0.97)
Penn	15/207	3/5	0.01 (0.00-0.02)	0.89 (0.81-0.98)	0.17 (0.01-0.33)	0.92 (0.88-0.97)

Cut off 15% for combined BRCA1/2

General comments:

- A 10% risk threshold was used
- Affected individuals
- It was concluded that the three models had similar impact on the pre-test probability of BRCA mutation. BRCAPRO had the best BRCA mutation carrier prediction value at a 10% cut off point.

References of Included Studies (For systematic reviews): Not applicable

Citation: Rosati, S., et al. "Correlation Between Brcapro Risk Estimate and Incidence of Brca1-Brca2 Mutation in 178 Patients with Familial Breast and/or Ovarian Cancer from Central Italy." Annals of Oncology 15 (2004)

Design: Unclear
Country: Italy
Aim: To study the ability of BRCAPRO to identify patients at high risk of BRCA1 and BRCA2 mutations among individuals with familial breast cancer and ovarian cancer

Inclusion criteria

- Patients with breast cancer and at least one first degree relative with breast cancer
- Patients with ovarian cancer and at least one first degree relative with ovarian cancer
- Diagnosed with breast or ovarian cancer before age 40
- Male breast cancer
- Patients with breast and ovarian cancer

Population
162 Italian individuals with familial breast cancer

Interventions
BRCAPRO

Outcomes
Observed and predicted carrier probabilities

Results
Published as an abstract – contained insufficient data to allow extraction of a 2x2 table

General comments

- Presented as an abstract only – limited information provided

References of Included Studies (For systematic reviews): Not applicable

Citation: Roudgari, H., Z. H. Miedzybrodzka, and N. E. Haites. "Probability estimation models for prediction of BRCA1 and BRCA2 mutation carriers: COS compares favourably with other models." Familial Cancer 7.3 (2008): 199-212.

Design: Retrospective cohort study
Country: Scotland
Aim: To apply four probability estimation models to Scottish families tested for BRCA 1 / 2 mutations

Inclusion criteria

- Families with completed genetic testing for both BRCA1 and BRCA2 genes
- First degree relatives of an affected individual (or second degree via intervening male relative) in a family with four or more families affected with either breast or ovarian cancer OR one first degree relative (or second degree via intervening male relative) with both breast and ovarian cancer

Population
275 Scottish families with completed genetic testing for both BRCA 1 and 2 mutation

Interventions
MSS, T-C, COS, BOADICEA

Outcomes
Sensitivity, specificity and area under ROC curve

Results

Manchester

	Mutation carrier	Non-mutation carrier	
≥ 20	126	78	204
< 20	13	58	71
Total	139	136	275

Sensitivity: 91
Specificity: 43
Positive predictive value: 62
Negative predictive value: 82

Tyrer-Cuzick

	Mutation carrier	Non-mutation carrier	
≥ 20	86	34	120
< 20	53	102	155
Total	139	136	275

Sensitivity: 62
Specificity: 75
Positive predictive value: 72
Negative predictive value: 66

COS

	Mutation carrier	Non-mutation carrier	
≥ 20	128	78	206
< 20	11	58	69
Total	139	136	275

Sensitivity: 92
Specificity: 43
Positive predictive value: 62
Negative predictive value: 84

BOADICEA

	Mutation carrier	Non-mutation carrier	

≥ 20	74	30	104
< 20	65	106	171
Total	139	136	275

Sensitivity: 53
Specificity: 78
Positive predictive value: 71
Negative predictive value: 62

General comments

- Carrier probability was calculated for first family member tested
- Family history information was only complete for 17% of the combined dataset
- The authors concluded that the COS and MSS models demonstrated the greatest sensitivities and area under ROC curves for the majority of family structures

References of Included Studies (For systematic reviews): Not applicable

Citation: Simard, J., et al. "Evaluation of BRCA1 and BRCA2 mutation prevalence, risk prediction models and a multistep testing approach in French-Canadian families with high risk of breast and ovarian cancer.[Erratum appears in J Med Genet. 2007 Jul; 44 (7):471]." Journal of Medical Genetics 44.2 (2007): 107-21.

Design: Prospective cohort study
Country: Canada
Aim: To report the results of multistep genetic testing for mutations in BRCA1 or BRCA2 in a large series of families with breast cancer in the French Canadian population of Quebec

Inclusion criteria
Participants were required to meet one or more of the following criteria:

- Four first or second degree relatives diagnosed with breast and/or ovarian cancer at any age.
- Three first degree relatives diagnosed at any age
- Family known to carry a deleterious gene (these individuals excluded from model comparisons)
- Over 18 years of age
- Mentally competent

Population
191 high risk families ascertained from regional familial cancer clinics throughout the province of Quebec with at least one DNA sample tested

Interventions
Manchester, Myriad prevalence tables, a logistic regression technique based on the data from this study

Outcomes
Predictive power

Results
Manchester

	Mutation carrier	Non-mutation carrier	
≥ 18	48	24	72
< 18	8	111	119
Total	56	135	191

Sensitivity: 86%
Specificity: 82%
Positive predictive value: 67%
Negative predictive value: 93%

It was not possible to extract 2x2 tables for the performance of Myriad prevalence tables or the logistic regression based on the dataset

General comments

- Multi-step mutation testing was evaluated. Participants were first tested for the panel of known mutations at the time of entry into the study
- The authors concluded that in the study population, a testing strategy with an initial test using a panel of reported recurrent mutations, followed by full sequencing in families with Manchester scores ≥ 18 represents an efficient test in terms of overall cost and sensitivity

References of Included Studies (For systematic reviews): Not applicable

Citation: Teller, P., et al. "Validation of the pedigree assessment tool (PAT) in families with BRCA1 and BRCA2 mutations." Annals of Surgical Oncology 17.1 (2010): 240-46.

Design: Retrospective cohort study
Country: USA
Aim: To validate and compare PAT, Myriad II and Pen II.

Inclusion criteria

- Complete cancer information spanning at least 3 generations.
- Information on ethnic background of family
- At least one case of breast or ovarian cancer in the family
- BRCA1 or BRCA2 test results available on at least one individual in the family affected with breast or ovarian cancer

Exclusion criteria

- Multiple subjects representing the same family were excluded from the study so that each family was only represented once in the data set

Population
520 families with at least one case of breast or ovarian cancer

Interventions

- PAT, Myriad, Penn

Outcomes

- Sensitivity, specificity, positive and negative predictive values, area under ROC curve for each risk model at the 10% risk threshold

Results

PAT

	Mutation carrier	Non-mutation carrier	
≥ 10	139	299	438
< 10	7	75	82
Total	146	374	520

Sensitivity: 95%
Specificity: 20%
Positive predictive value: 32%
Negative predictive value: 92%

Myriad

	Mutation carrier	Non-mutation carrier	
≥ 10	124	227	351
< 10	22	147	169
Total	146	374	520

Sensitivity: 85%
Specificity: 39%
Positive predictive value: 35%
Negative predictive value: 87%

Penn

	Mutation carrier	Non-mutation carrier	
≥ 10	135	316	451
< 10	11	58	69

Total	146	374	520

Sensitivity: 92%
Specificity: 16%
Positive predictive value: 30%
Negative predictive value: 84%

No. mutations

	BRCA1 carriers		BRCA2 carriers		Non BRCA1/2 carriers		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No. of patients	93	18	53	10	374	72	520	100

Risk assessment

	Proportion of carriers		Test parameters at 10% (Myriad and Penn)/8 point (PAT) threshold (No CIs given)				
	<10%	**≤10%**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**C statistic**
Combined							
PAT	Not reported	Not reported	0.96 (0.92-0.98)	0.20 (0.19-0.21)	0.32 (0.31-0.33)	0.93 (0.85-0.97)	0.70
Myriad II	Not reported	Not reported	0.85 (0.79-0.96)	0.39 (0.37-0.41)	0.35 (0.33-0.37)	0.87 (0.82-0.91)	0.68
Penn II	Not reported	Not reported	0.92 (0.88-0.96)	0.16 (0.14-0.17)	0.31 (0.29-0.32)	0.84 (0.74-0.90)	0.71

General comments

- 10% risk threshold (Myriad and Penn) / 8 points (PAT)

References of Included Studies (For systematic reviews): Not applicable

Citation: Vogel, K. J., et al. "BRCA1 and BRCA2 genetic testing in Hispanic patients: Mutation prevalence and evaluation of the BRCAPRO risk assessment model." Journal of Clinical Oncology 25.29 (2007): 4635-41.

Design: Retrospective cohort study
Country: USA
Aim: To report the mutation frequency and spectrum of BRCA1 and BRCA2 mutations in a Hispanic population and evaluate the BRCAPRO model in Hispanics

Inclusion criteria

- Hispanic individuals who underwent genetic testing
- White controls who underwent genetic testing

Population
78 Hispanic patients who underwent genetic testing evaluated between February 1997 and July 2006 and 79 White controls

Interventions
BRCAPRO

Outcomes
Observed and predicted carrier probabilities

Results
Insufficient data presented to allow extraction of a 2x2 table

BRCAPRO

Participants	AUROC
Hispanic participants	0.774 (95% CI, 0.63 to 0.90)
White participants	0.770 (95% CI, 0.65 to 0.89)

General comments

- First family member to undergo testing included
- Hispanic participants compared with white controls
- Hispanic defined as of Latin American or Spanish descent
- White controls were randomly selected from 900
- Authors concluded that deleterious BRCA1 and BRCA2 mutations occur at considerable frequency within the Hispanic population, many of which have been identified previously in other ethnic populations. The BRCAPRO model appears to perform equally well in Hispanic as white individuals

References of Included Studies (For systematic reviews): Not applicable

Citation: Zanna, I., et al. "The BRCAPRO 5.0 model is a useful tool in genetic counseling and clinical management of male breast cancer cases." European Journal of Human Genetics 18.7 (2010): 856-58.

Design: Prospective cohort study
Country: Italy
Aim: To evaluate the performance of BRCA1/2 mutation prediction models in male breast cancer

Inclusion criteria

- Male breast cancer diagnosed between 1991-2007
- Resident in Eastern Tuscany

Population
102 Italian male breast cancer sufferers recruited between 1991 - 2007

Interventions
IC model, BRCAPRO, Myriad

Outcomes
Sensitivity, specificity and positive and negative predictive values at the 10% threshold

Results

IC model

	Mutation carrier	Non-mutation carrier	
≥ 10	10	79	89
< 10	0	13	13
Total	10	92	102

Sensitivity: 100%
Specificity: 14%
Positive predictive value: 11%
Negative predictive value: 100%

BRCAPRO

	Mutation carrier	Non-mutation carrier	
≥ 10	8	20	28
< 10	2	71	73
Total	10	92	102

Sensitivity: 80%
Specificity: 77%
Positive predictive value: 29%
Negative predictive value: 97%

MYRIAD

	Mutation carrier	Non-mutation carrier	
≥ 10	10	92	102
< 10	0	0	0
Total	10	92	102

Sensitivity: 100%
Specificity: %
Positive predictive value:
Negative predictive value:

General comments

- Male breast cancer sufferers

- Overall 38% reported a first and/or second degree relative with a breast/ovarian family history
- The authors concluded that BRCAPRO 5.0 together with an experienced clinical evaluation is a useful tool in selecting cases of male breast cancer for mutation analysis

References of Included Studies (For systematic reviews): Not applicable

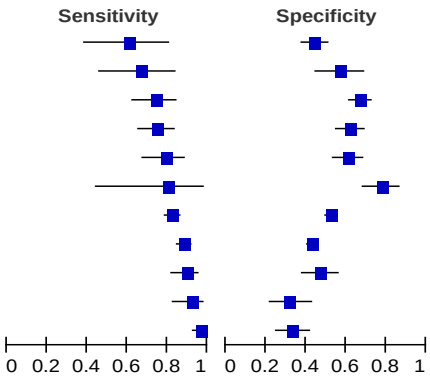
1.3.11 Appendix: sensitivities and specificities of carrier prediction models

BRCAPRO

The BRCAPRO risk assessment model has received more attention in the literature than any other. Fifteen studies evaluated the diagnostic accuracy of BRCAPRO. Ten studies used a cut-off of 10% (Evans et al. 2004; Capalbo et al. 2006a; Barcenas et al. 2006; Panchal et al. 2008; James et al 2006; Parmigiani et al 2007; Antinou et al . 2008; Oros et al. 2006; Euhus et al. 2002; Berry et al. 2002; Zanna et al. (2010)). At the 10% threshold, studies reported highly variable sensitivities, which ranged from 61% to 96%. Specificities were also varied, ranging from 32% to 78%. It is unclear why this was the case. At a cut-off threshold of 15%, sensitivities of 67% and 77%, and specificities of 54% and 68% were reported by Rao et al (2009a) and Kang et al (2006) respectively. One study used a threshold of 25% (Antinou et al (2006)), reporting a sensitivity of 70% and a specificity of 64%. Given the variability between studies, it is difficult to compare the performance of BRCAPRO to that of other models. Due to a paucity of studies evaluating the model at thresholds other than 10%, it is also impossible to ascertain with any confidence, the threshold at which BRCAPRO operates best.

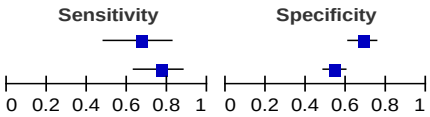
BRCAPRO ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Evans et al 2004	14	131	9	104	0.61 [0.39, 0.80]	0.44 [0.38, 0.51]
Capalbo et al 2006a	18	31	9	41	0.67 [0.46, 0.83]	0.57 [0.45, 0.69]
Barcenas et al 2006	52	101	18	205	0.74 [0.62, 0.84]	0.67 [0.61, 0.72]
Panchal et al 2008	75	76	25	124	0.75 [0.65, 0.83]	0.62 [0.55, 0.69]
James et al 2006	53	70	14	109	0.79 [0.67, 0.88]	0.61 [0.53, 0.68]
Zanna et al 2010	8	20	2	71	0.80 [0.44, 0.97]	0.78 [0.68, 0.86]
Parmigiani et al 2007	352	522	75	579	0.82 [0.78, 0.86]	0.53 [0.50, 0.56]
Antoniou et al 2008	322	893	43	676	0.88 [0.84, 0.91]	0.43 [0.41, 0.46]
Oros et al 2006	86	68	10	60	0.90 [0.82, 0.95]	0.47 [0.38, 0.56]
Euhus et al 2002	58	58	5	27	0.92 [0.82, 0.97]	0.32 [0.22, 0.43]
Berry et al 2002	162	89	6	44	0.96 [0.92, 0.99]	0.33 [0.25, 0.42]



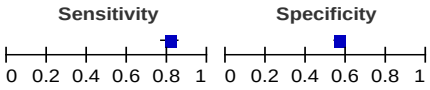
BRCAPRO ≥ 15

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rao et al 2009a	22	57	11	123	0.67 [0.48, 0.82]	0.68 [0.61, 0.75]
Kang et al 2006	40	150	12	178	0.77 [0.63, 0.87]	0.54 [0.49, 0.60]



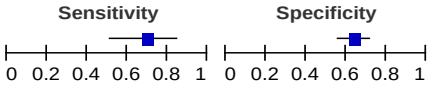
BRCAPRO ≥ 20

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2008	296	680	69	889	0.81 [0.77, 0.85]	0.57 [0.54, 0.59]



BRCAPRO ≥ 25

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2006	23	56	10	99	0.70 [0.51, 0.84]	0.64 [0.56, 0.71]

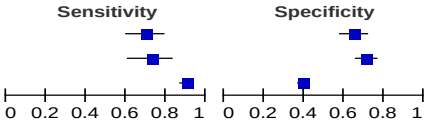


BOADICEA

BOADICEA was evaluated at cut-off points of 10, 16, and 20. As with BRCAPRO, there was considerable variability in terms of reported sensitivities and specificities at each threshold. Panchal et al (2008), Barcenas et al (2006), and Antoniou et al. (2006) evaluated the diagnostic accuracy of BOADICEA at a threshold of 10%, reporting sensitivities of 70% - 90%, and specificities of 40% - 71%. At a threshold of 16%, Antionu et al. (2006) reported a sensitivity of 82% and a specificity of 69%. Using a cut-off of 20%, Roudgari et al. (2008) and Antoniou et al. (2008) reported sensitivities of 53% and 81%, and specificities of 59% and 78%, respectively.

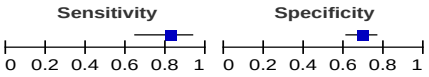
BOADICEA ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Panchal et al 2008	70	70	30	130	0.70 [0.60, 0.79]	0.65 [0.58, 0.72]
Barcenas et al 2006	51	88	19	218	0.73 [0.61, 0.83]	0.71 [0.66, 0.76]
Antoniou et al 2008	330	949	35	620	0.90 [0.87, 0.93]	0.40 [0.37, 0.42]



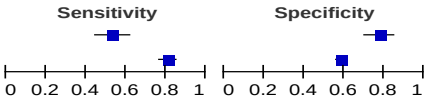
BOADICEA ≥ 16

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2006	27	48	6	107	0.82 [0.65, 0.93]	0.69 [0.61, 0.76]



BOADICEA ≥ 20

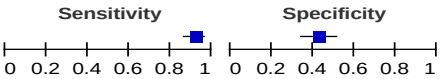
Study	TP	FP	FN	TN	Sensitivity	Specificity
Roudgari et al 2008	74	30	65	106	0.53 [0.45, 0.62]	0.78 [0.70, 0.85]
Antoniou et al 2008	295	651	70	918	0.81 [0.76, 0.85]	0.59 [0.56, 0.61]



COS

One study evaluated the diagnostic accuracy of the COS risk assessment model. At a cut-off threshold of 20%, Roudgari et al. (2008) reported a relatively high sensitivity of 92%, but a fairly low specificity of 43%.

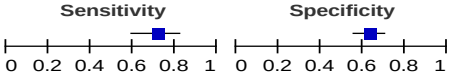
Study	TP	FP	FN	TN	Sensitivity	Specificity
Roudgari et al 2008	128	78	11	58	0.92 [0.86, 0.96]	0.43 [0.34, 0.51]



Couch

One study evaluated the diagnostic accuracy of the Couch risk assessment model. At a cut-off threshold of 20%, James et al. (2006) reported a sensitivity of 72%, and a specificity of 63%.

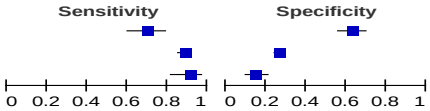
Study	TP	FP	FN	TN	Sensitivity	Specificity
James et al 2006	48	66	19	113	0.72 [0.59, 0.82]	0.63 [0.56, 0.70]



FHAT

Three studies evaluated the diagnostic accuracy of the FHAT risk assessment model. Panchal et al (2008), Parmigiani et al (2007), and James et al (2006), reported that the model performed well in terms of sensitivity (giving values of 70%, 89%, and 91% respectively), but poorly in terms of specificity (63%, 27%, and 15% respectively). Specificities were particularly low in the studies that reported a high sensitivity.

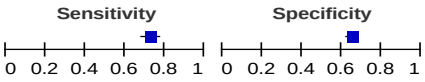
Study	TP	FP	FN	TN	Sensitivity	Specificity
Panchal et al 2008	70	74	30	126	0.70 [0.60, 0.79]	0.63 [0.56, 0.70]
Parmigiani et al 2007	378	803	49	298	0.89 [0.85, 0.91]	0.27 [0.24, 0.30]
James et al 2006	61	152	6	27	0.91 [0.82, 0.97]	0.15 [0.10, 0.21]



Finnish

One study evaluated the diagnostic accuracy of the Finnish risk assessment model. At a cut-off threshold of 10%, Parmigiani et al. (2007) reported a sensitivity of 73%, and a specificity of 65%.

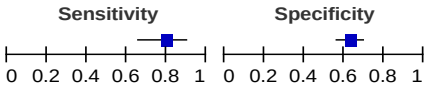
Study	TP	FP	FN	TN	Sensitivity	Specificity
Parmigiani et al 2007	284	358	106	673	0.73 [0.68, 0.77]	0.65 [0.62, 0.68]



Gilpin

One study evaluated the diagnostic accuracy of the Gilpin risk assessment model. At a cut-off threshold of 16%, Bodmer et al. (2006) reported a sensitivity of 80%, and a specificity of 63%.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bodmer et al 2006	39	79	10	135	0.80 [0.66, 0.90]	0.63 [0.56, 0.70]

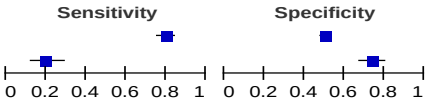


IBIS (Tyrer-Cuzick)

Three studies evaluated the diagnostic accuracy of the IBIS risk assessment model. At a cut-off threshold of 10%, Antoniou et al. (2008) and Panchal et al. (2008) vastly different sensitivities of 80% and 20% respectively. The specificities were 51% and 74% respectively. Outcomes reported by Antoniou et al (2008) at a cut-off threshold of 20% gave a marginally lower sensitivity than reported by the same study at the 10% threshold (68%), and a somewhat higher specificity (66%).

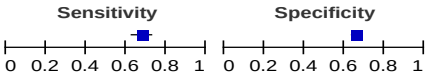
IBIS ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2008	285	757	72	775	0.80 [0.75, 0.84]	0.51 [0.48, 0.53]
Panchal et al 2008	20	52	80	148	0.20 [0.13, 0.29]	0.74 [0.67, 0.80]



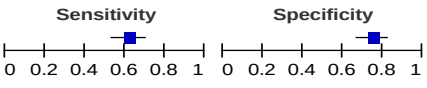
IBIS ≥ 20

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2008	242	519	115	1013	0.68 [0.63, 0.73]	0.66 [0.64, 0.68]



Roudgari et al. (2008) evaluated the Tyrer-Cuzick model at a cut-off of 20%, reporting a relatively low sensitivity of 62%, and a specificity of 75%.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Roudgari et al 2008	86	34	53	102	0.62 [0.53, 0.70]	0.75 [0.67, 0.82]

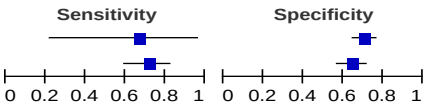


Manchester

The Manchester scoring system was evaluated at cut-off points of 10, 15, 17, 18, 20 and 24. At a cut off of 10, Evans et al. (2004) and James et al. (2006) reported sensitivities of 72% and 67%, and specificities of 71% and 64%, respectively. At a cut off of 15, Panchal et al. (2008) and Kang et al. (2006), and Antoniou et al. (2008) reported sensitivities of 58% - 92%, and specificities of 33% - 71%. Antoniou et al. (2008) reported a sensitivity of 87% and specificity of 43%. At a cut off of 18, Simard et al. (2007) reported a sensitivity of 86% and specificity of 82%. At a cut off of 20, Roudgari et al (2008) reported a sensitivity of 91% and specificity of 43%. At the highest threshold of 24, Oros et al. (2006) reported a sensitivity of 90% and specificity of 48%.

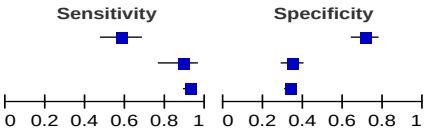
Manchester ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Evans et al 2004	4	74	2	178	0.67 [0.22, 0.96]	0.71 [0.65, 0.76]
James et al 2006	48	64	19	115	0.72 [0.59, 0.82]	0.64 [0.57, 0.71]



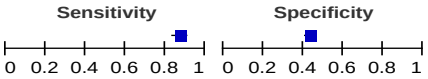
Manchester ≥ 15

Study	TP	FP	FN	TN	Sensitivity	Specificity
Panchal et al 2008	58	58	42	142	0.58 [0.48, 0.68]	0.71 [0.64, 0.77]
Kang et al 2006	46	215	6	113	0.88 [0.77, 0.96]	0.34 [0.29, 0.40]
Antoniou et al 2008	337	1045	28	524	0.92 [0.89, 0.95]	0.33 [0.31, 0.36]



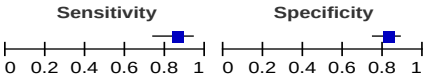
Manchester ≥ 17

Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2008	318	888	47	681	0.87 [0.83, 0.90]	0.43 [0.41, 0.46]



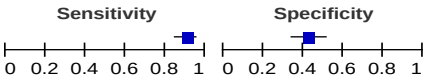
Manchester ≥ 18

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simard et al 2007	48	24	8	111	0.86 [0.74, 0.94]	0.82 [0.75, 0.88]



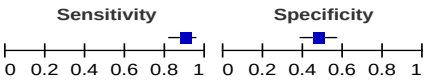
Manchester ≥ 20

Study	TP	FP	FN	TN	Sensitivity	Specificity
Roudgari et al 2008	126	78	13	58	0.91 [0.85, 0.95]	0.43 [0.34, 0.51]



Manchester ≥ 24

Study	TP	FP	FN	TN	Sensitivity	Specificity
Oros et al 2006	86	67	10	61	0.90 [0.82, 0.95]	0.48 [0.39, 0.57]

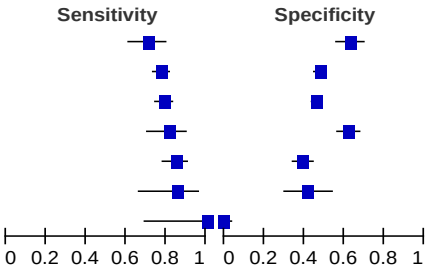


Myriad / Frank

The Myriad carrier probability assessment tool was evaluated at cut-off points of 10, 15, and 20. There was considerable variability in terms of reported sensitivities and specificities at each threshold. Panchal et al. (2008), Barcenas et al. (2006), Parmigiani et al. (2007), Antoniou et al. (2008), Teller et al. (2010), Capalbo et al (2006a), and Zanna et al. (2010) evaluated the diagnostic accuracy of Myriad at a threshold of 10%, reporting sensitivities of 71% - 100%, and specificities of 42% - 63%. Using a cut-off of 20%, Rao et al. (2008) and Kang et al. (2006) reported sensitivities of 73% and 85%, and specificities of 72% and 51%, respectively. At a threshold of 20%, Antoniou et al. (2008) reported a sensitivity of 51% and a specificity of 80%.

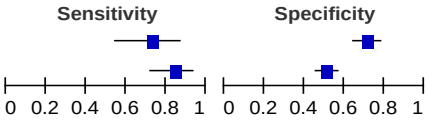
Myriad ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Panchal et al 2008	71	74	29	126	0.71 [0.61, 0.80]	0.63 [0.56, 0.70]
Parmigiani et al 2007	331	574	96	527	0.78 [0.73, 0.81]	0.48 [0.45, 0.51]
Antoniou et al 2008	288	843	77	726	0.79 [0.74, 0.83]	0.46 [0.44, 0.49]
Barcenas et al 2006	57	116	13	190	0.81 [0.70, 0.90]	0.62 [0.56, 0.68]
Teller et al 2010	124	227	22	147	0.85 [0.78, 0.90]	0.39 [0.34, 0.44]
Capalbo et al 2006a	23	42	4	30	0.85 [0.66, 0.96]	0.42 [0.30, 0.54]
Zanna et al 2010	10	92	0	0	1.00 [0.69, 1.00]	0.00 [0.00, 0.04]



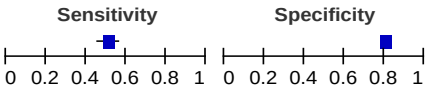
Myriad ≥ 15

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rao et al 2009a	24	51	9	128	0.73 [0.54, 0.87]	0.72 [0.64, 0.78]
Kang et al 2006	44	160	8	168	0.85 [0.72, 0.93]	0.51 [0.46, 0.57]



Myriad ≥ 20

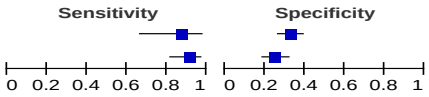
Study	TP	FP	FN	TN	Sensitivity	Specificity
Antoniou et al 2008	186	306	179	1263	0.51 [0.46, 0.56]	0.80 [0.78, 0.82]



Three studies evaluated the diagnostic accuracy of the Frank risk assessment model. At a cut-off threshold of 10%, Evans et al. (2004) and James et al. (2006) reported high sensitivities of 87% and 91% respectively. The specificities reported by these studies were correspondingly very low (33% and 25% respectively). Outcomes reported by Bodmer et al (2006) at a cut-off threshold of 16% gave a marginally lower sensitivity (84%), and a somewhat higher specificity (49%).

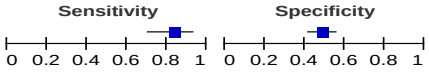
Frank ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Evans et al 2004	20	154	3	75	0.87 [0.66, 0.97]	0.33 [0.27, 0.39]
James et al 2006	61	134	6	45	0.91 [0.82, 0.97]	0.25 [0.19, 0.32]



Frank ≥ 16

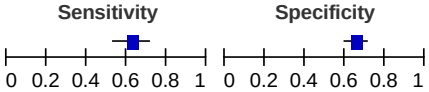
Study	TP	FP	FN	TN	Sensitivity	Specificity
Bodmer et al 2006	41	110	8	104	0.84 [0.70, 0.93]	0.49 [0.42, 0.56]



NCI

One study evaluated the diagnostic accuracy of the NCI risk assessment model. At a cut-off threshold of 20%, Parmigiani et al. (2007) reported a sensitivity of 63%, and a specificity of 66%.

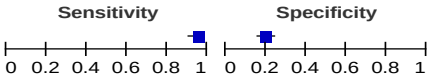
Study	TP	FP	FN	TN	Sensitivity	Specificity
Parmigiani et al 2007	75	101	45	192	0.63 [0.53, 0.71]	0.66 [0.60, 0.71]



PAT

Teller et al. (2010) evaluated the PATrisk assessment model at a cut-off of 10%, reporting a high sensitivity of 95%, and a low specificity of 20%.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Teller et al 2010	139	299	7	75	0.95 [0.90, 0.98]	0.20 [0.16, 0.24]

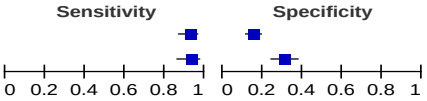


Penn

Teller et al (2010) and Panchal et al (2008) evaluated the diagnostic accuracy of the Penn risk assessment model at a threshold of 10%, reporting high sensitivities of 92% and 93%, but very low specificities of 16% and 31% respectively. At a threshold of 15%, Kang et al. (2006) reported a sensitivity of 69% and a specificity of 67%.

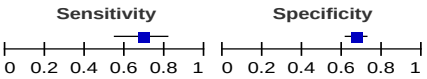
Penn II ≥ 10

Study	TP	FP	FN	TN	Sensitivity	Specificity
Teller et al 2010	135	316	11	58	0.92 [0.87, 0.96]	0.16 [0.12, 0.20]
Panchal et al 2008	93	138	7	62	0.93 [0.86, 0.97]	0.31 [0.25, 0.38]



Penn ≥ 15

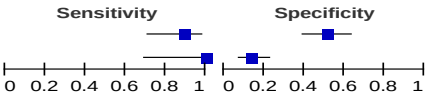
Study	TP	FP	FN	TN	Sensitivity	Specificity
Kang et al 2006	36	106	16	216	0.69 [0.55, 0.81]	0.67 [0.62, 0.72]



IC

Capalbo et al. (2006) and Zanna et al. (2010) evaluated the IC model at a cut-off of 10%, reporting high sensitivities of 89% and 100%, and specificities of 51% and 14%, respectively.

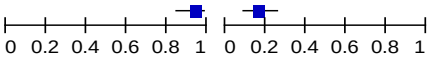
Study	TP	FP	FN	TN	Sensitivity	Specificity
Capalbo et al 2006a	24	35	3	37	0.89 [0.71, 0.98]	0.51 [0.39, 0.63]
Zanna et al 2010	10	79	0	13	1.00 [0.69, 1.00]	0.14 [0.08, 0.23]



Risk counselor

Euhus et al. (2002) evaluated the disgnostic accurarcy of a Risk Counsellor, reporting a relatively high sensitivity of 94%, but a very low specificity of 16%.

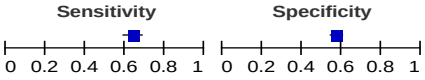
Study	TP	FP	FN	TN	Sensitivity	Specificity
Euhus et al 2002	59	71	4	14	0.94 [0.85, 0.98]	0.16 [0.09, 0.26]



Yale

Parmigiani et al. (2007) evaluated the Yale model at a cut-off of 10%, reporting a relatively low sensitivity of 64%, and a specificity of 57%.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Parmigiani et al 2007	273	469	154	632	0.64 [0.59, 0.68]	0.57 [0.54, 0.60]



1.4 Communicating Cancer Risks and Carrier Probabilities

1.4.1 Evidence statements

- There is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood. (IV)
- Risk communication improves the accuracy of the woman's perceived risk. (IV)
- Qualitative studies have indicated that in women who attended genetics clinics, many found personal risk information useful. (IV)
- There is some evidence that numerical risk values are preferred over risk categories. (IV)
- The use of a written summary of the consultation reinforces risks information and enhances recall. (IV)

1.4.2 Summary of evidence relating to breast cancer risk communication for women with a family history of breast cancer

Evidence relating to the communication of breast cancer risk in women with a family history of breast cancer is limited, relates to mainly qualitative research studies and has addressed various aspects concerning how cancer risk is communicated in this population of women.
Two studies have evaluated different risk information formats (Hallowell et al, 1997a,b; Schapira et al, 2001), and 7 further studies have investigated women's recall of risk information and whether written summaries have aided this, and the observed problems which clinicians encounter in translating scientific knowledge into their clinical management at a hereditary cancer clinic (Hallowell et al, 1997a,b; Hallowell et al, 1998; Sachs et al, 2001, Cull et al 1999, Evans et al 1994, Hopwood et al 1998, Watson et al 1999). A literature review of studies which have assessed the process of risk communication for familial cancer has concluded that there is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood.

1.4.3 Studies

Sachs et al (2001)
In a Swedish qualitative study, participant observation in 45 consultation sessions between clinicians and potential patients was conducted at a hereditary cancer clinic to explore the communication of genetic information. A main theme of the sessions was the numerical discussion of risk. Problems for clinicians are described in terms of the process of translating scientific knowledge into clinical management. Problems in providing information include unclear aims of the consultations; mixing types of background information and probabilities; recognising how low predictive values are; and difficulties in communicating the relationship between probability and conclusions Problems in communication about genetic risk of cancer relate to dilemmas arising from the uncertainty of the nature of the information itself, and in communicating information in a format that can be interpreted by patients.

Schapira et al (2001)

A US qualitative study used 4 focus groups involving a total of 41 women aged between 40-65 years to evaluate responses to various formats used in the communication of breast cancer risk. Frequency and probability formats with and without the use of graphic displays were explored; these formats are both based on the likelihood of an event being assigned a value of between 0 and 1. Results found that graphic discrete frequency formats using highlighted human figures were preferable compared to continuous probability formats using bar graphs, in that identical numerical risks were perceived as less when presented with bar graphs compared to highlighted human figures. The authors conclude that risk formats should be chosen to optimise patients' understanding and ability to use the information effectively, rather than for the purposes of persuasion.

Bottorff et al (1998)

The key findings of 75 published papers, research reports (including case studies) and clinical protocols relating to the communication of risk for familial cancer are presented in this review. On review of the evidence, the authors found that there was no clear evidence about how to sensitively and effectively communicate cancer risk information to individuals and families at risk for familial cancer, as well as those who are not, or about how to ensure that the probabilistic nature of risk estimates is accurately communicated and understood. There is also uncertainty about how to communicate the error-proneness of genetic tests; and strategies currently used to communicate cancer risk have not been adequately evaluated. The authors conclude that risk communication strategies need to be developed and tested to meet the information needs of the general public.

Hallowell et al (1998)

To investigate women's perceptions and use of written summaries of genetic consultations, 40 UK women (mean age 40 years, range 22-59) with family histories of breast and/or ovarian cancer took part in face-to-face interviews. The majority of women regarded a written summary of their genetic counselling session as valuable, with 92% saying that it facilitated their recall and/or understanding of the information provided in the consultation. Eight-five percent of women said that they had used, or intended to use, the summary to facilitate the communication of genetic information to their relatives. The authors note, however, that the summaries may lead women to perceive themselves as 'bearers of bad news', may have implications for medical confidentiality, or may generate an inappropriate demand for genetic counselling.

Hallowell et al (1997a & b)

In this UK study, the presentation of probabilistic information used during genetic consultations at a cancer family history clinic is described, and women's attitudes about, and preferences for, different types of breast cancer risk information formats are explored. The 46 women (mean age of 40 years; range 22-59, SD=8.8) reported a total of 132 female relatives affected by breast or ovarian cancer (mean 2.9, range 1-8) and a further 77 male and female relatives affected by other cancers. Clinic counsellors used a wide variety of qualitative and quantitative formats to describe women's risk of inheriting a genetic mutation or developing cancer; quantitative formats used were proportions, percentages, ratios, odds against and as comparisons with population risks. Results showed that women were positive about the way their cancer risk had been described. 73% preferred risks to be described using quantitative formats, with little difference in preference between percentages, proportions or population comparisons. In over 40% of cases, risk information was not presented in the women's preferred quantitative format during the consultation.

This UK study used questionnaires and interviews to evaluate women's recall of numerical risk information following genetic counselling for breast and/or ovarian cancer. Forty-six women took part in the study with a mean age of 40 years (range 22-59, SD=8.8). Results found that many of the women had difficulty in recalling the probabilities used to describe their risk of developing cancer and that recall failure increased with time. Recall accuracy was incorrect in 17/32 women (53%) and

6/32 (19%) had no recall at 6 weeks post-genetic counselling; at 12 months post- counselling, 11/25 women (44%) had incorrect recall and 11/25 (44%) had no recall. The authors suggest that women who failed to recall risk information may not have memorised their risk estimate because they had received written confirmation of their risk; or recall failure may be due to women regarding a numerical risk estimate as less important than having their pre-counselling risk perceptions confirmed or refuted.

1.4.4 Evidence Tables

Table 1.8: Evidence relating to breast cancer risk communication for women with a family history of breast cancer

Study	Design	Aim(s)	Population	Results
Hallowell et al (1997)	Qualitative study (interviews)/survey	To describe the presentation of cancer risk information used during genetic consultations; to explore women's attitudes and	46 UK women (mean age 40; range 22-59 years, SD=8.8). Women had 132 female relatives with breast/ovarian cancer (mean 2.9,	Clinic counsellors used wide range of qualitative/quantitative formats for communication women's cancer risks. Quantitative formats were: proportions, percentages, ratios, odds against, as comparisons with population risks. Overall, women were positive about how cancer risks had been described at the clinic. 73% preferred risks described using
Hallowell et al (1997)	Qualitative study (interviews)/survey	To evaluate women's recall of numerical risk information following genetic counselling for breast and/or ovarian cancer.	46 UK women (mean age 40; range 22-59 years, SD=8.8). 39% of women had family history of breast cancer, 35% of ovarian cancer, 22% of breast and ovarian, and 4%	Many women had difficulty recalling risk information they had received at genetic counselling; this recall failure increased with time. At 6 weeks post- counselling, recall accuracy was incorrect in 17/32 women (53%) and 6/32 women (19%) had no recall. At 12 months post-counselling, 11/25 women (44%) had incorrect recall and 11/25 (44%) had no recall. Conclusion: difficulties with recall may be due
Bottorff et al (1998)	Literature review	To review the literature relating to risk communication for familial cancer	75 published papers, research reports (including case studies) and clinical protocols	Evidence was assessed in terms of: the context of providing cancer risk information; how risk information is communicated; communicating risk when it is error prone; sequelae of communicating risk information. No clear evidence on how to sensitively and effectively communicate cancer risk information, and to ensure that risk estimates are
Hallowell et al (1998)	Qualitative study (interviews)	To investigate women's perceptions and use of written summaries of genetic consultations	40 UK women (mean age 40, range 22-59) with family histories of breast and/or ovarian cancer (123 relatives with	Most women found the written summary of their genetic counselling session to be valuable; 92% felt it facilitated their recall and/or understanding of the information provided in the consultation. 85% said they had used/intended to use the summary to facilitate risk communication to relatives.

Study	Design	Aim(s)	Population	Results
Sachs et al (2001	Qualitative study (participant observation)	To explore how genetic information is communicated at a hereditary cancer clinic	45 consultation sessions between clinicians and potential patients	Main theme was numerical discussion of risk. Problems for clinicians in terms of translating scientific knowledge into clinical management. Problems in providing information: unclear aims of consultations; mixing types of background information/probabilities; recognising how low predictive values are; difficulties in communicating link between
Schapira et al (2001)	Qualitative study (4 focus groups)	To evaluate responses to various formats used in the communication of breast cancer risk	Convenience sample from 2 local communities of 41 US women aged 40-65 years; 83% white, 12% black,	Frequency and probability formats with/without the use of graphic displays were explored. Results found that graphic discrete frequency formats using highlighted human figures were preferred to continuous probability formats using bar graphs: identical numerical risks were perceived as less when presented with bar graphs compared to highlighted human

1.5 References (2004)

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2 Information and Support

2.1 Patient Information and Support

The recommendations for this chapter are based on the consensus of the guideline development group, and reflect good clinical professional practice.

3 Care of People in Primary Care

3.1 Care and Management of Approach in Primary care

Several studies have reported on a wide range of issues relating to the management of women with a family history of breast cancer in primary care. These are described in detail in other relevant sections of the document (see family history taking, patient education and information). The evidence from these has informed the recommendations in this section.

The number of primary care consultations where family history of breast cancer is raised by women is relatively infrequent. A recent study reported that it may be of the order of 5/1000 consultations, which averages out at about 0.6 per clinician per month (Women's Concerns Study Group 2001). The same study illustrated that if list size and consultation rates were taken into account then an extrapolation of data might mean that for each 1000 women (aged 16 years or over) on a practice list, about 15 per year will raise the issue of family history of breast cancer. They also point out that about 10 times that number will consult for contraceptive advice and three times that number will consult for menstrual disorders. They also found that clinicians were 6.6 times more likely to raise the issue of family history of breast cancer than patients.
The provision of more genetics services, including risk assessment, in primary care to allow more appropriate referrals and use of specialist services is an important issue in the management of women with a family history of breast cancer. However studies have shown that many GPs lack required knowledge and confidence to take on this work. Studies have also shown however that the provision of educational materials to GPs can significantly improve referral decisions for patients with a family history of breast cancer and improve confidence (Watson et al 2001, Watson et al 2002).

3.2 Patient Education and Information

3.2.1 Summary of evidence relating to patient information in a primary care setting for women with a family history of breast cancer

Evidence from two qualitative studies and one survey has shown that women with a family history of breast cancer have unmet needs for information, support and reassurance either in the primary care setting (Chalmers et al, 1996; Grande et al, 2002), or whilst awaiting specialist genetics consultations having been referred by their GP (Andermann et al, 2001). The GP's role in providing information and reassurance was seen to be extremely important for these women, particularly for those who are not referred to secondary care, as the GP may be their only source of information and advice.

A further study which developed and evaluated a research-based leaflet for women with a family history of cancer for use in a primary care setting found that it was effective in meeting women's information (Andermann et al, 2002).

3.2.2 Studies

Andermann et al (2002)

In this UK study, an evidence-based information leaflet was developed after assessing the information needs of women with a family history of breast cancer, and was subsequently evaluated in a primary care setting. Information leaflets and questionnaires were sent to 190 women referred to a family cancer clinic for breast/ovarian cancer. One hundred and forty-four women returned the

questionnaire (response rate of 76%); women had a mean age of 42 years (SD=8.8), were mostly white (98%) and well educated, with 83% having a mother or sister diagnosed with breast cancer. Results showed that over 90% of women felt that the leaflet was easy to read and understand, was written in a caring way and was comprehensive. 80% felt that the leaflet was relevant and between 60-70% agreed that it helped them talk to doctors and to family members and was reassuring. Some women, however, felt that the leaflet should not be a substitute for talking to a health care professional.

Grande et al (2002)
In a UK qualitative study, women's views of GP consultations about family history of breast cancer were investigated using 72 telephone interviews and a further 20 face-to-face interviews with a subsample of 20 women. Participants were women from 18 GP practices (mean age 49 years; range 34-76 years) who had experienced a primary care consultation in which breast cancer family history was mentioned, as reported by the clinician. Results found that family history of breast cancer was rarely the main focus of consultations. Women's understanding of familial risk and disease was often lacking and they expressed a need for clarification, explanation and information. The authors' conclude that the GP's main role in relation to family history and cancer risk is to provide appropriate reassurance for the majority of patients not at increased risk.

Andermann et al (2001)
A survey of 128 UK women with a family history of breast cancer (mean age 38 years; SD=10.0) referred by their GP to secondary care (genetics or breast clinic) was carried out to explore women's views, expectations and experiences of the process. 90% of women wanted their GP to provide them with information and 87% wanted their GP to discuss their risks of developing breast cancer, and for most women these needs had not been met. Women often had unrealistic expectations of what they might expect from a secondary care referral, particularly in terms of genetic testing. 11% of women had returned to their GP within 1 month of attending the secondary care appointment to discuss family history and what had happened at the specialist clinic. Study results indicate that women want information and want to discuss their family history concerns in a primary care setting. Information provision in primary care is even more important for women who are not referred, as this may be their only source of information and advice.

Chalmers et al (1996)
The role of information, support and communication needs was evaluated in this Canadian qualitative study involving 55 at-risk women with at least one first-degree relative with breast cancer. Results showed that information, support and communication were important factors in enabling women to adjust to their personal risk of breast cancer, articulated as a 3-phase process: 'living the breast cancer experience' through the relative's experience; developing a risk perception; and 'putting risk in its place'. However, despite the importance of information and support, most women were dissatisfied with the amount and type of information they received and felt isolated and unsupported, and communication both within the family and with health care professionals was poor. The authors conclude that women's needs could be more effectively addressed by measures that identify at-risk women, assess their specific needs, and provide them with support and accurate, individualised information.

3.2.3 Evidence Tables

Table 3.1: Evidence relating to patient information in a primary care setting for women with a family history of breast cancer

Study	Design	Aim(s)	Population	Results
Chalmers et al (1996)	Qualitative study	To evaluate the role of information, support and communication in women with a family history of breast cancer	Community-based sample of 55 at- risk Canadian women with at least one 1st-degree relative with breast cancer. Women mostly well educated, middle-class; all were white.	Information, support and communication were important factors in helping women to adjust to their personal risk of breast cancer. This adjustment process articulated as 3-phase process: 'living the breast cancer experience' through the affected relative's experience; developing a risk perception; and 'putting risk in its place'. However, women were dissatisfied
Andermann et al (2001)	Survey	To explore women's views, expectations and experiences of the process of referral from primary to secondary care (genetics or breast clinic)	193 UK women with a family history of breast cancer referred by GP to secondary care, awaiting specialist appointment. Response rate was 69%. 128/193 women (mean age	90% of women wanted GP to provide them with information and 87% wanted GP to discuss their breast cancer risks: for most women these needs had not been met. Some women had unrealistic expectations of their secondary care referral, particularly in terms of genetic testing. Within 1 month of attending the secondary care appointment, 11% of women had returned to their GP to discuss family history/their
Andermann et al (2002)	Qualitative study/survey	To develop and evaluate an evidence-based information leaflet for women with a family history of breast cancer for use in a primary care setting	190 women with family history of breast cancer referred to family cancer clinic for breast/ovarian cancer. 144 women (mean age 38; SD=10.0) returned questionnaire (76%	90%+ of women felt that the leaflet was easy to read and understand, was written in a caring way/was comprehensive; 80% felt that the leaflet was relevant to present needs/provided enough information; and between 60-70% agreed that it helped them talk to doctors and to family members, and was reassuring. Some women, however, felt that the leaflet should not be a substitute for talking to a

Study	Design	Aim(s)	Population	Results
Grande et al (2002)	Qualitative study	To investigate women's views of GP consultations about family history of breast cancer	72 telephone interviews with women and 20 face-to-face interviews with subset of 20 women. Of women involved in face-to-face interviews, mean age was 49, range 34-76. All women had experienced primary care consultation in which family history of breast cancer was mentioned (as reported by clinician).	Family history of breast cancer was rarely the main focus of the GP consultation. Women often lacked understanding of breast cancer familial risk and disease and they expressed need for clarification, explanation and information. Conclusion: GPs need to provide more information, explanation and reassurance to this group of women.

3.3 References (2004)

Andermann AA, Austoker J, Watson EK et al (2002) Development and evaluation of a general information leaflet for women with a family history of breast cancer *Journal of Cancer Education* 17: 155-60.

Grande GE, Hyland F, Walter FM, Kinmonth AL. (2002) Women's views of consultations about familial risk of breast cancer in primary care. *Patient.Educ.Couns*; 48 (3):275-82.

Andermann AA, Watson EK, Lucassen AM, Austoker J. (2001) The Opinions, Expectations and Experiences of Women with a Family History of Breast Cancer Who Consult Their GP and Are Referred to Secondary Care. Community Genet; 4 (4):239-43

Chalmers, K., Thomson, K. (1996). Coming to terms with the risk of breast cancer: Perceptions of women with primary relatives with breast cancer. *Qualitative Health Research*, 6:256-282.

4 Care of Women in Specialist (Secondary and Tertiary) Care

4.1 Genetic Counselling with No Personal History of Breast Cancer

One meta-analysis and 1 systematic review have been identified which have evaluated the impact of genetic counselling on psychological morbidity and breast cancer risk perception. Results from both studies consistently show that counselling does not have an adverse effect on psychological morbidity, with results in the meta-analysis indicating a statistically significant decrease in generalised anxiety. Both studies also showed that counselling improved accuracy of perceived breast cancer risk perception, with a statistically significant improvement observed in the meta-analysis. Studies included in the systematic review, however, showed that many women still overestimated their risk of breast cancer. Studies with longer-term follow-up and improved study design are required to confirm these findings.

4.1.1 Evidence Statements (2004)

- Genetic counselling is associated with decreased anxiety, cancer worry and improvements in risk accuracy and knowledge, in the short term. (III)
- Genetic counselling is not associated with increased anxiety. (III)
- There is no difference in anxiety reduction and satisfaction between genetic counsellors compared to clinical geneticists. (IV)
- Many women who mistakenly perceive their risk as high can be reassured that they are at not at such high levels of risk and need no further interventions. (IV)
- Many women who consider taking a predictive test for *BRCA*1/2/TP53 are enabled by genetic counselling to make an informed choice about whether or not to proceed with the test. (IV)

4.1.2 Evidence Tables

Table 4.1: Evidence relating to genetic counselling for women with no personal history of breast cancer

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of** **participants: Total sample** **number**	**Outcome(s)**
Meiser et al (2002) What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A met-analytic review	To determine the impact of genetic counselling on women with a family history of breast cancer	Meta-analysis MEDLINE, PsychLIT and EMBASE, 1980 onwards. Manual search of specialist journals (titles listed) from 1990-April 2000 Rosenthal's	**Included:** published in peer-reviewed journal; English language; included women with family history of breast cancer but no previous breast cancer*; who had undergone genetic	12 studies which met criteria (10 studies excluded: reasons for exclusion provided in paper) Genetic counselling Various follow-	Total sample number not provided. Numbers of women provided when studies combined for each outcome measure. Age/age ranges not provided Ethnicity not reported	**Impact of genetic counselling on:** **Psychological distress** (any term relating to adverse emotional outcomes) **Accuracy of perceived risk** (any question assessing women's perceived chances of getting breast cancer) **Breast cancer screening**
Results						

Genetic counselling and generalised psychological distress (n=6 studies): These 6 studies surveyed 1,012 women. Psychological distress decreased in all studies post-counselling, although only one study reported a statistically significant decrease (P=0.0004). No significant heterogeneity between studies was observed (P=0.70). Combined results showed an average effect size, weighted for sample size of *r* = -0.074 (95% CI, -0.160 to 0.0145), approaching statistical significance (P=0.052).

Genetic counselling and generalised anxiety (n=5 studies): These studies surveyed 1,229 women. Analyses showed that generalised anxiety decreased in all studies post-counselling, with no significant heterogeneity of effect sizes (P=0.50). Average effect size across all studies, weighted for sample size, was *r* = -0.17 (95% CI, -0.303 to -0.147; P<0.01).

Genetic counselling and accuracy of perceived risk (n=6 studies): These studies surveyed 1,062 women. Heterogeneity of effect sizes was significant (P<0.001), so random effects analysis performed. Average weighted effect size across studies was *r* = 0.56 (95% CI, -0.95 to –0.17; P<0.01).

Impact of genetic counselling on other outcomes: Insufficient data (n=3 studies) to pool for impact on anxiety about developing breast cancer, although results were inconsistent. Studies measuring the impact of genetic counselling on breast cancer genetics (n=3 studies) showed significant increases in knowledge. In terms of impact on breast cancer screening (n=3 studies), findings are inconsistent.

Authors' conclusions: Findings show that genetic counselling leads to statistically significant decreases in generalised anxiety and improved accuracy of perceived risk. Psychological distress was also decreased, although this reduction did not quite reach statistical significance. The authors note that evaluations of the content and quality of genetic counselling are needed.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants:** **Total sample number** **Age**	**Outcome(s)**
Butow et al (2003) Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: a systematic review	To review the effects of genetic counselling and testing for familial breast cancer on risk perception and psychological morbidity	Systematic review MEDLINE; PsychLIT; EMBASE 1980-2001 Not applicable	**Included:** studies published in peer-reviewed journals; English language; included women with a family history of breast cancer who had genetic counselling or testing; prospective design (with pre- and at least 1	3 RCTs; 16 observational studies; 1 meta-analysis Genetic counselling or testing Immediate to 1 year post- counselling	Sample numbers provided for individual studies Details of age/age ranges or ethnicity not reported	Breast cancer risk perception Psychological morbidity
Results						

Risk perception after counselling (n=6 studies): Improvements in accuracy of perceived risk were observed consistently after genetic counselling, although 22-50% of women still overestimated their risk at this time. Of studies which had longer follow-ups to 1 year, one showed no changes in accuracy of perceived risk, and another showed maintenance of improvement. Overall, studies showed that genetic counselling was successful in improving accuracy of women's breast cancer, at least in the short term.

Psychological outcomes of counselling (n=9 studies): Results were varied, from showing some reduction in psychopathology to no changes. No study found that anxiety levels or psychological morbidity were related to a change in perceived risk, or that outcomes were worse for those who had initially underestimated their risk.

Impact of counselling on risk perception and psychological outcomes (n=1 meta-analysis): Synthesis of 12 studies showed that genetic counselling significantly decreased generalised anxiety, with an average weighted effect size of r = -0.17 (P<0.01), and significantly improved accuracy of perceived breast cancer risk (r = 0.56; P<0.01). A trend in reduction in psychological distress was observed, although this did not reach statistical significance (r = -0.074; P=0.052).

*[Study results relating to psychological outcomes of **genetic testing** are not reported here]*

Authors' conclusions: Genetic counselling does not appear to have an adverse effect on psychological outcomes and may reduce generalised anxiety. Counselling also appears to be effective in improving accuracy of perceived breast cancer risk, although many women continue to overestimate their risk. The authors note that only a few included studies were RCTs, which limited the strength of their conclusions. Also follow-up was short in all studies, and studies lacked data on other outcomes, such as depression and family functioning.

Table 4.2 Additional studies mentioned in text

Study ref	Outcome	Baseline to short-term follow-up (as reported in Meiser & Halliday)	Baseline to long-term follow-up (as reported by the authors)
Cull et al 1999	GHQ 30	Significant reduction (p<0.001) immediately post clinic	No difference from baseline to 1 yr (p=0.90)
Watson et al 1998	GHQ 12	33.6% cases at baseline, 29% at 1 month: no significant change	34% cases at 6 months: no significant change from baseline to 6 months
Watson et al 1999	GHQ 12	baseline to 1 month: no sig change, p=0.63	baseline to 6 months: p=0.13 baseline to 1 year: p=0.58

4.2 References (2004)

Butow PN, Lobb EA, Meiser B, Barratt A, Tucker KM. Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: a systematic review. Medical Journal of Australia 2003; 178: 77-81.

Meiser B,.Halliday JL. (2002) What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Social Science & Medicine; 54:1463-70.

5 Genetic Testing

5.1 Genes associated with inherited breast cancer risk

5.1.1 Review Question

What is the carrier probability at which genetic testing should be offered to people who are:

A. Unaffected but with a family history of breast, ovarian or related cancer
B. Unaffected with a family history and no living relative
C. Affected patients

5.1.2 Background

Current recommendations are that the carrier probability threshold for genetic testing *BRCA1* and *BRCA2* is set at 20%. The decision to set this threshold at 20% was a pragmatic decision based on the absence of definitive evidence and consequently there is still variation in clinical practice at what exact threshold people are referred for genetic testing.

It is important to recognise that the threshold used has a direct impact on the number of people with deleterious gene alterations that can be identified. For example changing the threshold for genetic testing to 10% would identify more people carrying deleterious gene alterations who could be suitable for risk reduction strategies. However this has to be balanced against the potential disbenefits of increased anxiety for the person and identifying genetic changes of unknown clinical significance.

5.1.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women and men • Unaffected (without cancer) with a living relative with a family history • Unaffected (without cancer) without a living relative and a family history • Affected patients (breast/ovarian/prostate/pancreatic cancer)	Genetic Testing at different carrier probability thresholds • 5% • 10% • 15% • 20% • 30% • 40% • 50%	Each Other No Genetic Testing	• Cost Effectiveness • Overall Survival in the family of the tested individual • Disease Specific Survival in the family of the tested individual • Health Related Quality of Life

5.1.4 Relative importance of these outcomes?

Cost effectiveness was deemed to be the most important outcome for this topic on the basis that the ability to provide the service to women in the lower threshold groups will be determined primarily by cost.
The GDG commented that certain types of testing are slower and more costly than others and that some testing methods, while not cost effective in small numbers becomes much more cost effective as numbers of samples tested increases. The GDG did not discount the importance of the clinical outcomes however but placed greater importance on Health related Quality of Life than on the

survival outcomes on the basis that the potential for impact on QoF as a result of uncertainty and stress surrounding the test.

5.1.5 How the information will be searched

Searches: *(To be Completed by subgroup lead)*	
Can we apply date limits to the search	As this is part update, part new short guideline topic the date limits cannot be set to the end of the previous guideline as would normally be the case when updating a topic however as the topic has identified clear population groups covered by both old and new, it may be possible to apply a date limit when sifting the evidence for those populations.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	This topic is unlikely to be addressed by RCT's therefore no filters should be used
List useful search terms.	None to add

If our original search finds nothing are we going to adjust the PICO and re-run the search? (*Note:* Due to time constraints, this is a situation we would make every effort to avoid and would only occur in exceptional circumstances)

5.1.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	Population Subgroups to be investigated at different carrier probability thresholds: • Unaffected (without cancer) with a living relative with a family history • Unaffected (without cancer) without a

	living relative and a family history • Affected (breast/ovarian/prostate/pancreatic cancer)

5.1.7 Search Results

Table 1: Literature search details and **Update search details**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-10/2011	2539	311	02/11/2011
Update search	10/2011-7/2012	271	43	04/07/2012
Premedline	All-10/2011	92	14	07/11/2011
Update search	10/2011-7/2012	57	19	04/07/2012
Embase	All-10/2011	1128	143	07/11/2011
Update search	10/2011-7/2012	624	53	04/07/2012
Cochrane Library	All-10/2011	571	15	11/11/2011
Update search	10/2011-7/2012	38	1	04/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-10/2011	171	22	11/11/2011
Update search	10/2011-7/2012	40	10	04/07/2012
PsyInfo	All-10/2011	250	7	11/11/2011
Update search	10/2011-7/2012	16	3	04/07/2012

Total References retrieved (after de-duplication): 454

Total References retrieved for Update Search (after de-duplication): 110

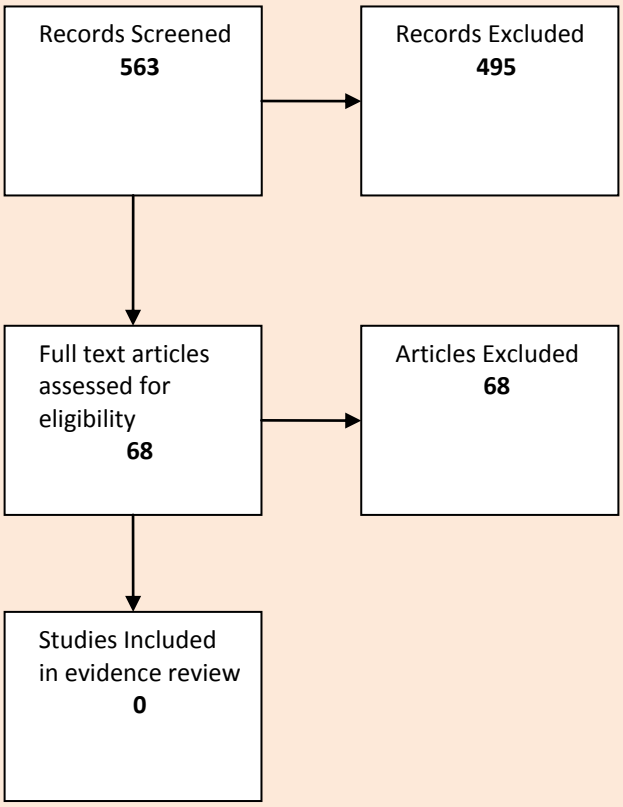
Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. 1 or 2 or 3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6

8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetic Predisposition to Disease/
12. (BRCA1 or BRCA2 or TP53).tw.
13. ((high adj risk) or (increas$ adj risk)).tw.
14. (mutation adj1 risk*).tw.
15. lifetime breast cancer risk*.tw.
16. (mutation adj carrier*).tw.
17. (genetic adj susceptib*).tw.
18. (inherited adj mutation*).tw.
19. or/9-18
20. 8 and 19
21. diagnostic genetic test*.tw.
22. predictive genetic test*.tw.
23. (Sanger adj sequenc*).tw.
24. MLPA*.tw.
25. Multiplex Ligation-dependent Probe Amplification*.tw.
26. Genetic Screening/
27. (probability adj1 threshold*).tw.
28. exp Genetic Testing/
29. exp Risk Assessment/
30. or/21-29
31. 20 and 30

There was no filter applied to the search.

5.1.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

5.1.9 Evidence Statements

There was no evidence about the outcomes of interest for this topic. Specifically there was a lack of published studies comparing different carrier probability thresholds for genetic testing in terms of overall or disease specific survival or health related quality of life.

5.2 Genetic Testing for People with a Family History but no Personal History of Breast Cancer

In terms of evidence for attitudes towards, and uptake of, genetic testing, identified studies generally lack rigorous design. The majority of studies are surveys carried out in the US, and some have small study samples.

Overall results, however, would indicate that expected and actual uptake of genetic testing in healthy men and women with a family history of breast and/or ovarian cancer is fairly high, indicating the acceptability of such programmes. Factors which appeared to positively influence uptake of genetic testing included a family history of breast/ovarian cancer, relief of uncertainty, older age, greater perceived risk, concerns about risks to children, cancer worry and need to learn more about surveillance options. Perceived risks of genetic testing included costs, anxiety about the possibility of a positive result, concerns about health insurance and the availability and demands of genetic testing programmes.

Overall, the evidence for psychosocial outcomes relating to genetic testing, again, lacks rigorous design, comprising mainly of surveys and observational studies, some with small study samples.

Findings for these studies indicate that, as would be expected, individuals who are found to be *BRCA1*/2 mutation carriers on disclosure of test results tend to have higher levels of psychological morbidity compared to non-carriers at post-test follow-ups (Lerman et al, 1996; Croyle et al, 1997; Meiser et al, 2002). There was some evidence that high-risk individuals who decline genetic testing were more vulnerable to an increase in depressive symptoms (Lerman et al, 1996; Lerman et al, 1998). Although most individuals cope well during the waiting period between blood sampling and results in terms of psychological functioning, some women and their partners experience increased anxiety and distress (Lodder et al, 1999; Broadstock et al, 2000). One qualitative study revealed the concerns of women deemed ineligible for genetic testing, in terms of their continued worries about their breast cancer risks despite their ineligibility and their frustration at the lack of information received (Bottorff et al, 2000).

5.2.1 Evidence statements

- There are over 500 different mutations in *BRCA1* that have been reported. (IIb)
- *BRCA1*/2 mutations account for the great majority of multiple case families with combinations of both breast and ovarian cancer and male and female breast cancer. (IV)
- *BRCA1*/2 mutations account for less than one third of the inherited component of female breast cancer only families. (III)
- There is some evidence to suggest that families that receive no results from a *BRCA1*/2 search/screen show some increased anxiety at a year. (III)
- Normal practice in the UK is that all reported predictive testing is carried out within a protocol that has at least two sessions of genetic counselling. Shorter protocols have not been studied. (IV)

- Once a mutation has been identified in a family this should provide near complete certainty about who has or has not inherited the high risk in the family. This allows unaffected individuals to undertake predictive genetic testing. (IV)

- Tests aid women with decision making with regard to risk reducing interventions (e.g. surgery) and surveillance, but may also give them greater certainty about the risks to themselves and their family. (IV)

- There is limited evidence which shows that about half of women who have a positive (high risk) predictive test for *BRCA1* & 2 undertake risk reducing surgery. The uptake in non-carriers is very low. (III/IV)

- Thus far, there have been no results from large prospective well designed studies on the results of *BRCA1*/2 predictive testing. (IV) (note: the outcomes of the CR-UK study are awaited).

- A negative predictive test for *BRCA1*/2 has been shown to reassure women in studies with short term follow-up. (IV)

- A positive predictive test (high risk) result may lead to higher levels of psychological morbidity compared to a negative result, but is not increased over baseline. (IV)

- Tests aid women with decision making with regard to risk reducing interventions (e.g. surgery) and surveillance but may also give them greater certainty about the risks to themselves and their family. (IV)

- *BRCA1* & 2 testing in the UK has not identified particular hot spots or founder mutations. Mutations in *BRCA1* & 2 are generally spread throughout the whole gene. (IV)

- There are ethnic populations within the UK which have strong founder mutations such as the Jewish population. (IV)

- Direct sequencing achieves high levels of sensitivity when used to identify sequence alterations. However, there are a number of other substantially cheaper options with virtually identical sensitivity such as MLPA, FAMA, DHPLC and DF. (III)

- Techniques other than direct sequencing may need to be used to detect deletions. (III)

5.2.2 Evidence Tables

Table 5.1: Summary of evidence for attitudes towards/uptake of genetic testing in women with a family history of breast cancer and/or BRCA1/2 mutations

Study	Design: origin	Population	Outcome measures	Results
Bernhardt et al (1997)	Qualitative study (focus groups): US	229 women aged 21-60 at higher-risk (one 1st- and two 2nd-degree relatives with breast cancer in same line) and lower-risk (negative family history or ≥1 distant affected relatives).	Semi-structured discussion guide. Topics included: assessment of risk/benefits of testing; interest in testing; expectations of how testing decisions should be made; preferences for learning about	Women would most want to learn about test accuracy, practicalities of testing, options if result was positive. Perceived benefits of testing: information leading to risk reduction, relief of uncertainty, more responsible parenting, assisting in research. Perceived risks: discomfort of testing, costs, anxiety after positive result. Insurance discrimination rarely mentioned. Women would want
Bowles Biesecker et al (2000)	Follow-up: US	172 adult (≥18 years) men/women from families with BRCA1/2 mutations and either: at least 2 cases of ovarian cancer in 1st-degree relatives; or 3 cases of breast cancer and at least 1 case	Factors affecting decisions to undergo genetic testing, in terms of sociodemographics, personality traits and family functioning	After pre-test education and counselling, 135 (78%) chose to undergo genetic testing and 37 (22%) chose not to be tested. Those who chose testing were more likely to be older (≥40 years), to be less optimistic and to report higher levels of cohesiveness in their families
Cappelli et al (2001)	Cohort: Canada	108 women: Group 1 (n=58) had at least 1 female relative with breast cancer diagnosed within past 2 years; Group 2 (n=50) from general population aged 18-50 years with no history of any cancer or family history of breast cancer.	Breast Cancer Survey; Health Belief Model (HBM); perceived benefits/costs of genetic testing; intent to be tested.	Women from Group 1 were more likely to want genetic testing than Group 2 women (P<0.05). Increased risk perceptions for ovarian cancer were associated with interest in genetic testing for BRCA1/2 in women with family history of the disease. Greater perceived psychological benefits and fewer perceived costs of BRCA1/2 testing were associated with genetic testing for women in both groups.
Durfy et al (1999)	Survey: US	4 groups of women with a family history of breast cancer of at least 1 relative (any degree) with breast cancer; 307 white women; 36 African American women; 87 lesbian/bisexual women; 113 Ashkenazi Jewish women.	Cancer Worry Scale; perceived risk of breast cancer; beliefs about/interest in genetic testing; actions anticipated based on test results.	Women in all groups favoured ready access to testing, believed the testing decision should be a personal choice and that test results should be confidential. Women anticipated using results to increase frequency of breast screening methods (in all groups, >69% would increase mammograms, >85% clinical examinations, >92% breast self- examination). In all, >80% probably or definitely would

Study	Design: origin	Population	Outcome measures	Results
Foster et al (2002)	Survey: UK	298 healthy individuals (227 females; 71 males) from families with identified BRCA1/2 mutation (97% response rate). Female median age: 41 (range 21-72 years); male median age: 48 (range 22-86 years). 85% were white.	Mental health and cancer-related worry; risk perception; risk management; role of anxiety/risk perception in risk management; reasons for predictive genetic testing	No gender differences found in rates of psychiatric morbidity. Younger women (<50 years) more worried about developing cancer than older women. Few women provide accurate figures for population risk of breast (37%) or ovarian (6%) cancer but most perceived they are at higher risk of breast (88%) and ovarian (69%) cancer than average woman. Cancer- related worry not associated with perceived risk or uptake of risk management options (except breast self-examination). Younger women may be particularly vulnerable at time of offer of predictive genetic testing. Most common reason for wanting testing was for the sake of children.
Hailey et al (2000)	Cohort study: US	51 women (25 had 1st-degree relative with breast cancer and 26 had no family history [comparison group]). Mean age of sample was 41 (range 24-58 years).	Breast Cancer Attitude Inventory (BCAI); Revised Beck Depression Inventory (BDI); perceptions of risk; anticipated impact of results; IES; assessment of benefits/risks of testing.	Large proportion of women overall would want genetic testing (difference between groups not significant). Having a family history did not affect perceptions about positive/negative aspects of testing. Larger proportion of women with a family history expected negative consequences of testing than women without a history.
Hughes et al (1997)	Survey (baseline interview prior to RCT): US	310 Caucasian women and 97 African American women (mean age 43, range 18-75). 76% had ≥1 relative with breast cancer; 14% had ≥1 relative with ovarian cancer; 21% had ≥2 relatives with breast cancer; <1% had >2	Knowledge about breast cancer genetics and genetic testing; attitudes about benefits, limitations and risks of testing.	Average knowledge score was 6.0 out of total of 11 (SD=2.15). African American women had lower levels of knowledge and more positive attitudes about benefits of genetic testing, compared to Caucasian women. No significant ethnic differences in attitudes about risks of testing; however, income was negatively associated. Women generally had positive attitudes about genetic testing

Study	Design: origin	Population	Outcome measures	Results
Jacobsen et al (1997)	Survey: US	74 women aged 32-59 years (mean age 44) with ≥1 1st-degree relative with breast cancer	Perceived risk of breast cancer scale; Readiness Scale (to undergo genetic testing); Decisional Balance Scale for Breast Cancer Genetic Testing (perceptions of pros and cons of testing).	46% planned to seek testing as soon as possible, 35% planned to seek testing in the future, and 19% did not plan to seek testing. Greater readiness for testing was associated with a positive decisional balance (P<0.0001). Older age and greater perceived risk also associated with greater readiness (P=0.05 and P=0.02, respectively).
Julian-Reynier et al (2000)	Survey: French	211 healthy women and 187 women with breast/ovarian cancer who had at least one 1st or 2nd-degree relative with breast/ovarian cancer: mean age 43.6 years (SD=12.2).	Attitudes towards disclosing positive genetic test results to 1st-degree relatives; factors associated with patterns observed	Of 383 women who had at least one 1st-degree relative to inform, 8.6% would inform none, 33.2% would inform at least one, and 58.2% would inform all of them. Sisters and brothers (86.9% and 79%, respectively) would be most frequently informed compared to mothers (71.4%), children (70.4%) and fathers (64.9%). Women would be informed
Kinney et al (2001)	Survey: US	95 male and female members of a large African American family with a BRCA1 mutation (mean age 43; range 18-78 years). 77% were female.	Health care attitudes and utilisation; psychological distress (CES-D and revised IES); knowledge/attitudes about breast cancer and BRCA1; BRCA1 testing intentions.	Knowledge about breast/ovarian cancer was low. Adherence to screening recommendations also low in females with no personal breast/ovarian cancer history. Most participants (82%) would want a genetic test if available. Significant predictors of intent to undergo testing: having ≥1 1st- degree relative with breast and/or ovarian cancer (OR=5.1; 95% CI, 1.2-
Lerman et al (1994)	Survey: US	121 women, age range 18-74 years, with a 1st-degree family history of ovarian cancer	Attitudes towards BRCA1 testing; psychological/emotional factors	75% of women said they would definitely want to be tested for BRCA1 and 20% said they probably would. Perceived likelihood of being a gene carrier was associated with interest (OR=3.7;
Lerman et al (1995)	Survey: US	105 healthy women with at least one 1st- degree relative with breast cancer: age range 30-75 years	Interest in, and anticipated psychological impact of, genetic testing	91% of women reported that they would want to be tested, 4% that they would not, and 5% were uncertain. Reasons for wanting genetic testing: learn about children's risk, increase use of screening tests, and take better self-care. Most women expected a negative psychological impact of positive test results: increased anxiety (83%),

Study	Design: origin	Population	Outcome measures	Results
Lerman et al (1996)	Prospective observational study (with baseline interview of predictor variables): US	279 adult males and females of families with BRCA1-linked hereditary breast/ovarian cancer. Mean age 43; white; 67% females.	BRCA1 testing decisions; depression symptoms (CES-D Scale); functional health status (Medical Outcomes Study [MOS]); medical decision-making.	43% of all participants requested BRCA1 test results. Requests for results more frequent in participants with health insurance (OR=3.74; 95% CI, 2.06-6.80); more 1st-degree relatives affected with breast cancer (OR=1.59; 95% CI, 1.16-2.16); more knowledge about BRCA1 testing (OR=1.85; 95% CI, 1.36-2.50); who indicated that test benefits are more important (OR=1.45; 95% CI, 1.12-1.86)
Lerman et al (1997)	Survey: US	149 participants (37% male) from families where BRCA1 mutations had recently been identified. Mean age was 44 (range 21-84 years); all participants were white.	Breast cancer-specific distress (Impact of Event Scale [IES]); general distress (CES-D); intention to receive BRCA1 test results.	58% of participants requested BRCA1 test results, and 42% declined to learn genetic status. After controlling for demographic factors and risk status, cancer-specific distress was significantly and positively related to BRCA1 test use (P<0.01), whereas general distress was unrelated.
Loader et al (1998)	Survey: US	99 women with ≥2 1st-degree relatives or one 1st- and one 2nd-degree relative with breast and/or ovarian cancer; 41 women with personal and family history of breast/ovarian cancer (mean age 44)	Psychological status; breast cancer knowledge, attitudes, surveillance practices; decision about testing.	Most common reasons for accepting testing were to take extra precautions if a mutation were found (42.9%); and to determine if children were at risk (24.5%). Most common reasons for declining were anxiety and absence of specific interventions. Factors predicting who chose testing were years of education (P<0.005) and family closeness (P<0.02).
Meijers-Heijboer et al (2000)	Follow-up: Dutch	682 healthy individuals with 50% risk (275 women/271 men) or 25% risk (136 women) of carrying BRCA1/2 mutation	Uptake of presymptomatic DNA testing and prophylactic surgery	48% (198/411) of women and 22% (59/271) of men requested DNA testing (OR for difference between sexes = 3.21 [95% CI, 2.27-4.51; p<0.001]). DNA testing significantly more frequent at young age, if a parent, and at high risk of carrying mutation. In women found to have mutation who were eligible for prophylactic surgery, 51% (35/68) chose

Study	Design: origin	Population	Outcome measures	Results
Patenaude et al (1996)	Survey: US	36 members of 2 BRCA1 families and 57 members of Li-Fraumeni syndrome families invited for testing.	Uptake/refusal of BRCA1 and p53 cancer predisposition testing programmes. General emotional status, depression, suicidal intentionality, self-esteem, coping, locus of control, social support.	29/36 (80%) of members of BRCA1 families accepted testing; 22/57 (39%) of Li-Fraumeni family members accepted. Factors which may affect uptake: demands of the programmes, nature/immediacy of cancer risk, demographic factors, perceived outcomes of cancer, efficacy of screening, ego-strength and family experience of cancer. Findings similar in both groups.
Reichelt et al (1999)	Survey: Norway	232 individuals from 27 families with BRCA1 mutations who were offered testing.	IES; Hospital Anxiety and Depression Scale (HADS); General Health Questionnaire (GHQ); Beck Hopelessness Scale.	78% chose to be tested; 6% had not decided; and 16% declined testing. A higher proportion of females with a history of cancer had abnormal scores on the IES and GHQ questionnaires (P<0.001) compared to females without a history. Healthy females who were deciding on testing had the same or lower levels of mental distress compared to general population (4.3%-18.0% measured by different
Richards et al (1997)	Survey: US	309 Ashkenazi Jewish adults (272 females, 37 males). 67% had negative family history; 22% had one 1st-degree relative or two 2nd-degree relatives with breast/ovarian cancer; 7% had positive personal history; 4% had	Reasons for uptake or refusal of genetic testing. Effectiveness of education programme.	Group education was effective (improved scores from pre- to post- education tests). Of 289 (94%) who requested genetic testing, the major reasons included concern for their own risk and of their children, and desire to learn about surveillance options. Most common reason for declining testing was concern about health insurance.
Shiloh et al (1998)	Survey: Israel	150 women (54 high risk and 96 average risk, based on self-reported data). Mean age 37 (SD=10.88).	Intentions to be tested; reasons for uptake/decline of testing; risk perceptions; differences in coping styles associated with intentions to be tested.	Most women would consider being tested, different factors influence reasons for and against testing; motivations for testing differ between the 2 risk groups; 'unrealistic optimism' observed in average risk women only; intentions to be tested related to risk perceptions and individual differences in average risk women only.

Study	Design: origin	Population	Outcome measures	Results
Struewing et al (1995)	Survey: US	91 females and 49 males with family history of breast/ovarian cancer	Interest in BRCA1 genetic testing and anticipated impact of test results	79% indicated that they would definitely want to be tested, 16% would probably want to be tested. Those with a high risk perception of being BRCA1 mutation carrier were more likely to want testing (P=0.02). Females were significantly more likely to definitely want testing (p=0.005)

Table 5.2: Summary of evidence for psychosocial outcomes relating to genetic testing in women with a family history of breast cancer and/or BRCA1/2 mutations

Study	Design: origin	Population	Outcome measures	Results
Lerman et al (1996)	Prospective observational study (with baseline interview of predictor variables): US	279 adult males and females of families with BRCA1-linked hereditary breast/ovarian cancer. Mean age 43; white; 67% females.	BRCA1 testing decisions; depression symptoms (CES-D Scale); functional health status (Medical Outcomes Study [MOS]); medical decision-making.	After disclosure of test results, non-carriers of BRCA1 mutations showed significant reduction in depression compared to carriers and decliners (P<0.001 and P<0.001, respectively), and in functional impairment compared to carriers and decliners (P=0.001 and P=0.004, respectively).
Watson et al (1996)	Survey/data report: UK	32 unaffected individuals (17 females, 15 males) from 2 families with ≥4 cases of breast and ovarian cancer including ≥1 ovarian cancer and 2 early onset breast cancers (diagnosed at <50 years). Posterior probability of linkage to BRCA1 of >95%, 14/32 (10	Uptake of testing; psychological morbidity (GHQ); reasons for wanting test; risk management.	Uptake of testing was 41% overall. Psychological morbidity and cancer- specific concerns were not unusually high (means ranged from 30.3-35.8). Indication that unanticipated unfavourable test result can cause subsequent psychological distress. At 12-month follow-up, none (including the 3 identified gene carriers) had had problems with insurance or employment.
Croyle et al (1997)	Survey: US	60 women (mean age 47, range 19-83 years) from a large family of N European descent at high risk of breast and ovarian cancer, undergoing testing for BRCA1 mutations.	General psychological distress (State-Trait Anxiety Inventory); test-related distress (IES)	25/60 women tested were found to be mutation carriers. At 1-2 week post-test follow-up, carriers had significantly higher levels of test-related distress compared to non-carriers (P<0.001). Highest distress levels observed among carriers with no history of cancer or cancer-related surgery.

Study	Design: origin	Population	Outcome measures	Results
Lynch et al (1997)	Qualitative study: US	181 individuals (46 males and 135 females) with mean age of 42 (range 19-84) tested for BRCA1 mutations from 14 families with a history of breast/ovarian cancer	Reasons for seeking testing; expectations about test results; emotional responses; intentions to undergo prophylactic surgery.	Results of testing available 1-5 years after blood sampling. 78/181 were positive for BRCA1 mutation. Reasons for seeking testing were concerns about risk to children and about surveillance/prevention. Those with positive results had more emotional responses of sadness, compared to relief in those with negative results. 25% of sample were concerned about discrimination from insurance companies.
Lerman et al (1998)	Prospective cohort: US	327 members (106 males, 221 females) of 33 BRCA1/2 hereditary breast/ovarian cancer families, identified as carriers, non-carriers or decliners of genetic testing. Mean age 45, range 18-84 years.	Cancer-related stress symptoms (subscale of Revised IES); depression symptoms (CES-D Scale).	Cancer-related stress at baseline strongly predictive of depression in participants who declined testing: depression rates increased in decliners from 26% at baseline to 47% at 1-month follow-up, whereas depression rates in non-carriers decreased and in carriers showed no change (OR for decliners v non-carriers=8.0; 95% CI, 1.9-33.5; P=0.0004). These significant differences in depression rates still evident at 6-month follow-up (P=0.04).
Lodder et al (1999)	Survey: Netherlands	85 healthy women (mean age 38) with 25% or 50% risk of BRCA1/2 mutation carrier status, and 66 partners (mean age 39).	General distress (HADS); cancer-related distress (IES); expected consequences of mutation carrier status; personality traits; experiences of hereditary breast/ovarian cancer.	Results for psychological functioning in 6-8 week waiting period between blood sampling and results. Mean pre-test anxiety/depression similar to normal Dutch population. Most women and partners coped well during this period, though some were quite distressed. Distress more likely to occur in at risk carriers who: expect problems to increase after an unfavourable test result; consider prophylactic mastectomy if found to be mutation carrier; are unoptimistic; tend to suppress emotions; are <40 years; are familiar with serious aspects of having a family history.
Smith et al (1999)	follow up interviews: US	759 mailed, 500 received full project information, men and women, BRCA1 mutation study (Kindred 2082) baseline interview: 408 1st genetic counselling session: 296 blood drawn for mutation testing: 269	IES (used to measure test related distress) information re their and their siblings test results in terms of carrier of mutation	male carriers, relative to noncarriers, experiences significantly more distress if they were the first tested when all of their tested siblings were already known to be negative; noncarrier males whose siblings all tester positive also encountered significant test-related distress; the largest adverse psychological consequences for female carriers, relative to noncarriers, were for those who were tested first and those whose tested siblings were noncarriers

Study	Design: origin	Population	Outcome measures	Results
Bottorff et al (2000)	Qualitative study (interviews): Canada	20 women who do not meet eligibility criteria for genetic testing; 10 of their referring physicians	Interviews with women: how women became interested in breast cancer risk; came to consider genetic testing; experiences relating to ineligibility. Interviews with physicians: referral practices for testing; experiences in counselling about breast cancer risk and genetic testing.	Interviews with women found 3 main themes: deep concerns about breast cancer risk, despite ineligibility; belief that test was simple and would give definitive answer; anger/frustration relating to lack of information. Interviews with physicians: they were concerned that women did not understand the implications of genetic testing.
Broadstock et al (2000)	Survey: UK	21 unaffected women aged 22-62 (mean age 36) eligible for mutation searching in their family (living affected relative willing to give blood sample).	Uptake of mutation searching; reasons for not initiating mutation searching; general anxiety and distress (GHQ and State-Trait Anxiety Inventory [STAI]); cancer-specific worries (Cancer Worries Scale and IES).	Mutation searches initiated in 15/21 families; 2 received results within 12 months. For 13 families still waiting for results, anxiety and distress was within normal ranges at all time-points. Reduced worries about cancer reported at 6 and 12 months post-search offer compared to earlier assessments, but increase in anxiety was experienced 12 months since search offer. Changes in anxiety over time not observed in those where mutation searches not initiated.
Lodder et al (2001)	Survey/qualitative interviews: Netherlands	28 men (mean age 47, range 29-67) at 25% (n=4) or 50% (n=24) risk of being a BRCA1/2 mutation carrier, requesting genetic testing. 23 partners (mean age 44, range 25-65).	General distress (HADS); intrusion and avoidance (IES); reasons for testing/expected consequences of testing; optimism.	Distress in men and partners pre-test result was low. Many men and partners expected test result to be problematic for their children, but not themselves. Distress particularly low in men without daughters and those who were optimistic. Most men denied avoidance of issue. 4/28 men identified as mutation carriers. High distress reported post-test result in one mutation carrier and 3 non-mutation carriers. Large variation in psychological reactions in mutation carriers, eg feelings of guilt. Low pre-test distress did not necessarily indicate avoidance of the issue.

Study	Design: origin	Population	Outcome measures	Results
Tercyak et al (2001)	education sessions, disclosure, anxiety measures: US	107 women self referred to cancer risk assessment programme; eligibility for programme required minimum 10% prior probability of having BRCA1/2 mutation	State Anxiety subscale of the State-Trait Anxiety Inventory (STAI)	mean scores: baseline: 34.6 (SD=8.7, range 23-57) predisclosure: 38.6 (SD=10.7, range 23-72) postdisclosure: 36.6 (SD=11.2, range 23-70) all within normal limits all three scores were moderately correlated with coping style younger women, college graduates, individuals who had never been diagnosed with care or undergone cancer surgery and high monitors (ie those who vigilantly attend to threatening cues) were more anxious during the anticipatory period in terms of postdisclosure anxiety, those who graduated from college and those informed of their positive mutation status were more anxious (regardless of coping style)
Meiser et al (2002)	Cohort: Australia	90 women with family history of breast/ovarian cancer who had undergone genetic testing for BRCA1/2 mutations (30 carriers and 60 non-carriers); 53 women with a family history of breast/ovarian cancer not offered testing (had no living affected relative for blood sampling). Mean age of sample was 40 years.	Psychological adjustment: IES, STAI, Beck Depression Inventory; satisfaction with decision to undergo testing.	Mutation carriers had significantly higher breast cancer distress 7-10 days (P=0.005) and 12 months (P=0.045) post-test result compared to women not offered testing. Non-carriers showed a significant decrease in state anxiety 7-10 days post-result (P=0.024) and in depression 4 months post-result (P=0.024) compared to women not offered testing.

5.3 Carrier probability at which genetic testing should be offered.

5.3.1 Background

BRCA1/2 testing may identify important aetiological factor in a woman's breast cancer that can inform her own future management as well as allow accurate predictive testing in her close relatives. Without knowledge of a familial mutation, genetic testing in an unaffected relative is less clinically useful since it cannot exclude a mutation undetectable by current methods. Given that BRCA1/2 mutations will only explain a small proportion of all breast cancers as well as a small proportion of all women with a family history of breast cancer and that current testing costs at best are around £500, it is not cost effective use of health resources to test all women with breast cancer. The stronger a woman's family history of cancer, the higher the chance she will harbour a pathogenic BRCA1/2 mutation, so the object of this question is to identify a threshold that will pick up a significant proportion of BRCA1/2 carriers whilst keeping specificity of testing as high as possible.

5.3.2 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Affected Women and men with a family history of breast cancer	Genetic testing at different carrier probability thresholds: • 5% • 10% • 15% • 20% • 30% • 40% • 50%	Each Other	1. Future care (surveillance, chemoprevention, surgery etc) 2. Genetic testing for relatives 3. number/ percentage of mutations identified

5.3.3 Relative importance of these outcomes

The outcomes have been ranked according to importance with future care of the affected women/man considered to be the most important of the outcomes of interest.

5.3.4 How the information will be searched

What sources will be searched, e.g. will we look at Cinahl?

Are there any study design filters to be used (RCT, systematic review, diagnostic test).

Can we apply date limits to the search	No date limits were applied to this topic
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	It is unlikely that there will be RCT's available for this topic and so no filters will be applied.
List useful search terms	Nothing added by GDG members

If our original search finds nothing are we going to adjust the PICO and re-run the search? (*Note:* Due to time constraints, this is a situation we would make every effort to avoid and would only occur in exceptional circumstances)

5.3.5 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	Threshold groups are identified in the PICO

5.3.6 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-10/2011	2539	311	02/11/2011
Update search	10/2011-7/2012	271	43	04/07/2012
Premedline	All-10/2011	92	14	07/11/2011
Update search	10/2011-7/2012	57	19	04/07/2012
Embase	All-10/2011	1128	143	07/11/2011
Update search	10/2011-7/2012	624	53	04/07/2012
Cochrane Library	All-10/2011	571	15	11/11/2011
Update search	10/2011-7/2012	38	1	04/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-10/2011	171	22	11/11/2011
Update search	10/2011-7/2012	40	10	04/07/2012
PsyInfo	All-10/2011	250	7	11/11/2011
Update search	10/2011-7/2012	16	3	04/07/2012

Total References retrieved (after de-duplication): 454

Total References retrieved for Update Search (after de-duplication): 110

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.

4. 1 or 2 or 3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetic Predisposition to Disease/
12. (BRCA1 or BRCA2 or TP53).tw.
13. ((high adj risk) or (increas$ adj risk)).tw.
14. (mutation adj1 risk*).tw.
15. lifetime breast cancer risk*.tw.
16. (mutation adj carrier*).tw.
17. (genetic adj susceptib*).tw.
18. (inherited adj mutation*).tw.
19. or/9-18
20. 8 and 19
21. diagnostic genetic test*.tw.
22. predictive genetic test*.tw.
23. (Sanger adj sequenc*).tw.
24. MLPA*.tw.
25. Multiplex Ligation-dependent Probe Amplification*.tw.
26. Genetic Screening/
27. (probability adj1 threshold*).tw.
28. exp Genetic Testing/
29. exp Risk Assessment/
30. or/21-29
31. 20 and 30

There was no filter applied to the search.

5.3.7 Screening Results

Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

5.3.8 Evidence Statements

Outcomes

Our searches identified no studies of the effect of varying the carrier probability threshold on the outcomes of interest.

5.4 Genetic testing for BRCA1 BRCA2 and TP53 within 4 weeks of diagnosis of breast cancer.

5.4.1 Review Question

Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options and/or does it usefully inform immediate decisions about risk reducing options?

5.4.2 Background

Standard breast cancer treatments are aimed at removing the original cancer and mitigating the risk of any future relapse. Treatment is based largely on the risks and benefits of the differing options according to the likelihood of relapse (stage and biology) and the likely efficacy of any given treatment option (tumour grade, immunohistochemistry). In BRCA gene carriers decisions are made in the same way as for sporadic breast cancers at present and do not usually take into account the BRCA mutation status even when known. The exception may be for BRCA carriers who already know their genetic status and have already considered risk reducing surgical options in the past and who may then express a preference for their surgical management. If there is evidence that conventional breast cancer management (often including the option of breast conserving surgery) leads to worse clinical outcomes in patients (greater mortality) OR that different treatment options applied to BRCA carriers clearly improve long term outcomes for those patients, without causing greater harm, then there would be an overall benefit to rapid early BRCA testing in breast cancer patients. If robust evidence exists for a benefit of identifying BRCA gene carriers in order to determine best cancer treatment then there would be grounds for the pathway to genetic testing being altered to facilitate rapid early genetic testing as part of the onco-pathological work up with the emphasis around testing to benefit the individual rather than the current emphasis which in reality is often more on benefit to the wider family. In considering this topic it is important to note that both medical interventions and particularly irreversible surgical risk reducing interventions (mastectomy and oophorectomy) are usually made after a considerable period of information exchange and reflection and may not be ideally made as urgent decisions at a time when decisions about cancer treatment are also being made. Prevention strategies for future cancers have little relevance to cancer treatment decisions particularly within the first 4 weeks and have no impact on the risk of developing metastatic cancer from the presenting primary. The main strategy for this topic then is to determine whether there is sufficient evidence currently to recommend different oncological management based on inherited BRCA mutation status rather than the current approach based on presenting tumour characteristics: clear evidence that alternative treatment is better than standard is required i.e. that the BRCA carrier specific treatment either decreases mortality and morbidity in newly diagnosed cancer patients or has any other beneficial clinical or psychological impact on patients or is more cost effective than delayed testing.

5.4.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients recently diagnosed with first breast cancer who meet the threshold	Treatment with knowledge of patient mutation status	Treatment without knowledge of patient mutation	• Rate of risk reducing surgery (mastectomy/oophorectomy) • Rate of targeted treatments

for genetic testing (subgroup: BRCA carriers and non-carriers – in patients with knowledge of mutation status)	Risk Reducing Surgery (Mastectomy Bilateral Salpingo Oophorectomy Combination) Surgery Chemotherapy Radiotherapy	status Risk Reducing Surgery (Mastectomy Bilateral Salpingo Oophorectomy Combination) Surgery Chemotherapy Radiotherapy	(chemotherapy, surgery etc) • Disease Specific Survival • Recurrence • Health Related Quality of Life • Patient satisfaction with choices

5.4.4 Relative Importance of these outcomes

The listed outcomes were the only outcomes considered to be of importance to the topic in question

5.4.5 How the information will be searched

Can we apply date limits to the search	1998 1994 FF but unlikely to be that many papers I would have though prior to 2000 or even later as fast track testing not been a possibility for very long and mutation testing was only offered from 1995.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No. plus case studies
List useful search terms.	Case studies ovarian/breast cancer, rapid genetic testing, fast-track genetic testing, treatment focussed genetic testing, adjuvant therapy, cisplatin/platinum based therapy , PARP inhibitor trial, contra lateral prophylactic mastectomy/surgery, risk- reducing mastectomy/surgery, psychological, psychosocial, quality of life, ethics,

5.4.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and

	presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	None of specific relevance to this topic

5.4.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1998-current	611	77	22/02/2012
Premedline	1998-current	21	3	22/02/2012
Embase	1998-current	1173	79	29/02/2012
Cochrane Library	1998-current	90	0	29/02/2012
Web of Science (SCI & SSCI) and ISI Proceedings	1998-current	708	47	05/03/2012

Total References retrieved (after duplicates removed): 130

Medline search strategy *(This search strategy is adapted to each database.)*

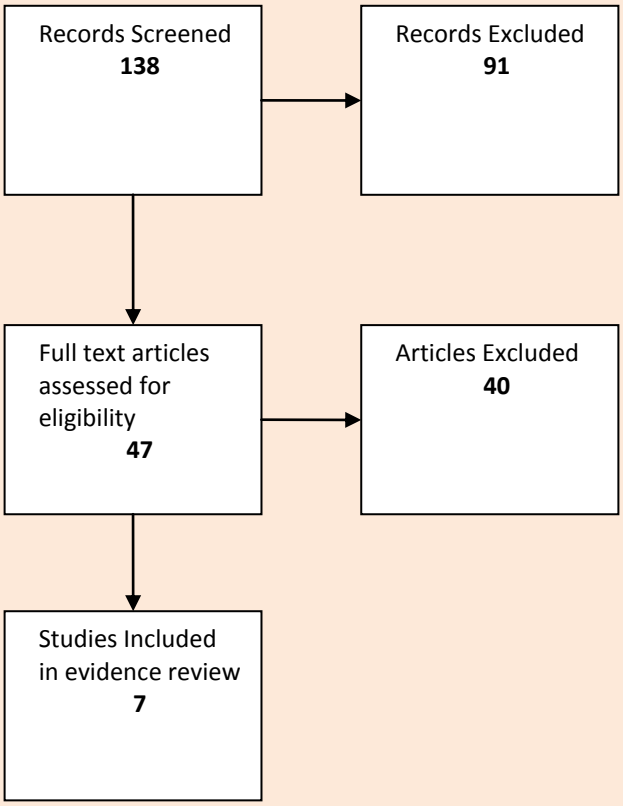
1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. exp Mastectomy/
25. mastectom$.tw.
26. mammaplast$.tw.
27. mammoplast$.tw.
28. mammectom$.tw.
29. or/24-28
30. *Ovariectomy/
31. (oophorectom$ or salpingooophorectom$).tw.
32. 30 or 31

33. Surgery/
34. (risk reduc$ adj surger$).tw.
35. (breast conserv$ adj surger$).tw.
36. or/33-35
37. Antineoplastic Combined Chemotherapy Protocols/
38. chemotherap$.tw.
39. exp Antineoplastic Agents/
40. or/37-39
41. exp Radiotherapy/
42. radiotherap$.tw.
43. (radiation adj (therap$ or treatment$)).tw.
44. or/41-43
45. ((therap$ or treatment$) adj adjuvant).tw.
46. Combined Modality Therapy/
47. 45 or 46
48. 29 or 32 or 36 or 40 or 44 or 47
49. 23 and 48
50. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
51. (primary or first or new or prior).tw.
52. 50 and 51
53. 49 and 52
54. (mutation$ or BRCA1 or BRCA2 or TP53).tw.
55. (gene$ adj status).tw.
56. exp Mutation/
57. genes, brca1/ or genes, brca2/
58. brca1 protein/ or brca2 protein/
59. Tumor Suppressor Protein p53/tu [Therapeutic Use]
60. Genes, p53/
61. or/54-60
62. 53 and 61

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	01/02/2012-18/07/2012	26	2	18/07/2012
Premedline	01/02/2012-18/07/2012	16	1	18/07/2012
Embase	02/2012-07/2012	25	1	18/07/2012
Cochrane Library	02/2012-07/2012	2	0	18/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	02/2012-07/2012	54	7	23/07/2012

Total references retrieved after duplicates removed: 8

5.4.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=)
Case Series Studies (n=7)
Qualitative Study (n=0)

Table 5.3: Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcome
Evans et al (2005)	Retrospective Case Series	N=70	To establish the uptake of contralateral risk reducing mastectomy in women informed of their risks and options at time of diagnosis of primary, unilateral breast cancer	This study reported on treatment decisions for women who were diagnosed with breast cancer and provided with relevant information on risk prior to treatment.		Uptake of risk reducing surgery
Forquet et al (2009)	Retrospective Case Series	N=90	To determine if breast cancers in BRCA1/2 mutation carriers were more responsive to induction treatments than in non-carriers	Chemotherapy Radiotherapy The study reported outcomes for response to chemotherapy and radiotherapy however the study was not designed to investigate a comparison between the two treatments – rather to retrospectively report outcomes for patients undergoing each treatment.		Tumour Response
Kauff et al (2008)	Retropsective Case Series	N=1079	To investigate the appropriateness of RRSO in risk reduction for women with BRCA1/BRCA2 mutations and provide information specifically for BRCA2 carriers and to investigate the efficacy of RRSO in the prevention of future breast and BRCA associated gynaecological cancers when BRCA1 and BRCA2 carriers are assessed separately.	Risk reducing salpingo oophorectomy		Treatment Decision Gynaecological Cancer Breast cancer
Kiely et al (2010)	Retrospective Case Series	N=1018	To determine the prevalence and predictors of contralateral risk reducing mastectomy in Australasisan women at high familial risk of second primary breast cancer	Risk reducing mastectomy		Rates of risk reducing surgery New cancers Reccurence
Pierce et al (2010)	Retrospective Case Series	N=655	To compare long term outcomes in patients with BRCA1/2 mutations following breast conserving therapy or mastectomy	Breast Conserving Therapy	Each Other	Recurrence (local, regional and

				Mastectomy		systemic)
Scheuer et al (2002)	Prospective Case Series	N=251	To determine the impact of genetic testing and counselling on risk reduction strategies and cancer incidence in a cohort of individuals at hereditary risk for breast and ovarian cancer	Genetic counselling and testing	Non comparative	Rate of risk reducing surgery Outcome of cancer surveillance Impact of counselling and treatment on screening behaviour
Schwartz et al (2004)	Retrospective Case Series	N=194 (85% of the eligible population)	To evaluate the impact on surgical decision making of pre-treatment genetic counselling and BRCA1/2 testing among breast cancer patients who are at high risk of carrying a mutation	Genetic Counselling and rapid genetic testing	Non-comparative	Definitive treatment decisions Predictors of bilateral mastectomy

5.4.9 Evidence Statements

Treatment Decision

Low quality evidence suggests that genetic test results influence treatment decisions (GRADE Profile 1). A prospective case series (Scheuer et al 2002) reported changes in treatment decision based on genetic test results for both breast and ovarian surgeries. Another retrospective case series of low quality (Schwartz et al, 2004) reported that patients found to carry a BRCA1/2 mutation were significantly more likely to undergo bilateral mastectomy as compared with patients with uninformative results or women who opted not to be tested (48% versus 24% versus 4%; p<0.001).

Response to chemotherapy

Very low quality evidence suggests that response to chemotherapy may differ in BRCA1/2 carriers and non carriers (Forquet et al, 2009; GRADE Profile 1). BRCA1/2 mutation was significantly associated with complete response to chemotherapy (RR=3.61; 95% CI 1.19-10.9).

Response to radiotherapy

There was insufficient evidence to say whether response to radiotherapy differs in BRCA1/2 carriers and non carriers. From one retrospective case series of very low quality (Forquet et al, 2009; GRADE Profile 1) in 6 BRCA1/2 carriers, 1 had a complete response and 5 had a major response compared with 3 complete responses, 4 major responses and 6 minor/no response in the non-mutated tumours .

Relative effectiveness of mastectomy and breast conserving therapy

There was insufficient evidence to say whether knowledge of mutation status before making decisions about surgery influences outcome. Low quality evidence from an observational study (Pierce et al 2010; GRADE Profile 1) suggests local failure is significantly more likely following breast conserving therapy (BCT) than after mastectomy in patients with BRCA1/2 mutation. Median time to failure was 7.8 years for BCT patients and 9 years for mastectomy patients. But the clinical significance of this is unclear and no there was significant difference between the overall survival of the two treatment groups .

Risk reducing Salpingo Oophorectomy versus Surveillance

Very low quality evidence suggests that salpingo oophorectomy lowers the incidence of gynaecological cancer compared to surveillance in women with BRCA1/2 mutation (Kauff et al, 2008; GRADE Profile 1). Following salpingo oophorectomy the incidence rate was 3/509 compared with 12/283 in the surveillance group (HR=0.12, 95% CI, 0.03-0.41).

Very low quality evidence suggests that salpingo oophorectomy lowers the incidence of breast cancer when compared to surveillance in women with BRCA1/2 mutation (Kauff et al, 2008; GRADE Profile 1). Following salpingo oophorectomy the incidence rate was 19/303 compared with 28/294 in the surveillance group (HR=0.53, 95% CI, 0.29-0.96).

5.4.10 Evidence Summaries

A total of seven retrospective case series studies provided the evidence base for this topic (Evans et al, 2005; Kauff et al, 2008; Schwartz et al, 2004, Kiely et al, 2010, Pierce et al, 2010, Forquet et al, 2009, Scheuer et al, 2002). All included studies were considered to be low quality on assessment using GRADE (GRADE Profile 5.1).

Four retrospective studies of low quality reported on the treatment decisions made by patients with a family history or breast cancer and who were eligible for BRCA testing (Evans et al, 2005; Schwartz et al, 2004, Kauff et al, 2008 and Kiely et al, 2010).

Changes in treatment decision based on genetic test results for both breast and ovarian surgeries were reported in one prospective case series study of low quality (Scheuer et al 2002) (GRADE Profile 5.1)

Incidences of gynaecological cancer and breast cancer in BRCA1 and BRCA2 mutation carriers treated with risk reducing salpingo oophorectomy were reported in a single retrospective case series (Kauff et al, 2008). This study did not compare incidence rates with non mutated tumours and patients in this study were all aware of their mutation status at the time of treatment. This should be considered indirect, low quality evidence.

Clinical response to chemotherapy and radiotherapy was reported in a single, retrospective case series study (Forquet et al, 2009) (GRADE Profile 5.1).

Cancer recurrence was reported in one study comparing recurrence rates in BRCA1 and BRCA2 mutated tumours following breast conserving therapy or mastectomy (Pierce et al, 2010). This study did not compare recurrence with non mutated tumours and patients in this study were all aware of their mutation status at the time of treatment. This should be considered indirect, low quality evidence.

Treatment Decision

A total of 20 patients carried a BRCA1/2 mutation; 8/20 patients had received the result of BRCA testing and were aware they carried a BRCA1/2 mutation underwent definitive treatment (Evans et al, 2005).

4/8 women were aware of the BRCA mutation carrier status prior to breast cancer diagnosis and 4/8 women received their test results within 4 weeks of diagnosis and prior to definitive surgery (Evans et al, 2005).

Table 5.4: Treatment Decisions made with and without knowledge of mutation status

	Mutation status known	**Mutation status unknown**
	N=8	*N=12*
Rate of risk reducing mastectomy	75% (n=6)	58% (n=7)
Rate of unilateral mastectomy	12.5% (n=1)	42% (n=5)
Rate of wide local excision	12.5% (n=1)	0% (0)

All patients were offered rapid genetic testing and 167/194 patients (86%) chose to receive BRCA test results prior to definitive treatment (Schwartz et al, 2004).

Patients found to carry a BRCA1/2 mutation were significantly more likely to undergo bilateral mastectomy as compared with patients with uninformative results or women who opted not to be tested (48% versus 24% versus 4%; p<0.001) (Schwartz et al, 2004).

In the 167 patients who underwent genetic testing, test results were significantly associated with definitive treatment (p=0.005) (Schwartz et al, 2004).

23% of patients underwent genetic testing but went ahead with definitive treatment before receiving results (Schwartz et al, 2004).

Of the 77% of patients who waited for their test results before proceeding with surgery, surgical decision was significantly associated with test result (p=0.004) with 52% of patients receiving a positive result opting for bilateral mastectomy compared with 24% of patients with an uninformative result (Schwartz et al, 2004).

188 patients were aware they carried a BRCA mutation and 18% underwent contralateral risk reducing mastectomy compared with 12% of patients who did not know their results (n=808). BRCA1/2 status was not a significant predictor of contralateral risk reducing mastectomy (p=0.4) (Kiely et al, 2010).

A total of 792 patients were assessable for gynaecological cancer end points (498 BRCA1 and 294 BRCA2); 65% of BRCA1 mutation carriers and 63% of BRCA2 carriers underwent RRSO a median of 5.5 months and 4.1 months after receiving genetic test results (Kauff et al 2008).

A total of 597 participants were assessable for breast cancer end points (368 BRCA1 and 229 BRCA2); 52% of BRCA1 mutation carriers and 49% of BRCA2 mutation carriers underwent RRSO a median of 5 months and 4 months after receiving genetic test results (Kauff et al 2008).

20/233 (8.6%) had previously undergone risk-reducing mastectomies and 19/233 had undergone bilateral mastectomies leaving 194/233 women with breast tissue at risk at the time of receiving their genetic test results.

- 14.9% underwent RRM at a median of 5.3 months (range: 0.1-34.8 months) after receiving test results
- Women electing to undergo surgery were younger than those not (mean, 43 years versus 46.8 years, p=0.015)
- Women electing to undergo surgery had a greater number of breast and ovarian malignancies in first and second degree relatives compared with women not opting for surgery (mean, 2.7 versus 2.1 cancers, p=0.046) (Scheuer et al, 2002).

25/233 women had a personal history of ovarian cancer and 29/233 had undergone bilateral oophorectomy for benign gynaecological indications or risk reduction leaving a total of 179/233 women with ovarian tissue at risk at the time of receiving test results

- 50.3% (90/233) underwent risk reducing salpingo oophorectomy at a median of 3.4 months (range: 0.1-49.7 months) after receiving results (19% included hysterectomies and 81% were bilateral oophorectomy only)
- Women electing for risk reducing oophorectomy were older than those opting not to undergo surgery (mean 47.3 years versus 41.6 years; p<0.001);

- 64% (77/120) women older than 40 opted for RRSO compared with 22% (13/59) of younger women
- Women electing to undergo RRSO were more likely to have had a prior breast cancer diagnosis (74.4% versus 49.4%, p=0.001) (Scheuer et al, 2002).

Clinical Response to Chemotherapy

Complete clinical response was achieved in 46% of BRCA1/2 mutated tumours and in 17% of non-mutated tumours (p=0.008) (Forquet et al, 2009).

Complete or major clinical response was observed in 74.3% of tumours treated with chemotherapy

- 81% of mutated tumours versus 68% of non-mutated tumours (NS)
- No difference in response between BRCA1 and BRCA2 carriers
- BRCA1/2 mutation was significantly associated with complete response (RR=3.61; 95% CI 1.19-10.9, p=0.02) (Forquet et al, 2009).

Following neoadjuvant chemotherapy, breast conserving treatments were performed in 85% of BRCA1/2 mutated tumours and in 54% of non-mutated tumours (p=0.004). Breast conservation was achieved in 89% of BRCA1/2 mutated tumours with a major or complete clinical response to chemotherapy compared with 67% of non-mutated tumours (Forquet et al, 2009).

Clinical Response to Radiotherapy

Overall complete or major clinical response rate in tumours treated with radiotherapy was 68% (13/19 tumours).

In 6 BRCA1/2 carriers, 1 had a complete response and 5 had a major response compared with 3 complete responses, 4 major responses and 6 minor/no response in the non-mutated tumours (Forquet et al, 2009).

Breast Conserving Surgery versus Mastectomy

Local and Regional Failures

Cumulative incidence estimates of local failure as first failure were significantly greater following BCT compared with mastectomy (p<0.0001) and median time to failure was 7.8 years for BCT patients and 9 years for mastectomy patients (Pierce et al, 2010)

Type of gene mutation and not receiving adjuvant chemotherapy were independent predictors of recurrence among patients treated with BCT. Rates of local failure were higher for women treated with BCT and receiving chemotherapy compared with women treated with mastectomy though the difference was not significant (8.1% versus 3.5% at 10 years; 10.7% versus 5.5% at 15 years respectively, p=0.08) (Pierce et al, 2010.

When comparing BRCA1 and BRCA2 patients undergoing BCT, there was a non statistically significant reduction in recurrence in those patients receiving hormonal therapy (p=0.08 for BRCA2 and p=0.13 for BRCA1) (Pierce et al, 2010.

Oophorectomy did not significantly impact local failure rates among BCT patients:

- Total BCT cohort HR=0.88, p=0.75
- BRCA1 subset HR=1.63, p=0.27
- BRCA2 subset HR=0.2, p=0.125 (Pierce et al, 2010

The presence of invasive lobular cancer was the only significant factor associated with local failure in patients treated with mastectomy (Pierce et al, 2010.

Distant Failures

The cumulative incidence estimates of distant failure as first failure were not significantly different according to treatment type.

- 10 year distant failure rate: BCT=7.1% versus mastectomy=11.1%
- 15 year distant failure rate BCT=7.4% versus mastectomy=9.1%

On multivariate analysis, factors significantly impacting distant failure rates included BRCA2 mutation (HR=1.9, p=0.05) and the presence of an invasive lobular component (HR=3.1; p=0.01) (Pierce et al, 2010).

Breast cancer Specific Survival and Overall Survival

No significant difference in breast cancer specific or overall survival was observed by treatment type (p=0.73).

Breast cancer specific survival was 93.6% at 10 years and 91.7% at 15 years for BCT patients

Breast cancer specific survival was 92.1% at 10 years and 87.3% at 15 years for mastectomy patients

Factors associated with breast cancer specific survival included the presence of infiltrating lobular cancer (HR=4.3, p=0.01) and the development of a contralateral breast cancer (HR=2.5, p=0.02) (Pierce et al, 2010.

The only factor significantly related to increases in rates of death was the development of ovarian cancer (HR=5.0, p=0.0001) (Pierce et al, 2010.

Risk reducing Salpingo Oophorectomy versus Surveillance

<u>Gynaecological Cancer</u>

During 38 months of follow-up, 12 BRCA associated cancers were diagnosed a median of 37 months after ascertainment in the 283 women undergoing surveillance compared with 3 peritoneal cancers diagnosed a median of 16 months after RRSO during 40 months of follow-up in 509 women opting for RRSO: **HR=0.12, 95% CI, 0.03-0.41, p=0.001** (Kauff et al 2008)

In BRCA1 only there were 10 gynaecological cancers in 173 carriers electing surveillance compared with 3 primary peritoneal cancers in 325 patients opting for RRSO: **HR=0.15, 95% CI, 0.04-0.56, p=0.005** (Kauff et al 2008)

In BRCA2 patients there were 2 BRCA associated gynaecological cancers developed in 110 women opting for surveillance compared with no peritoneal cancers in the 184 women undergoing RRSO during 39 months of follow-up: **HR=0.00, 95% CI, not estimatable** (Kauff et al 2008)

Breast Cancer

A total of 597 patients were assessable for breast cancer end points;

During 33 months follow-up there were a total of 28 breast cancers diagnosed a median of 23 months after ascertainment in the 294 women electing for surveillance compared with 19 breast cancers in the 303 women electing for RRSO: **HR=0.53, 95% CI, 0.29-0.96, p=0.036**

In BRCA1 carriers only (n=368), 190 underwent RRSO a median of 5 months after receipt of genetic test results.

- 19/178 patients who opted for surveillance developed breast cancer compared to 15 breast cancers in the 190 women opting for RRSO: **HR=0.61, 95% CI, 0.30-1.22, p=0.16**

113 BRCA2 carriers underwent RRSO a median of 4 months after test results. 9/116 women opting for surveillance developed breast cancer compared 4/113 breast cancers in women opting for RRSO: **HR=0.28, 95% CI, 0.08-0.92, p=0.036**

GRADE Profile 5.1:

Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options (rate of risk reducing mastectomy, rate of risk reducing salpingo oophorectomy), treatment outcomes (clinical response to chemotherapy and/or radiotherapy), incidence of future breast or ovarian cancer and/or does it affect the treatment decision?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Rate of risk reducing mastectomy							
Evans et al (2005); Kiely et al (2010); Schwartz et al (2004)							
3[1]	observational studies	serious[2]	very serious[3]	no serious indirectness[4]	serious[5]	none	VERY LOW
Rate of Risk Reducing Salpingo Oophorectomy							
Scheuer et al (2002)							
1[6]	observational studies	serious[7]	no serious inconsistency[8]	serious[9]	serious[10]	none	VERY LOW
Change in treatment decision							
Scheuer et al (2002)							
1[6]	observational studies	serious[8,11]	no serious inconsistency[8]	serious[12]	serious[13]	none	VERY LOW
Clinical Response to Chemotherapy or Radiotherapy							
Forquet et al (2009)							
1[14]	observational studies	serious[15]	no serious inconsistency[8]	no serious indirectness	serious[16]	none	VERY LOW
Incidence of gynaecological cancer							
Kauff et al (2008)							
1[22]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[19]	none	VERY LOW

Incidence of breast cancer							
Kauff et al (2008)							
1[22]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[20]	none	VERY LOW
Cancer Recurrence							
Pierce et al (2010)							
1[23]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[21]	none	VERY LOW

[1] Evans et al (2005), Kiely et al (2010) and Schwartz et al (2004)
[2] Non of the included studies were raandomised trials, all were retrospective case series studies with no blinding apparent and no indication as to whether all available eligible patients were included in each study.
[3] All three studies reporting on the rates of mastectomy were reporting on different elements of the same outcome. Mastectomy outcomes included bilateral risk reducing mastectomy and unilateral mastectomy. Populations included in each study varied slightly in relation to timing of genetic testing and knowledge of test results and therefore could not be compared and pooled.
[4] Overall the populations included in each of the three studies were considered to be directly relevant to the topic in question. In particular, Evans et al (2005) included only patients with a family history and recent diagnosis of breast cancer and also identified decisions made with and without knowledge of genetic test result. In addition, this study represents the only study carried out in a UK population.
[5] Two of the included studies (Evans et al, 2005 and Schwartz et al, 2004) included populations of only 70 patients and 194 patients respectively. Kiely et al (2010) included a population of 1018 and would therefore be considered likely to provide the most precise results.
[6] Scheuer et al (2002)
[7] The only study reporting on rates of risk reducing salpingo oophorectomy as a primary outcome was not a randomised trial.
[8] There was only a single study available to address this outcome in a relevant population therefore no comment can be made on the consistency of the result.
[9] The study included only patients with known BRCA mutations, comparing BRCA1 mutation carriers with BRCA2 mutation carriers. The BRCA mutation carrier population and their outcomes following treatment are of relevance to this topic however the comparision of interest was to patients who do not have a knowledge of the BRCA status. This study should be considered indirect for two reasons: it does not identifiy whether the BRCA1/2 patients included in this study were aware of their mutation status prior to treatment and it does not include a comparison of patients who were and were not aware of mutation status prior to treatment.
[10] This was a smallobservational study with a total population of 251 patients.
[11] There was only a single, retrospective case series available to address this outcome
[12] The population for this study included patients who were unaware of their mutation status at time of diagnosis and who underwent treatment prior to

receiving test results, some of whom then underwent further treatment following receipt of genetic test results. There is no comparison with patients receiving definitive treatment only after receiving genetic test results.

[13] Small study with only 251 patients included

[14] Forquet et al (2009)

[15] The study was a retrospective case series which examined clinical repsonse to treatment with chemotherapy and radiotheraoy without any comparison to each other or to no treatment. The preferred study type for such a comparision would be a randomised controlled trial

[16] This was a small study with only 90 patients included

[17] Not a randomised Controlled Trial

[18] Only women known to be BRCA1/BRCA2 carriers were included in the study and no information provided on whether they had knowledge of mutation status or not prior to surgery

[19] No explanation was provided

[20] The number of events recorded during the study follow-up period was small (n=28 breast cancers in the surveillance group and 19 breast cancers in the surgery group)

[21] The total numbers in the study were small (n=302 treated with breast conserving therapy and 353 treated with mastectomy); numbers for recurrence were not reported

[22]Kauff et al (2008)

[23]Pierce et al (2010)

5.4.11 Evidence Tables

Citation: Evans DG et al (2005) Surgical decisions made by 158 women with hereditary breast cancer aged <50 years *European Journal of Surgical Oncology* 31;10:1112-1118

Design: Retrospective case series

Country: UK

Setting: Follow up

Aim: to establish the uptake of contralateral risk reducing mastectomy in women informed of their risks and options at time of diagnosis of primary, unilateral breast cancer

Inclusion criteria
Asymptomatic women with a family history of breast cancer aged younger than 50 years.

Exclusion criteria
No details

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=70

Study Duration
January 1990-December 2004

Interventions
Unclear ; appears to be access to information on contralateral breast cancer risk

Outcomes
Uptake of risk reducing surgery

Results
3 patients were found to have contralateral tumours (1 at mammography and 2 following bilateral mastectomy for a diagnosis of carcinoma in situ.

21/70 women underwent bilateral mastectomy as first procedure and 5 proceeded to bilateral surgery after initial unilateral mastectomy.
21/70 patients opted for a unilateral mastectomy
23/70 patients opted for wide local excision
Ongoing screening was carried out in those patients who did not opt for risk reducing surgery

20/70 women were found to be carriers of BRCA1/2 mutations (11 BRCA1 and 9 BRCA2)

	Mutation status known	**Mutation status unknown**
	N=8	*N=12*
Rate of risk reducing mastectomy	75% (n=6)	58% (n=7)

Rate of unilateral mastectomy	12.5% (n=1)	42% (n=5)
Rate of wide local excision	12.5% (n=1)	0% (0)

More women under the age of 40 years were found to be mutation carriers compared with women aged 40-49 years (12/27 (56%) versus 5/43 (12%) respectively).
17/34 patients at 33%+ risk before diagnosis had a BRCA1/2 mutation.
4/20 mutation carriers were aware of their mutation status prior to diagnosis; 2 women indicated a desire for bilateral risk reducing mastectomy with1 opting for immediate bilateral mastectomy and the second undergoing TRAM flap surgery and was advised to have delayed surgery on the contralateral breast and a third women opted for immediate bilateral mastectomy with reconstruction following diagnosis.

4 women received test results within 4 weeks of testing and prior to definitive surgery.
2 women were Ashkenazi Jewish and were offered testing for the three common BRCA1/2 mutations with both testing positive. One underwent unilateral mastectomy while the second opted for wide local excision
In the other two women, one opted for immediate bilateral mastectomy and one delayed contralateral mastectomy for a year.

12 women received results between 3 and 36 months after diagnosis and in only one patient did test results prompt the decision to choose a contralateral mastectomy having opted not to undergo risk reducing mastectomy initially.

Women with high grade IDC, lobular cancer/LCIS tumours were more likely to opt for bilateral mastectomy
There was a trend towards opting for risk reducing surgery depending on original risk category
Size was not a major predictor of choice: 39% of those with the smallest tumours (<11mm) opted for bilateral mastectomy versus 33% of those with tumours <11mm.

Of the control group, 9/88 (10%) of women proceeded to contralateral surgery after counselling
No external mutation carrier indicated that RRM had been discussed at initial diagnosis or subsequently as a delayed option.
No women in the control group had metastatic disease at the time of surgery or genetic assessment though one had metastatic disease at the time of being informed of a positive test result.
None of the patients opting for risk reducing mastectomy had died at the time of publication though 4 of the patients not opting for RRM have died.
18/88 women in the control group were dead at the time of publication including 1 patient who opted for RRM prior to genetic assessment.

3/13 patients in with a family history and who opted for RRM were nulliparous compared with 1/7 not opting for RRM.
In the control group, 5/9 patients opting for RRM were nulliparous compared with 9/79 of the non RRM mutation carriers.

Uptake of RRM was 65% of FHC mutation carriers compared with 18% of FHC women at lower risk and 10% of external BRCA1/2 carriers ($p<0.001$).

General comments
This paper is an audit and does not appear to add a great deal of evidence to the topic.

Citation: Forquet A et al (2009) Familial breast cancer: clinical response to induction chemotherapy or radiotherapy related to BRCA1/2 mutations status *American Journal of Clinical Oncology* 32;2:127-131

Design: Retrospective case series analysis

Country: France

Setting: Follow-up

Aim: to determine if breast cancers in BRCA1/2 mutation carriers were more responsive to induction treatments than in non-carriers

Inclusion criteria
Women with breast cancer and a family history of breast and ovarian cancer and who had received chemotherapy or radiotherapy as first treatment

Exclusion criteria
None given

Sample Size
No details

Randomisation Method
Not applicable

Population
N=90

Study Duration
Treatment occurred between January 1991 and July 1998

Interventions
Chemotherapy
Radiotherapy

Outcomes
Complete Response (no residual palpable disease)
Major Response (more than 50% tumour reduction in two diameters)
Minor Response (less than 50% reduction)
Stable disease or progressive disease

Results

The median probability of being a mutation carrier was 85% (range: 6%-99%)

28 patients (31%) had a BRCA1 mutation, 9 (10%) patients had a BRCA2 mutation and one patient carried both a BRCA1 and BRCA2 mutation and was considered a BRCA1 mutation carrier for the purposes of the study.

59% of patients with a family history had no mutations.

Median pregenetic testing probability of being a mutation carrier was 99% (34%-99%) in patients eventually found to be a BRCA1 mutation carriers; 89% (51%-90%) in patients found to be BRCA2 carriers and 74% (6%-98%) in patients not found to carry a mutation ($p<0.0001$).

Median time interval between breast cancer diagnosis and genetic testing was 32.5 months (0-215) for BRCA1 carriers, 31 months (1-164) for BRCA2 carriers and 21 months (1-166) for non-carriers.

85% of BRCA1/2 carriers were treated with chemotherapy and 15% were treated with radiotherapy.
76% of tumours in non carriers were treated with chemotherapy and 24% were treated with radiotherapy.

Clinical Response to Chemotherapy
Complete clinical response was achieved in 46% of BRCA1/2 mutated tumours and in 17% of non-mutated tumours (p=0.008).
Complete or major clinical response was observed in 74.3% of tumours treated with chemotherapy
81% of mutated tumours versus 68% of non-mutated tumours (NS)
No difference in response between BRCA1 and BRCA2 carriers
BRCA1/2 mutation was significantly associated with complete response (RR=3.61; 95% CI 1.19-10.9, p=0.02)
Following neoadjuvant chemotherapy, breast conserving treatments were performed in 85% of BRCA1/2 mutated tumours and in 54% of non-mutated tumours (p=0.004).
Breast conserving therapy consisted of:
radiotherapy alone (11/28 in mutated tumours and 4/22 in non-mutated tumours)
wide excision and radiotherapy (17/28 mutated tumours and 18/22 in non-mutated tumours)
Breast conservation was achieved in 89% of BRCA1/2 mutated tumours with a major or complete clinical response to chemotherapy compared with 67% of non-mutated tumours.

Clinical Response to Radiotherapy
Overall complete or major clinical response rate in tumours treated with radiotherapy was 68% (13/19 tumours).
In 6 BRCA1/2 carriers, 1 had a complete response and 5 had a major response
In the 13 non-mutated tumours there were 3 complete responses, 4 major responses and 6 minor/no response.
4/6 BRCA1/2 carriers and 12/13 non BRCA1/2 carriers underwent breast conserving surgery after radiotherapy.

Following induction treatment by either chemotherapy or radiotherapy, breast conserving surgery was possible in more mutation carriers than non carriers (82% versus 63%; p=0.045)

As sole locoregional treatment, radiotherapy was used more often in BRCA1/2 mutation carriers than in non-carriers (36% versus 20%).

General comments
Carrier probability was determined using the MLINK program.

Tumour response was determined at the end of treatment and without knowledge of BRCA status.

Citation: Kauff ND et al (2008) Risk reducing salpingo oophorectomy for the preention of BRCA1 and BRCA2 associated breast and gynaecologic cancer: a multicentre, prospective study *Journal of Clinical Oncology* 26;8:1331-1337

Design: Prospective Case Series

Country: USA

Setting: Follow-up

Aim: to investigate the appropriateness of RRSO in risk reduction for women with BRCA1/BRCA2 mutations and provide information specifically for BRCA2 carriers and to investigate the efficacy of RRSo in the prevention of subsequent breast and BRCA associated gynaecologic cancers when BRCA1 and BRCA2 carriers are assessed separately.

Inclusion criteria
A documented deleterious mutation in BRCA1 or BRCA2
At least one ovary in situ at time of genetic testing
No personal history of BRCA associated gynaecological cancer before genetic testing
Older than 30 years of age at time of testing

Participants with a personal history of breast cancer without evidence of distant metastasis at the time of genetic testing were also eligible.

Exclusion criteria
No details

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=1079

Study Duration
Recruitment: November 1994 – December 2004
Follow up ended: November 2005:**Min =1 year, Max=11 years**

Interventions
Risk reducing salpingo oophorectomy

Outcomes
Gynaecologic Cancer
Breast Cancer

Results
Gynaecologic Cancer

- A total of 792 patients were assessable for gynaecological cancer end points (498 BRCA1 and 294 BRCA2).
    - 65% of BRCA1 mutation carriers and 63% of BRCA2 carriers underwent RRSO a median of 5.5 months and 4.1 months after receiving genetic test results.
    - During 38 months of follow-up, 12 BRCA associated cancers were diagnosed a median of 37

months after ascertainment in the 283 women undergoing surveillance
    - 3 peritoneal cancers were diagnosed a median of 16 months after RRSO during 40 months of follow-up in 509 women opting for RRSO: **HR=0.12, 95% CI, 0.03-0.41, p=0.001**
- In BRCA1 only there were 10 gynaecological cancers in 173 carriers electing surveillance compared with 3 primary peritoneal cancers in 325 patients opting for RRSO: **HR=0.15, 95% CI, 0.04-0.56, p=0.005**
- In BRCA2 patients, 2 BRCA associated gynaecological cancers developed in 110 women opting for surveillance compared with no peritoneal cancers in the 184 women undergoing RRSO during 39 months of follow-up: **HR=0.00, 95% CI, not estimatable**

Breast Cancer

- A total of 597 participants were assessable for breast cancer end points (368 BRCA1 and 229 BRCA2); 52% of BRCA1 mutation carriers and 49% of BRCA2 mutation carriers underwent RRSO a median of 5 months and 4 months after receiving genetic test results (Kauff et al 2008).
    - During 33 months follow-up there were a total of 28 breast cancers diagnosed a median of 23 months after ascertainment in the 294 women electing for surveillance compared with 19 breast cancers in the 303 women electing for RRSO: **HR=0.53, 95% CI, 0.29-0.96, p=0.036**
- In BRCA1 carriers only (n=368), 190 underwent RRSO a median of 5 months after receipt of genetic test results.
    - 19/178 patients who opted for surveillance developed breast cancer compared to 15 breast cancers in the 190 women opting for RRSO: **HR=0.61, 95% CI, 0.30-1.22, p=0.16**
- 113 BRCA2 carriers underwent RRSO a median of 4 months after test results. 9/116 women opting for surveillance developed breast cancer compared 4/113 breast cancers in women opting for RRSO: **HR=0.28, 95% CI, 0.08-0.92, p=0.036**

- Examining invasive and non-invasive breast cancers were examined independently, RRSO appeared to be more protective against non-invasive breast cancer (HR=0.32, 95% CI, 0.08-1.25, p=0.10) than non-invasive cancers (HR=0.73, 95% CI, 0.37-1.45, p=0.37).

- RRSO appeared to be more protective against ER positive breast cancer (HR=0.22, 95% CI, 0.05-1.05, p=0.058) but not ER negative invasive breast cancer (HR=1.10, 95% CI, 0.048-2.51, p=0.82).

General comments

Citation: Kiely BE et al (2010) Contralateral risk reducing mastectomy in BRCA1 and BRCA2 mutation carriers and other high-risk women in the Kathleen Cunningham Foundation Consortium for Research into familial breast cancer (kConFab) *Breast Cancer Research and Treatment* 120;3:715-723

Design: Retrospective Case Series

Country: Australia

Setting: Follow-up

Aim: to determine the prevalence and predictors of contralateral risk-reducing mastectomy in Australasian women at high familial risk of second primary breast cancer.

Inclusion criteria
Women who had surgery for unilateral invasive breast cancer either prior to or after entering kConFab.

Exclusion criteria
Women from mutation carrying families who were found not to carry the family gene mutation
Women with a prior history of another invasive cancer (apart from non-melanoma skin cancer), bilateral synchronous breast cancer or metastatic disease at diagnosis

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=1018 patients were eligible to take part

Study Duration
Details not given

Interventions
No specific interventions

Outcomes
Rates of risk reducing surgery
New Cancers and Recurrences

Results
Risk Reducing Surgery
Contralateral risk reducing mastectomy (CRRM) was undertaken by 154 women (15%) and 326 (32%) women undertook risk reducing oophorectomy.
37 women (24%) who opted for CRRM had already undergone ipsilateral breast conservation as initial treatment and all later underwent ipsilateral mastectomy.
21 patients (57%) had ipsilateral risk reducing completion mastectomy at the time of CRRM and 16 had ipsilateral mastectomy as treatment for a recurrent cancer either concurrent with CRRM or prior to CRRM.

Independent predictors of CRRM included:
Younger age at diagnosis (odds of CRRM decreased 6% per year of age at diagnosis (95% CI, 4%-9%), p<0.001)
More recent diagnosis (odds of CRRM increased 16% per calendar year (95% CI, 11%-21%), p<0.001)
RRSO (OR=3.35, 95% CI, 2.08-5.40, p<0.001)

Mastectomy as first treatment for breast cancer (OR=5.25, 95% CI, 3.08-8.95, p<0.001)

188 women who knew they carried a BRCA1 or BRCA2 mutation
34 (18%) underwent CRRM
808 women did not know their result or were aware the was no mutation
98 (12%) opted for CRRM
BRCA1/2 status was not a significant predictor of CRRM (p=0.4)
66 women (43%) underwent CRRM within 12 months of breast cancer diagnosis
Having a mastectomy as definitive surgery for first breast cancer was a significant predictor of early versus late CRRM (OR=4.5, 95% CI 1.6-12.7, p=0.005).
75 women (49%) who had CRRM underwent breast reconstruction with 73% of reconstructions occurring within 1 year of CRRM.
The average age of first breast cancer diagnosis in women electing for reconstruction was 6 years younger than for women not having reconstruction (40.8 versus 46.8 years, mean age difference, 5.9 years, SE, 1.4 years, p<0.0001).
Reconstruction rate was 56% in women diagnosed before age 50 years and 28% in women diagnosed with breast cancer at age 50 years or older (p=0.08).

New Cancers and Recurrences
There were 117 contralateral breast cancer events during 11,759 women years observation for the 864 women who did not opt for CRRM and there was one chest wall event during 1,440 woman-years follow-up in women opting for CRRM (15.1 versus 0.7 per 1,000 woman years, p<0.0001).
82/177 (46%) of women who developed contralateral breast cancer were mutation carriers, 71 had uninformative results and 24 were untested.

At last follow-up, 93.5% of CRRM patients and 92.6% of the non-CRRM patients were still alive
Systemic breast cancer recurrence was reported in 95 women during the study follow-up period at a median time of 5 years from initial breast cancer diagnosis.
The systemic recurrence rate was 6.2 per 1,000 woman years for CRRM patients and 10.4 per 1,000 woman years for non CRRM women (p=0.04).

9% of women reported a new, non breast primary.

General comments

Citation: Pierce LJ et al (2010) Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: a comparison of breast conservation and mastectomy *Breast Cancer Research and Treatment* 121;2:389-398

Design: Retrospective Comparative Case Series

Country: Multi centre (patients were treated in the US, Spain, Israel, Australia and New Zealand)

Setting: Follow-up

Aim: to compare long term outcome in patients with BRCA1/2 mutations following breast conserving therapy or mastectomy.

Inclusion criteria
Women with a BRCA1/2 mutation and stage I-III breast cancer treated with either breast conserving therapy or mastectomy

Exclusion criteria
Women with sequence variants of uncertain significance in BRCA1 and BRCA2.

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=655
(302 were treated with BCT and 353 were treated with mastectomy)

Study Duration
No details

Interventions
Breast Conserving Therapy (surgical excision and radiotherapy)
Mastectomy

Outcomes
Recurrence (local, regional and systemic)

Results

- The treatment groups differed significantly in relation to menopausal status (p=0.003), BRCA gene mutation (p=0.01), clinical stage (p=0.0007), pathologic t stage (p=0.001) oestrogen receptor (p=0.006), final microscopic surgical margins (p=0.003), positive lymph nodes removed (p=0.004) and prophylactic contralateral mastectomy (p<0.0001)

- Comparing BRCA1 and BRCA2 carriers specifically, BRCA1 carriers were:
  - more likely to be pre-menopausal (85.3% versus 68.6%, p=0.002)
  - more likely to have oestrogen receptor negative cancers (79.9% versus 29.5%, p<0.0001)
  - less likely to receive hormone therapy (77.2% versus 47.6%, p<0.0001)
  - less likely to have positive axillary nodes (22.4% versus 36.1%, p=0.06)

Local and Regional Failures

- Median follow-up was 8.2 years in the BCT group and 8.9 years in the mastectomy group

- Cumulative incidence estimates of local failure as first failure were significantly greater following BCT compared with mastectomy (p<0.0001)
- Median time to failure was 7.8 years for BCT patients and 9 years for mastectomy patients
- Type of gene mutation and not receiving adjuvant chemotherapy were independent predictors of recurrence among patients treated with BCT. Rates of local failure were higher for women treated with BCT and receiving chemotherapy compared with women treated with mastectomy though the difference was not significant (8.1% versus 3.5% at 10 years; 10.7% versus 5.5% at 15 years respectively, p=0.08).
- When comparing BRCA1 and BRCA2 patients undergoing BCT, there was a non statistically significant reduction in recurrence in those patients receiving hormonal therapy (p=0.08 for BRCA2 and p=0.13 for BRCA1).
- Oophorectomy did not significantly impact local failure rates among BCT patients:
    - Total BCT cohort HR=0.88, p=0.75
    - BRCA1 subset HR=1.63, p=0.27
    - BRCA2 subset HR=0.2, p=0.125
- The presence of invasive lobular cancer was the only significant factor associated with local failure in patients treated with mastectomy.

Distant Failures

The cumulative incidence estimates of distant failure as first failure were not significantly different according to treatment type.

10 year distant failure rate: BCT=7.1% versus mastectomy=11.1%
15 year distant failure rate BCT=7.4% versus mastectomy=9.1%

On multivariate analysis, factors significantly impacting distant failure rates included BRCA2 mutation (HR=1.9, p=0.05) and the presence of an invasive lobular component (HR=3.1; p=0.01).

Contralateral Breast Cancers

148/643 patients developed contralateral breast cancer (patients presenting with synchronous bilateral cancers were excluded from the analysis).

No significant difference was observed between patients receiving adjuvant radiotherapy and those not (p=0.44)

On univariate analysis, the presence of BRCA1 compared to a BRCA2 mutation was significantly associated with a 1.8fold increase in contralateral breast cancer (p=0.003).

Young age at diagnosis was associated with increased risk of contralateral breast cancer: patients aged ≤35 years had a 1.8 fold increase in risk relative to women aged 36-50 years (p=0.04).

Breast cancer Specific Survival and Overall Survival

No significant difference in breast cancer specific or overall survival was observed by treatment type (p=0.73).

Breast cancer specific survival was 93.6% at 10 years and 91.7% at 15 years for BCT patients

Breast cancer specific survival was 92.1% at 10 years and 87.3% at 15 years for mastectomy patients

Factors associated with breast cancer specific survival included the presence of infiltrating lobular cancer (HR=4.3, p=0.01) and the development of a contralateral breast cancer (HR=2.5, p=0.02).

The only factor significantly related to increases in rates of death was the development of ovarian cancer (HR=5.0, p=0.0001).

General comments

Citation: Scheuer, L et al (2002) Outcome of preventative surgery and screening for breast and ovarian cancer in BRCA mutation carriers *Journal of Clinical Oncology* 20;5:1260-1268

Design: Prospective Case Series Study

Country: USA

Setting: Follow-up

Aim: to determine the impact of genetic counselling and testing on risk reduction strategies and cancer incidence in a cohort of individuals at hereditary risk for breast and ovarian cancer.

Inclusion criteria
BRCA1 or BRCA2 mutation carriers

Exclusion criteria
Individuals with missense variants of uncertain significance

Sample Size
No details given

Randomisation Method
Not applicable

Population
N=267 individuals tested

N=251 included in the study (8 declined participation or withdrew and 8 were lost to follow-up)

Study Duration
Recruitment: June 1st 1995 to October 31st 2000

Interventions
Genetic Testing

Outcomes
Rate of risk reducing surgery
Outcome of cancer surveillance
Impact of counseling and treatment on screening behaviour

Results
Mean age at testing was 47.7 years (range: 24.1-79 years)

164 patients had a BRCA1 mutation (154 women and 8 men)
87 patients had a BRCA2 mutation (77 women and 10 men)
59.4% of participants had a personal history of breast cancer
12 participants had a history of other malignancies
Median time from prior cancer diagnosis and genetic testing was 4.8 months (range: 0.1-39 months)

Incidence rates

- After genetic testing, 14 breast cancers and 7 ovarian/primary peritoneal/fallopian tube cancers were detected over a mean follow up of 24.8 months (range, 1.6-66 months); 2 breast and 2 ovarian cancers were found at time of surgery, 6 breast and 5 ovarian cancers were detected by radiographic or tumour marker based screening and 6 breast cancers were found by physical exam between

radiographic screening.

- There were 344 woman years of follow up for women who had not undergone bilateral mastectomy and had breast tissue at risk corresponding to a breast cancer incidence rate of 41 per 1,000 woman years (95% CI 20-62) for women with breast tissue at risk
- Incidence rate in women with no prior breast cancer history was 25.3 per 1000 woman years, 95% CI 0-51.
- Incidence rate for women with prior history of breast cancer was 53.0 per 1,000 woman years, 95% CI 22 to 86.
- There were 221 woman-years of follow up for women who had not undergone bilateral oophorectomy.
- Incidence of ovarian and related cancers was 32 per 1,000 woman years, 95% CI 9-55.

Risk Reducing Surgery

- 20/233 (8.6%) had previously undergone risk-reducing mastectomies and 19/233 had undergone bilateral mastectomies
- 194/233 women had breast tissue at risk at the time of receiving their genetic test results.
    - 14.9% underwent RRM at a median of 5.3 months (range: 0.1-34.8 months) after receiving test results
    - Women electing to undergo surgery were younger than those not (mean, 43 years versus 46.8 years, p=0.015)
    - Women electing to undergo surgery had a greater number of breast and ovarian malignancies in first and second degree relatives compared with women not opting for surgery (mean, 2.7 versus 2.1 cancers, p=0.046).

- 25/233 women had a personal history of ovarian cancer and 29/233 had undergone bilateral oophorectomy for benign gynaecological indications or risk reduction.
- 179/233 women had ovarian tissue at risk at the time of receiving test results
    - 50.3% (90/233) underwent risk reducing salpingo oophorectomy at a median of 3.4 months (range: 0.1-49.7 months) after receiving results (19% included hysterectomies and 81% were bilateral oophorectomy only)
    - Women electing for risk reducing oophorectomy were older than those opting not to undergo surgery (mean 47.3 years versus 41.6 years; p<0.001);
    - 64% (77/120) women older than 40 opted for RRSO compared with 22% (13/59) of younger women
    - Women electing to undergo RRSO were more likely to have had a prior breast cancer diagnosis (74.4% versus 49.4%, p=0.001).

Outcome of Cancer Surveillance

- Women opting not to undergo RRM were advised to clinical surveillance with monthly breast self examination, clinical breast exam 2-4 times a year and annual mammography. Some women also received screening ultrasound or MRI at the discretion of their treating physician.
- Mean follow up was 24.1 months (range, 1.6-66 months)
    - 7.3% (12/165 women were diagnosed with a new primary
    - In 6 women breast cancer was detected by radiographic surveillance at a mean of 20.2 months after BRCA results transmission
    - 2 non-invasive and 3 invasive cancers (all less than 2cm) were detected by mammography
    - One case of DCIS was identified on MRI in a woman in whom mammography and ultrasound

showed nothing of note.
    - A single lymph node metastasis was identified in a woman with a negative mammogram 16 months prior.
- Breast cancer was detected by physical examination in 6 women in the interval between radiographic screening
    - Interval cancers were detected at a mean of 10.1 months after receipt of genetic test results
    - Women with interval cancers were younger than those with screen detected disease (41.3 versus 56.7 years, p=0.048).
    - Self examination detected 5 palpable masses and physician examination detected 1. In 5 cases, last mammogram had been obtained within 6-10 months prior and in 1 case mammogram had been deferred due to pregnancy but last screen had been 1.5 years prior to diagnosis.
    - Pre-surgical imaging at the time of presentation showed radiographic abnormalities in 4/6 cases

- Women opting not to undergo RRSO were advised to undergo clinical surveillance with semi-annual transvaginal ultrasonography and CA-125 measurement.
- Mean follow-up was 17 months (range, 2.3-40.2 months)
    - 5.6% (5/89) of women who retained their ovaries were found to have ovarian or primary peritoneal cancer during surveillance
    - No cases of ovarian cancer were diagnosed in the intervals between radiographic screenings
    - Surgical exploration was prompted by an abnormal transvaginal ultra sonogram in 4/5 cases and by elevated CA-125 levels in 1/5 cases.
    - All women received chemotherapy with no evidence of gynaecological cancer at a mean follow-up of 18.4 months (range, 0.2-38.9 months).
    - Ovarian screening date was available for 84/89 women who did not undergo RRSO and who had ovarian tissue at risk and of these, 62 received ovarian surveillance.
    - 22/62 women recorded abnormal ultrasonograms or CA-125 measurements, 5 of whom were found to have ovarian or primary peritoneal cancer.
    - 5 patients with abnormal results underwent surgery and were found to have benign tumours
    - In 12 cases, follow-up ultrasonograms or CA-125 measurements normalised over time and no interventions were required.
    - Sensitivity of ovarian cancer screening by serial ultrasound and CA-125 measurements was 71% and specificity was 90.9%
    - A further 6 cancers were detected during follow-up.

Impact of counselling and testing on screening behaviour

For women who did not undergo risk reducing surgery before testing and who reported pre and post counselling screening frequency, there was an overall increase in mean number of mammograms and CA-125 determinations performed after genetic testing.

The effect of genetic testing on breast cancer screening was not statistically significant in the subset of patients with prior breast cancer.

On average, 15 months after BRCA risk notification, 83% of patients were performing breast self examinations compared with 77% at the time of initial visit (p=0.14).

Frequency of transvaginal ultrasound increased from one every 24 months to one every 9 months

CA-125 determination frequency increased from once every 2.8 years to once every 10.1 months.

In women with a history of breast cancer at the time of genetic testing, tamoxifen use was reported in 56 and raloxifene in 10.

In the 90 women with no prior history of breast cancer, 6 initiated tamoxifen and 3 started raloxifene after counselling.

In the 18 men in study, 6 had a prior history of breast cancer (all BRCA2 mutation carriers). 5/10 BRAC2 mutation carriers were participating in screening prior to genetic testing, rising to 8/10 following testing. 5 men reported tamoxifen use as part of breast cancer treatment.
General comments

Citation: Schwartz M et al (2004) Impact of BRCA1/BRCA2 counselling and testing on newly diagnosed breast cancer patients *Journal of Clinical Oncology* 22;10:1823-1829

Design: Case Series (appears prospective)

Country: USA

Setting: Treatment and follow-up

Aim: to evaluate the impact on surgical decision making of pre-treatment genetic counselling and BRCA1/2 testing among breast cancer patients at high risk for carrying a mutation

Inclusion criteria
Newly diagnosed breast cancer patients who were eligible for genetic testing and completed baseline assessment
Female
Not yet received definitive treatment (mastectomy or BCT)

Exclusion criteria
No details

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=194 (represents 85% of the eligible population)

Study Duration
No Details

Interventions
Genetic counselling and rapid genetic testing

Outcomes
Definitive Treatment Decisions

Predictors of Bilateral Mastectomy

Results
86% (167/194) of participants chose to receive BRCA1/2 results

Definitive Treatment Decisions
25% (n=49) of patients opted for immediate bilateral mastectomy
22% (n=43) undergoing unilateral mastectomy
53% (n=102) undergoing breast conserving therapy
Patients found to carry a BRCA1/2 mutation were significantly more likely to undergo bilateral mastectomy as compared with patients with uninformative results or women who opted not to be tested (48% versus 24% versus 4%; p<0.001).
In the 167 patients who underwent genetic testing, test results were significantly associated with definitive treatment (p=0.005).
23% of patients underwent genetic testing but went ahead with definitive treatment before receiving results.

Of the 77% of patients who waited for their test results before proceeding with surgery, surgical decision was significantly associated with test result (p=0.004) with 52% of patients receiving a positive result opting for bilateral mastectomy compared with 24% of patients with and uninformative result

Predictors of bilateral mastectomy

Among all patients opting for genetic testing, test result, number of affected first degree relatives, TNM system stage, physician BRCA1/2 testing recommendation and surgeon recommendation for bilateral mastectomy were all significant associated with the receipt of bilateral mastectomy.

Test Result: p=0.007

Number of affected first degree relatives: p=0.05

TNM stage: p=0.03

Physician BRCA1/2 testing recommendation: p<0.001

Surgeon recommendation: p<0.001

Logistic regression analysis showed that positive test results were associated with a 3 fold increase in the odds of receiving a bilateral mastectomy: OR=3.53; 95% CI, 1.43-8.69.

Recommendation for BRCA testing (OR=3.28, 95% CI, 1.34-8.03) and recommendation from surgeon to consider surgery (OR=5.15, 95% CI, 2.21-12.03) were also independently associated with increased odds of having bilateral mastectomy.

Number of first degree relatives with breast or ovarian cancer (p=0.02), ethnic background other than Askenazi Jewish (p=0.06), physician recommendations for BRCA1/2 testing (p<0.01) and surgical recommendation to consider bilateral mastectomy (p<0.01) were all significantly associated with bilateral mastectomy uptake in patients opting to undergo surgery before their test results were available.

General comments

Eligibility for genetic testing was determined by standard clinical criteria used by the Lombardi Comprehensive Cancer Centre Cancer Assessment and Risk Evaluation program

Citation: Brandberg Y et al (2012) Less correspondence before and cosmetic results after risk reducing mastectomy in women who are mutation carriers *European Journal of Surgical Oncology* 38;1:38-43

Design: Retrospective analysis

Country: Sweden

Setting: Follow up

Aim: to ascertain the level of satisfaction with various aspects of the cosmetic results at six and twelve months after risk reducing mastectomy and to assess whether there were any associations between ratings on 'correspondence between overall results and expectations before RRM and age, carrier status, salpingo oophorectomy before surgery, overall body image, sexual pleasure or discomfort.

Inclusion criteria
Consecutive women with a hereditary risk of breast cancer who underwent risk reducing mastectomy

Exclusion criteria
None given

Sample Size
No details

Randomisation Method
Not applicable

Population
N=100 patients underwent risk reducing mastectomy but 9 patients declined to partake leaving a total population of 91 women.

Study Duration
Surgery between October 1997 and December 2005
Follow-up questionnaire at 12 months so final data collection: December 2006

Interventions
Risk reducing mastectomy with immediate reconstruction

Outcomes
Satisfaction with cosmetic results and correspondence between overall results and expectations before risk reducing mastectomy
Association between 'correspondence between overall results and expectations before RRM' and age, carrier status, salpingo oophorectomy before RRM, body image and sexual pleasure and discomfort.

Results
36% of participants were BRCA1 carriers, 13% were BRCA2 carriers and it is not stated whether the remaining 51% of participants were non-carriers, had not undergone testing or a combination of both.

75% of women indicated that the overall results of the operation corresponded to a high degree with their expectations at six months, dropping to 71% at 12 months.
83-90% (n=58-70) of women reported satisfaction with breast size
51% (n=20) of women responding reported satisfaction with the softness of both breasts and 49% indicated that at least one breast was too hard. Of these 36% (n=14) women indicated that both breasts were too hard.
73% of women indicated that they had minor or no sensitivity in the breasts at both assessment points.

A higher proportion of mutation carriers gave negative responses compared with non carriers; adjusted OR=6.7, 95% CI, 1.1-40.1 (p=0.037).
General comments

5.5 Discussing the outcomes of genetic testing

5.5.1 Review Question

Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

5.5.2 Background

If the tailoring of risk reducing breast surgery and/or adjuvant therapy on the basis of BRCA mutation status results in improved outcomes for patients, then there may be an argument for recommending BRCA mutation testing of newly diagnosed breast cancer patients who reach the threshold for genetic testing.
The genetic testing of newly diagnosed breast cancer patients raises a number of practical and ethical issues, such as by whom, when and how this information should be raised with patients.
The existing NICE guideline (CG14) recommends that the discussion of genetic testing with patients should be undertaken by someone with appropriate training. In reality this usually means a genetics specialist (a genetics counsellor or clinical geneticist). It is recommended that pre-test counselling (preferably two sessions) is carried out prior to testing. If patients are to undergo and receive results of genetic tests within four weeks of diagnosis of breast cancer it may not be possible for all patients to be seen by a genetics specialist to discuss these results. In this situation the results of genetic testing could be discussed with patients by other appropriately trained members of the multidisciplinary team which could include the GP, surgical specialist, breast care nurse or oncologist. As well as being appropriately trained they would have to have adequate knowledge of how to interpret the results of the genetic test. It may be that discussion with different members of the multidisciplinary team leads to different understanding by patients and this may affect their decision making and outcome. If this is the case there could be an argument for recommending that a particular member of the team discuss the genetic results with the patient.

5.5.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients recently diagnosed with first breast cancer who meet the threshold for genetic testing without knowledge of their mutation status	Discussed with: • GP • Surgical Specialist • Genetic Specialist • Breast Care Nurse • Family history nurse • Oncologist	Each Other	• Dissemination of information to family members • Improved decision making (rate of uptake depending on who the discussion was with) • Patient understanding and comprehension • Patient satisfaction (surgical outcomes, satisfaction with treatment) • Family member's satisfaction

5.5.4 How the information will be searched

Can we apply date limits to the search	See section 5.4.5
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	See section 5.4.5 case studies, descriptive studies, normative papers
List useful search terms.	As in section 5.4.5 PLUS ethics ,ethical issues, families/family communication/dissemination, genetic counsellors/geneticists/oncologists/multi-disciplinary teams , breast care nurses ...duties of care, genetic counselling, qualitative, interviews, patient understanding written information/ counselling /counselling ....

If our original search finds nothing are we going to adjust the PICO and re-run the search? (Note: Due to time constraints, this is a situation we would make every effort to avoid and would only occur in exceptional circumstances)

5.5.5 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced. Extra Comment from GDG: I suspect most of this research will be qualitative although there are a couple of quant. papers from the Schwartz group in Georgetown and a couple of RCTs (one ongoing on the delivery of info/counselling in Australia. The other completed in Netherlands (Wevers et al, 2011))
List subgroups here and planned statistical analyses.	None of specific relevance to this topic
What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data

	relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	No details

5.5.6 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1996-current	521	65	27/03/2012
Premedline	1996-current	25	0	27/03/2012
Embase	1996-current	662	58	18/04/2012
Cochrane Library	1996-current	129	4	28/03/2012
Web of Science (SCI & SSCI) and ISI Proceedings	1996-current	807	98	18/04/2012
PsycInfo	1996-current	38	9	28/03/2012
CINAHL	1996-current	443	36	28/03/2012

Total References retrieved (after duplicates removed): 201

Medline search strategy for Part One *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.

22. or/9-21
23. 8 and 22
24. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
25. (primary or first or new).tw.
26. 24 and 25
27. 23 and 26
28. (mutation$ or BRCA1 or BRCA2 or TP53).tw.
29. (gene$ adj status).tw.
30. genes, brca1/ or genes, brca2/
31. brca1 protein/ or brca2 protein/
32. Tumor Suppressor Protein p53/
33. Genes, p53/
34. exp Mutation/
35. or/28-34
36. 27 and 35
37. exp Medical Staff/
38. exp Nurses/
39. exp Physicians/
40. exp Family/
41. Patient Care Team/
42. 37 or 38 or 39 or 40 or 41
43. (surgeon$ or specialist$ or doctor$ or physician$ or clinician$ or oncologist$ or MDT$ or nurse$ or health$ worker$ or health$ professional$ or general practioner$ or gp).tw.
44. (geneticist$ or counsel?or$).tw.
45. (famil$ or relati$).tw.
46. 43 or 44 or 45
47. 42 or 46
48. 36 and 47
49. Patient Education as Topic/
50. Attitude of Health Personnel/
51. Physician-Patient Relations/
52. Nurse-Patient Relations/
53. Patient Participation/
54. exp Patient Satisfaction/
55. Professional-Family Relations/
56. exp Decision Making/
57. exp Ethics, Medical/
58. (discuss$ or disseminat$ or inform$ or communicat$ or interview$ or counsel$ or talk$ or tell$ or decid$ or decision$ or written or document$).tw.
59. or/49-58
60. 48 and 59

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	01/02/2012-17/07/2012	15	2	18/07/2012

Premedline	01/02/2012-17/07/2012	25	8	18/07/2012
Embase	02/2012-07/2012	9	1	18/07/2012
PsycInfo	02/2012-07/2012	4	1	24/07/2012
Cochrane Library	02/2012-07/2012	20	1	23/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	02/2012-07/2012	42	7	23/07/2012
CINAHL	02/2012-07/2012	5	1	25/07/2012

Premedline: 1 new reference added 31/07/2012

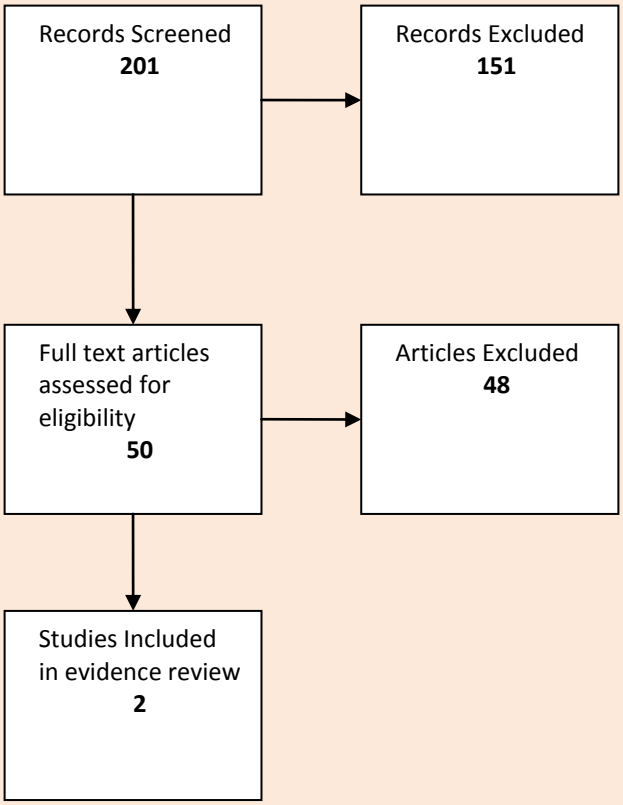
Premedline: 1 new reference added 05/09/2012

Premedline: 1 new reference added 06/09/2012

Embase: 1 new reference added 01/10/2012

Total references retrieved after duplicates removed: 27

5.5.7 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=1)
Qualitative Study (n=1)

Table 5.4: Characteristics of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Brown et al (2005)	Retrospective cross-sectional survey	N=551	To explore if women with early onset breast cancer are referred for BRCA1/2 genetic testing and how they respond to being offered testing and use the results.	Not applicable	Not applicable	RReferral to genetic counselling/testing Satisfaction with counselling/testing
Arden-Jones et al (2005)	Qualitative study	N=13 patients; 17 health professionals	To investigate whether women diagnosed with breast cancer under the age of 40 would want to be offered genetic testing close to the time of diagnosis. To explore whether health professionals treating these women support the idea of genetic testing at the time of breast cancer diagnosis.	Not applicable	Not applicable	Themes emerging from the focus groups and interviews

5.5.8 Evidence Statements

Low quality evidence (Brown et al, 2005; GRADE profile 1) suggests the majority of women are satisfied with the information they receive during counselling. In this study Satisfaction was highest among women who had been counselled by a genetics professional compared with a non-professional (98.5% versus 72.2%; p=0.0013).

One qualitative study exploring patient preference about which health professional they would like to discuss genetic testing with reported that the women agreed that how the information was delivered was very important and that they wanted someone who had time and was an expert in the field with the majority of women preferring the information to be presented by a member of the genetics team.

There was no evidence about the impact of who discusses genetic testing on the dissemination of information to family members, improved decision making or patient understanding.

5.5.9 Evidence Summaries

There was no good quality evidence with which to address this topic; apart from one low quality study exploring patient satisfaction, no available study directly investigated the outcomes of interest nor did any study include all the comparisons of interest (GRADE Profile 1).

One low quality cross-sectional survey study (Brown et al., 2005) of women diagnosed with breast cancer before the age of 45 years, found that 90/551 (37%) participants had undergone genetic testing. Of the 90 women who had genetic testing, 68 had been counselled by a genetic counsellor and 22 had been counselled by a physician, including medical oncologists (n=7), surgeons (n=8), primary care providers (n=3), gynaecologists (n=3), and a medical geneticist (n=1). A majority of women (92%) were very satisfied or satisfied with the information they received during counselling. Satisfaction was higher among women counselled by a genetics professional compared to a non-genetics professional (98.5% vs 72.7%, p=0.0013).

One qualitative study (Arden-Jones at el., 2005) explored patients' preferences about which health professional they would like to discuss genetic testing with. However, this referred to receiving information about genetic testing after a diagnosis of breast cancer, rather than the discussion of genetic test results. Women previously diagnosed with breast cancer who subsequently were found to be BRCA mutation carriers were asked for their opinions on genetic testing near the time of breast cancer diagnosis. The women agreed that how genetic information was delivered was very important. They wanted someone who had the time and was an expert in the field:

'If you had a surgeon who actually took out the time, and you know, you had that kind of relationship with...In the end, I think it's not so much who but certainly how the information is given.' (age 44, 2 primary breast cancers, had ovaries removed, planning on bilateral mastectomies)

The vast majority preferred genetic testing information to be presented by a member of the genetics team:

'I think the Genetics Department here, and I don't know whether it's the same elsewhere. You feel like it's a sisterhood. It makes you feel very comfortable and...you know that the information is accurate and I think that was very important, and that there's no rush.' (age 42, 1 breast cancer, planning to have bilateral prophylactic mastectomies).

The health professionals interviewed for this study generally agreed that the breast surgeons and perhaps the oncologists should initially raise the issue of genetic testing. While most of the professionals and the women were more comfortable with the genetics team handling the genetic aspects, there was a disparity of opinion between the breast surgeons. Two breast surgeons felt strongly that it was part of their responsibility to offer patients genetic information, and felt that they were capable of doing so. Others took the opposite position and felt that breast care nurses and surgeons could not fully answer patient's questions about genetics:

'...they should have the opportunity to discuss it with the genetics team. I don't think the standard breast care nurses or surgeons should do this because I don't think we would be able to answer the questions' (Breast surgeon).

One oncologist also agreed that genetic testing should be separate from the clinical side:

'I think that the way they are doing it is the right way...to see the counsellor and then offer them the test'

Several health professionals raised the issue of time constraints in the clinic environment. They felt that though breast surgeons do not have the time, the women have a right to know genetic testing is available. Information and leaflets about genetic testing should be part of the breast surgeon consultation, giving the women some time to think about it before being referred to genetics services:

'I think you should allow people to see a clinical geneticist or nurse counsellor...you're talking to surgeons and physicians who don't have that half an hour of time to spend with them talking about really sensitive issues, which demand time and pause and reflection (Medical Geneticist)

This qualitative study is limited by retrospective and hypothetical questions as participants were asked to say what they would have done if the option of genetic testing was available at the time of their breast cancer diagnosis. This is not necessarily indicative of what they would actually do in that situation. Indeed several women said it would be difficult to say what they would have done at the time.

GRDAE Profile 5.2: Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

Quality assessment							Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Patient satisfaction with counselling							
(Brown et al (2005)							
1	observational studies	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	VERY LOW
Patient Preference							
Arden-Jones et al (2005)							
1	observational study	serious[1]	no serious inconsistency	serious[4]	serious[3]	none	VERY LOW

[1] This was a retrospective survey study with patient reported outcomes, and is therefore prone to participant recall bias. There was a high risk of selection bias due to the population from which participants were recruited

[2] The average time passed since diagnosis was 2 years 11 months (Range = 1 – 81 months) which suggests many participants were recently diagnosed. However, there is no data about time between breast cancer diagnosis and referral to genetic counselling which limits the relevance of this study to the PICO.
[3] This study had a small sample size, of which only a minority actually received genetic testing (n=90), which reduces the precision of the data.[4]referred to receiving information about genetic testing after a diagnosis of breast cancer, rather than the discussion of genetic test results

5.5.10 Evidence Tables

Citation: Arden-Jones, A., et al. "Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40." European Journal of Cancer Care 14.3 (2005): 272-81.

Design: Retrospective qualitative study
Country: UK
Setting: Participants recruited from a major cancer hospital
Aim: To investigate whether women diagnosed with breast cancer under the age of 40 would want to be offered genetic testing close to the time of diagnosis. To explore whether health professionals treating these women support the idea of genetic testing at the time of breast cancer diagnosis.

Inclusion criteria

- Women who had been diagnosed with breast cancer under age 40 and who were identified as BRCA carriers.
- Health professionals who are involved in breast cancer care

Exclusion criteria: N/A

Sample Size: 13 women in total participated in one of three focus groups. 17 health professionals were interviewed.

Randomisation Method: N/A

Population: 13 women who had been diagnosed with breast cancer under age 40 and who were identified as BRCA carriers took part in a focus group. 8 carried a BRCA1 mutation, 5 carried a BRCA2 mutation, and 6 had also developed more than one breast cancer. Women were aged 39-49 years. All had partners, 11 had children. All were White and ranged from secretary to professional status.
Health professionals involved in breast cancer care – breast surgeons, oncologists, geneticists, breast care nurses and cancer genetic nurses were interviewed.

Study Duration: N/A

Interventions: Patients took part in a focus group to discuss their perceptions of what it might feel like to have a genetic test at the time of a breast cancer diagnosis. Health professionals took part in a brief interview to ascertain their opinions on the issue.

Outcomes: Themes identified from the focus group and interview data.

Results:

Focus groups

- *'Too much too soon'*

The majority of women stated that they could not have coped with a cancer diagnosis and a genetic diagnosis at the same time, but many gave varied responses. For example, one woman said she would have been able to cope with the idea of a genetic test if it had been offered after she had begun treatment.
'I felt at the time I was diagnosed that there was so much information...I think if they'd said at the end of it, 'And we're going to give you a genetics test', I'm afraid, I think it would have been just one bit of information too many for me in that particular circumstance.' (age 43, 2 primary breast cancers, no prophylactic surgery)

- *'No perfect time'*

There was no perfect time that the women felt genetic counselling and testing should be offered. The time after chemotherapy and radiotherapy were completed seemed best for some as they recalled that they were

still in the cancer diagnosis part of their lives and were more able to cope with genetic information at that point. They did not want to wait until later because it would bring back all the fear and anxiety and they wanted to go on with their normal lives.
'I think...after diagnosis and just after treatment. You know, that stage where you're making decisions. You're told that this is available if you want it.' (age 42, 2 primary breast cancers, had oopherectomy, considering bilateral prophylactic mastectomies)

All agreed that there was no right time for everyone and the right time was when the woman was ready. Many felt that being told that information about genetic testing was available if they wanted it was better than being offered a genetic test at the time of cancer diagnosis.

- *'Wanted to be tested immediately'*

One woman stated she wanted genetic testing immediately due to her strong family history of cancer and desire for prophylactic surgery. She was tested within a month of her breast cancer diagnosis and received her test results within 2 months.
'I felt the diagnosis (of BRCA1 gene carrier) *helped me to shorten the time span of complete treatment. You know, first surgery, chemo, mastectomy, and finished. You know all done and finished.'* (age 40, 1 primary breast cancer, had one breast removed with cancer and a prophylactic mastectomy on other breast).

Another woman for whom genetic testing wasn't available at the time of her diagnosis would have liked to undergone genetic testing at that time in order to make treatment decisions.
'I think I would have liked to have known straight away, because I think from a practical point of view I might have decided on a different option.' (age 42, 1 breast cancer, planning to have bilateral prophylactic mastectomies)

- *'Benefits of waiting'*

A few women highlighted the possibility of decision regret. The joint timing of genetic and cancer diagnosis could result in women making quick decisions which they may later regret. Decision making was often influenced by the meaning women attached to their breasts.
'If I had been given the gene diagnosis at the time of surgery, I would have had everything off. But now, even though I have had cancer twice...I am glad that I have my breasts...Somehow it matters much more now.' (age 42, 2 primary breast cancers, no prophylactic surgery)

- *'The delivery of genetic information'*

The women agreed that how genetic information was delivered was very important. They wanted someone who had the time and was an expert in the field.
'If you had a surgeon who actually took out the time, and you know, you had that kind of relationship with...In the end, I think it's not so much who but certainly how the information is given.' (age 44, 2 primary breast cancers, had ovaries removed, planning on bilateral mastectomies)

The vast majority preferred genetic testing information to be presented by a member of the genetics team.
'I think the Genetics Department here, and I don't know whether it's the same elsewhere. You feel like it's a sisterhood. It makes you feel very comfortable and...you know that the information is accurate and I think that was very important, and that there's no rush.' (age 42, 1 breast cancer, planning to have bilateral prophylactic mastectomies)

<u>Health professionals</u>

- *'Too much too soon'*

Like many of the other health professionals interviewed, one oncologist felt strongly about not adding to

women's burden by giving genetic information immediately after a cancer diagnosis.
'I would be very anti offering this right up front'

The professionals, like the women, could see the advantages of providing treatment options but expressed concern about emotional duress. Health professionals also expressed concern about women making decisions under stress, which they would then later regret.
'A potential problem might be, as far as I can see, the psychological stress for a woman who is trying to handle that issue at the same time, or very close to the time of diagnosis'. (Medical Geneticist).

'I can see the advantages in terms of giving them more options for treatment. But again some people are in such a state of shock that I suppose my worry would be that they make a decision then that they might later regret...as there's a sort of urgency that's perhaps generated by giving the two results together.' (Breast Surgeon).

- *'Value of early genetic testing'*

Several health professionals believed that offering genetic testing at the time of diagnosis would be the practice of the future if the early research were supported by new data. The value of testing was especially relevant in terms of predicting responses to certain drugs and informing treatment options.
'Genetics will, I suppose, more accurately be fingerprinted with microarrays particularly genotypes – not just the grade and things, but all the other things you're going to find with microarrays'. (Breast Surgeon).

- *'Who should give the genetic information'*

Health professionals generally agreed that the breast surgeons and perhaps the oncologists should initially raise the issue of genetic testing. While most of the professionals and the women were more comfortable with the genetics team handling the genetic aspects, there was a disparity of opinion between the breast surgeons. Two breast surgeons felt strongly that it was part of their responsibility to offer patients genetic information, and felt that they were capable of doing so. Others took the opposite position and felt that breast care nurses and surgeons could not fully answer patient's questions about genetics.
'...they should have the opportunity to discuss it with the genetics team. I don't think the standard breast care nurses or surgeons should do this because I don't think we would be able to answer the questions' (Breast surgeon).
One oncologist also agreed that genetic testing should be separate from the clinical side
'I think that the way they are doing it is the right way...to see the counsellor and then offer them the test'

Several health professionals raised the issue of time constraints in the clinic environment. They felt that though breast surgeons do not have the time, the women have a right to know genetic testing is available. Information and leaflets about genetic testing should be part of the breast surgeon consultation, giving the women some time to think about it before being referred to genetics services.
'I think you should allow people to see a clinical geneticist or nurse counsellor...you're talking to surgeons and physicians who don't have that half an hour of time to spend with them talking about really sensitive issues, which demand time and pause and reflection (Medical Geneticist)

- *'Money speaks'*

All participants responded in terms of expertise, time constraints, emotional overloads, and information processing. Only one professional bought up funding as a major factor. The medical geneticist pointed out that funding from the NHS would in reality determine whether the concept of genetic testing at the time of diagnosis would be more widely implemented.

General comments

Limited by retrospective and hypothetical questions - Participants were asked to say what they would have done if the option of genetic testing was available at the time of their breast cancer diagnosis. Indeed several women said it would be difficult to say what they would have done at the time.

The time participants received a cancer diagnosis to the time of genetic testing varied from 2 months to 10 years. Time also varied from the time of initial cancer diagnosis to the time of the focus group from 1 to 7 years.

Citation: Brown, K. L., et al. "Referral and experience with genetic testing among women with early onset breast cancer." Genetic Testing 9.4 (2005): 301-05.

Design: Retrospective cross-sectional survey
Country: USA
Setting: No details
Aim: To explore how women with early onset breast cancer respond to being offered BRCA1/2 testing and use the results of genetic testing

Inclusion criteria:

- Women diagnosed with breast cancer ≤ 45 years old

Exclusion criteria: No details

Sample Size: n=551

Randomisation Method: N/A

Population:. Average age of diagnosis was 33.5 years (Range 17-45 years). Average time passed since diagnosis = 2 years 11 months (Range 1 month – 9 years). 57% had at least one family member with breast and/or ovarian cancer.

Study Duration: No details

Interventions: Participants completed a web-based questionnaire

Outcomes:

- *Socio-demographics*
- *Medical and treatment history*
- *Referral to genetic testing*
- *Satisfaction with decision to undergo testing*

Results

Referral for genetic testing

- 44% had ever discussed genetic testing with their physician and/or been referred to a genetic counsellor (12% discussed genetic testing with physician, 32% had been referred to genetics).
- No significant difference in the rate of referral between those diagnosed aged before 35 years and those diagnosed between 35-45 years (46% vs 43%, p=0.432).
- No significant difference in referral rate between those diagnosed less than 1 year ago, versus 1 to 3 years ago, versus 3 to 5 years ago (48% vs 44% vs 45%, p=0.765).

Genetic testing process

- Of the women who had discussed testing and/or been referred, 37% (n=90) had undergone BRCA testing.
- Of the 90 women who had genetic testing, 68 had been counselled by a genetic counsellor and 22 had been counselled by a physician, including medical oncologist (n=7), surgeons (n=8), primary care providers (n=3), gynaecologist (n=3).
- A majority of women (92%) were very satisfied or satisfied with the information they received during counselling. Satisfaction was higher among women counselled by a genetics professional compared to a non-genetics professional (98.5% vs 72.7%, p=0.0013**).**
- 19 (20%) women had a BRCA1/2 mutation. Of these 74% (n=14) pursued prophylactic surgery: 7 had prophylactic mastectomy, 4 had prophylactic oopherectomy, 3 had both surgeries.
- Among women who had not been tested, 7.3% (n=34) had undergone prophylactic mastectomy.

- Of women who had undergone testing, 90% (n=83), including all those who had tested positive, had shared their test result with at least one member of their family.
- Overall 89% were very satisfied or satisfied with their decision to undergo testing.

General comments

Quality
Sample bias – Participants were affluent, educated women who were members of an advocacy organization for early onset breast cancer (Young Survival Coalition).

Recall bias from retrospective survey design.

No comparison between those counselled by physician or genetic counsellor except on satisfaction scores. No data about time between breast cancer diagnosis and referral to genetic counselling – limits utility of this study.

5.6 References (2004)

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5.7 References (2013)

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Reason: Not relevant to PICO

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Reason: Not relevant to PICO

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Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

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Reason: Not relevant to topic A – relates to genetic testing threshold rather than carrier probability

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Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

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Reason: Expert Review

Armstrong, K et al (2005) Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. *JAMA* 293;14:1729-1736.
Reason: Comparison not relevant to PICO

Armstrong, K et al (2003) Early adoption of BRCA1/2 testing: Who and why. *Genetics in Medicine*.5;2:92-98
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Armstrong, K et al (2000) Factors associated with decisions about clinical BRCA1/2 testing. *Cancer Epidemiology, Biomarkers & Prevention* 9;11:1251-1254
Reason: Not relevant to PICO carrier probability not a factor

Armstrong, K., et al. "Early adoption of BRCA1/2 testing: who and why." Genetics in Medicine 5.2 (2003): 92-98.
Reason: Not relevant to PICO

Balmana, J., et al. (2004) Genetic counseling program in familial breast cancer: analysis of its effectiveness, cost and cost-effectiveness ratio. *International Journal of Cancer* 112;4: 647-52.
Reason: Outcomes not relevant to PICO

Bakos, A. D et al (2008). BRCA mutation-negative women from hereditary breast and ovarian cancer families: a qualitative study of the BRCA-negative experience. *Health Expectations* 11;3:220-231
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Barcenas, C. H et al (2006) Assessing BRCA carrier probabilities in extended families. *Journal of Clinical Oncology* 24;3:354-360
Reason: *Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability*

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Reason: Cannot separate treatments

Beckmann, M. W et al (2007) Risk and risk assessment for breast cancer: molecular and clinical aspects. [Review] [46 refs]. *Maturitas* 57;1: 56-60
Reason: Expert Review

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Reason: Not relevant to PICO

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Reason: Abstract Only

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Reason: Not relevant to PICO

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Reason: unaffected population not relevant to PICO

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Reason: not relevant to PICO

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Reason: not relevant to PICO

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Reason: Not relevant to PICO

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Reason: Comparison not relevant to PICO

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Reason: No data on carrier probability

Broeks, A. (2007) Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. *Breast cancer research* : BCR 9;2:R26
Reason: Population not relevant to PICO

Campitelli, M. A et al (2011) Adherence to breast and ovarian cancer screening recommendations for female relatives from the Ontario site of the Breast Cancer Family Registry. *European Journal of Cancer Prevention* 20;6:492-500
Reason: Comparison not relevant to PICO

Costa S et al (2012) Evaluation of the program BRCAPRO in a breast cancer centre *European Journal of Cancer* 48;S52
Reason: Abstract Only

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Reason: No comparison group

Chabner, E. et al (1998) Family history and treatment outcome in young women after breast-conserving surgery and radiation therapy for early-stage breast cancer. *Journal of Clinical Oncology* 16;6:2045-2051.
Reason: Comparison not relevant to PICO

Chen, S. and Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. *Journal of Clinical Oncology* 25;11:1329-1333
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

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Reason: not relevant to PICO

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Reason: not relevant to PICO

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Reason:No threshold data

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Reason: Not relevant to PICO

Domchek, S. M et al (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 304:9:967-975
Reason: Not relevant to PICO

Eccles, D et al (2001) Familial breast cancer: an investigation into the outcome of treatment for early stage disease. *Familial Cancer* 1[2];65:72.
Reason: Comparison not relevant to PICO

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Reason: Consensus guidelines

Eccles, D., et al (2007) Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH): study protocol. *BMC Cancer* 7;160.
Reason: No results

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Reason: expert review

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Reason: *Expert Review*

Ertmanski, S et al (2009) Identification of patients at high risk of psychological distress after BRCA1 genetic testing. *Genetic Testing & Molecular Biomarkers* 13;3:325-330
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Euhus, D. M et al (2002). Pretest prediction of BRCA1 or BRCA2 mutation by risk counselors and the computer model BRCAPRO. *Journal of the National Cancer Institute* 94;11:844-851
Reason: Not relevant to PICO

Evans, D. G et al (2008) Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* 8;155
Reason: No carrier probability data

Evans, D. G et al (2009) Risk reducing mastectomy: outcomes in 10 European centres. *Journal of Medical Genetics* 46[4], 254-258.
Reason: Not relevant to PICO (unaffected women)

Evans, D. G et al (2009) Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. *Cancer Epidemiology, Biomarkers & Prevention* 18;8:2318-2324.
Reason: Not relevant to PICO (unaffected women)

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Reason: Does not compare methods

Fatouros, M et al (2008) Outcomes of breast cancer patients with and without BRCA1/2 mutations. *International Journal of Cancer* 122;8:1918-1919.
Reason: Abstract

Firth, C., et al. "Novel one-stop multidisciplinary follow-up clinic for BRCA1/2 carriers: patient satisfaction and decision making." Psycho-Oncology 20.12 (2011): 1301-08.
Reason: Not relevant to PICO

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Reason: conference abstract

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Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

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Reason: Comparison not relevant to PICO

Gadzicki, D et al (2011). Genetic testing for familial/hereditary breast cancer - Comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. *Journal of Community Genetics* 2;2:53-69
Reason: No relevant data

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Reason: Not relevant to PICO

Gilpin, C. A et al (2000) A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. *Clinical Genetics*.58;4:299-308
Reason: Not relevant to PICO

Goffin, J. R., et al (2003). Impact of germline BRCA1 mutations and overexpression of p53 on prognosis and response to treatment following breast carcinoma: 10-year follow up data. *Cancer* 97[3], 527-536. 1-2
Reason: Not relevant to PICO (population not relevant)

Goelen, G., et al. (1999)"Moral concerns of different types of patients in clinical BRCA1/2 gene mutation testing." *Journal of Clinical Oncology* 17.5: 1595-600.
Reason: not relevant to PICO

Gurmankin, A. D., et al.(2005) "Patients' resistance to risk information in genetic counseling for BRCA1/2." *Archives of Internal Medicine* 165.5: 523-29.
Reason: not relevant to PICO

Haffty, B. G., et al (2002). Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet* 359[9316], 1471-1477. 27-4.
Reason: Comparison not relevant to PICO

Hall, M. J. and Neugut, A. I. Review: only women with specific family histories should be referred for counseling or evaluation for BRCA breast and ovarian cancer susceptibility testing. *ACP Journal Club* 144;2:37
Reason: Abstract Only

Hallowell, N., Ardern-Jones, A., Eeles, R., Foster, C., Lucassen, A., Moynihan, C., and Watson, M. Men's decision-making about predictive BRCA1/2 testing: the role of family. [Review] [31 refs]. *Journal of Genetic Counseling* 14;3:207-217
Reason: *Not relevant to PICO*

Hallowell, N., et al. (2002) "Genetic testing for women previously diagnosed with breast/ovarian cancer: examining the impact of BRCA1 and BRCA2 mutation searching." *Genetic Testing* 6.2: 79-87.
Reason: not relevant to PICO

Hallowell, N., et al. (2003) "Balancing autonomy and responsibility: the ethics of generating and disclosing genetic information." *Journal of Medical Ethics* 29.2: 74-79.
Reason: Data not relevant to PICO

Hallowell, N. and N. Hallowell. (2004) "Accommodating risk: Responses to BRCA1/2 genetic testing of women who have had cancer. [References]." *Social Science & Medicine* .59.3.
Reason: Data not relevant to PICO

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Reason: comparisons not relevant to PICO

Hampel, H. (2009) "Recontacting patients who have tested negative for BRCA1 and BRCA2 mutations: how, who and why?" *Journal of Genetic Counseling* 18.6: 527-29.
Reason: expert commentary

Hampel, H et al (2004) Referral for cancer genetics consultation: A review and compilation of risk assessment criteria. *Journal of Medical Genetics*.41;2:81-91
Reason: No carrier probability data

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Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Heemskerk-Gerritsen, B et al (2010) Is risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer beneficial with respect to distant disease free survival and overall survival? *European Journal of Cancer, Supplement* Conference[var.pagings], 206
Reason: Abstract Only

Heisey, R. E., et al. (1999) Hereditary breast cancer: Identifying and managing BRCA1 and BRCA2 carriers. *Canadian Family Physician*.45;114-124
Reason: Expert Review

Hofferbert, S., et al. (2000) "Simultaneous interdisciplinary counseling in German breast/ovarian cancer families: First experiences with patient perceptions, surveillance behavior and acceptance of genetic testing." *Genetic Counseling* 11.2: 127-46.
Reason: not relevant to PICO

Holland, M. L., A. et l (2009). Cost-effectiveness of testing for breast cancer susceptibility genes. *Value in Health* 12;2: 207-16.

Reason: Expert Review

Holloway, S. M et al (2008). Uptake of testing for BRCA1/2 mutations in South East Scotland. *European Journal of Human Genetics*.16;8:906-912
Reason: Not relevant to current topic

Hoskins, K. F et al (2006) Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. *Cancer* 107;8:1769-1776
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Hutson, S. P. (2003) Attitudes and psychological impact of genetic testing, genetic counseling, and breast cancer risk assessment among women at increased risk. *Oncology nursing forum*.30;2:241-246
Reason: Expert Review

James, P. A et al (2006) Optimal selection of individuals for BRCA mutation testing: a comparison of available methods. *Journal of Clinical Oncology* 24;4:707-715
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Julian-Reynier, C., et al. (2000)"Disclosure to the family of breast/ovarian cancer genetic test results: patient's willingness and associated factors." *American Journal of Medical Genetics* 94.1: 13-18.
Reason: not relevant to PICO

Kang, H. H et al (2006) R. Evaluation of models to predict BRCA germline mutations. *British Journal of Cancer* 95;7:914-920
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Kauff, N. D et al (1999) BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast-conserving management in patients with BRCA1/BRCA2 mutations. *Journal of Clinical Oncology* 17;10:3017-3024
Reason: Not relevant to PICO

KENEN, R., et al. (2006)"Social separation" among women under 40 years of age diagnosed with breast cancer and carrying a BRCA1 or BRCA2 mutation." *Journal of Genetic Counseling* 15.3: 149-62.
Reason: not relevant to PICO

KENEN, R., et al. (2011) "Ownership of uncertainty: healthcare professionals counseling and treating women from hereditary breast and ovarian cancer families who receive an inconclusive BRCA1/2 genetic test result." *Genetic Testing & Molecular Biomarkers* 15.4: 243-50.
Reason: not relevant to PICO

Kilbride, K. (2010) Initial experience of a breast cancer risk assessment program in a community hospital. *Annals of Surgical Oncology.Conference: 11th Annual Meeting of the American Society of Breast Surgeons* (var.pagings).17;pp S178
Reason: Not relevant to PICO

Kirova, Y. M et al (2010) Is the breast-conserving treatment with radiotherapy appropriate in BRCA1/2 mutation carriers? Long-term results and review of the literature. [Review] [57 refs]. *Breast Cancer Research & Treatment* 120;1:119-126
Reason: Comparison not relevant to PICO

Kirova, Y. M et al (2005) Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. European *Journal of Cancer* 41[15], 2304-2311
Reason: Comparison not relevant to PICO

Kriege, M et al (2009) Sensitivity to first-line chemotherapy for metastatic breast cancer in BRCA1 and BRCA2 mutation carriers. *Journal of Clinical Oncology* 27;23:3764-3771.
Reason: Comparison not relevant to PICO

Kwon, J. S., et al. (2010) "Expanding the Criteria for BRCA Mutation Testing in Breast Cancer Survivors." *Journal of Clinical Oncology* 28.27: 4214-20.
Reason: not relevant to PICO

Kwon, J. S., et al (2008) Opportunities for future cancer prevention by BRCA mutation testing of women with ovarian cancer. *Gynecologic Oncology.Conference: 40th Annual Meeting of the Society of Gynecologic Oncologists San Antonio, TX United States*. 112; S98
Reason: Abstract Only

Lapointe, J. (2010) "Incidence and correlates of positive and negative effects of BRCA1/2 genetic testing on familial relationships: A three-year follow-up study." *Psycho-Oncology* Conference.var.pagings: May.
Reason: conference abstract

Langballe, R., et al (2011) Risk for second primary non-breast cancer in pre- and postmenopausal women with breast cancer not treated with chemotherapy, radiotherapy or endocrine therapy. *European Journal of Cancer* 47;6:946-952
Reason: Not relevant to PICO (population not relevant)

Lech, R. and Przemyslaw, O. Epidemiological models for breast cancer risk estimation. [Review]. *Ginekologia Polska* 82;6:451-454
Reason: Expert Review

Leeson, S et al (2001) Developing a cancer genetics service in Wales: opinions of gynaecologists on the management of women at risk of familial ovarian cancer. *European journal of cancer care*.10;3:172-178
Reason:No carrier probability data

Leonard, C. et al (2002) Lumpectomy and breast radiotherapy in breast cancer patients with a family history of breast cancer, ovarian cancer, or both. *Breast Journal* 8:3:154-161
Reason: No comparison

Lerman, C. (1996) "BRCA1 testing in families with hereditary breast-ovarian cancer: A prospective study of patient decision making and outcomes." *Journal of the American Medical Association* 275.24: 1885-92.
Reason: Unaffected participants – not relevant to PICO

Levy, D. E et al (2011) Underutilization of BRCA1/2 testing to guide breast cancer treatment: black and Hispanic women particularly at risk. *Genetics in Medicine* 13;4:349-355
Reason: No carrier probability data

Lizardnacol, S et al (1997) p53 gene alterations are associated with a decreased responsiveness to neoadjuvant chemotherapy in human breast cancer. International *Journal of Oncology* 10;6:1203-1207.
Reason: Population not relevant to PICO

Lobb, E. A., et al. (2010) "Treatment-focused DNA testing for newly diagnosed breast cancer patients: some implications for clinical practice." *Clinical Genetics* 77.4: 350-54.
Reason: outcomes not relevant to PICO

Lynch, Henry T., Watson, Patrice, Tinley, Susan, Snyder, Carrie, Durham, Carolyn, Lynch, Jane, Kirnarsky, Yulia, Serova, Olga, Lenoir, Gilbert, Lerman, Caryn, and Narod, Steven A. An Update on DNA-Based BRCA1/BRCA2 Genetic Counseling in Hereditary Breast Cancer. Cancer Genetics and Cytogenetics 109[2], 91-98. 1-3-1999.
Reason: not relevant to PICO

MacDonald, D. J et al (2007) Selection of family members for communication of cancer risk and barriers to this communication before and after genetic cancer risk assessment.[Erratum appears in Genet Med. 2007 Jul;9(7):483]. *Genetics in Medicine* ;5:275-282
Reason: Not relevant to current topic

Maheu, C et al (2011) French women breast self-examination practices over time following genetic testing for BRCA1/2. *Psycho-Oncology Conference[var.pagings],* 56-57.
Reason: Abstract Only

Maheu, C. and S. Thorne. (2008)"Receiving inconclusive genetic test results: an interpretive description of the BRCA1/2 experience." *Research in Nursing & Health* 31.6 (2008): 553-62.
Reason: not relevant to PICO

Marchina, E et al (2010) BRCA1 and BRCA2 genetic test in high risk patients and families: counselling and management. *Oncology Reports* 24;6:1661-1667
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

McQuirter, M et al (2010) Decision-making process of women carrying a BRCA1 or BRCA2 mutation who have chosen prophylactic mastectomy. *Oncology Nursing Forum* 37:3:313-320
Reason: Qualitative Study not reporting outcomes of interest

Meijers-Heijboer, H et al (2003) Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. *Journal of Clinical Oncology* 21;9:1675-168.
Reason: Not relevant to PICO

Meiser, B. (2010)"Acceptance, experiences and information preferences of young women newly diagnosed with breast cancer regarding treatment-focused genetic testing." *Twin Research and Human Genetics* Conference.var.pagings (2010): 654.
Reason: conference abstract

Meiser, B. and Halliday, J. L. (2002) What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer: a meta-analytic review (Provisional abstract). *Social*

Science and Medicine 54;1463-1470
Reason: Not relevant to PICO no carrier probability data

Mellon, S., et al. (2006) "Communication and decision-making about seeking inherited cancer risk information: findings from female survivor-relative focus groups." *Psycho-Oncology* 15.3: 193-208.
Reason: not relevant to PICO

Metcalfe, K et al (2010) Family history of cancer and cancer risks in women with BRCA1 or BRCA2 mutations. *Journal of the National Cancer Institute* 102;24:1874-1878
Reason: No carrier probability data

Metcalfe, K et al (2011) Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Research and Treatment* 127;1:287-296.
Reason: Not relevant to PICO

Metcalfe, K. A. (2004) Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Journal of Clinical Oncology* 22[12], 2328-2335.
Reason: Relevant population were excluded from the study

Metcalfe, K. A., et al (2005). The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. *Gynecologic Oncology* 96;1:222-226.
Reason: Cannot separate patients with and without a mutation

Metcalfe, K. A., et al. (2000) "An evaluation of needs of female BRCA1 and BRCA2 carriers undergoing genetic counselling." *Journal of Medical Genetics* 37.11: 866-74.
Reason: not relevant to PICO

Metcalfe, K et al (2010) Family history of cancer and cancer risks in women with BRCA1 or BRCA2 mutations. *Journal of the National Cancer Institute* 102;24:1874-1878
Reason: No carrier probability data

Morgan, D., et al. (2010)"Hereditary breast and ovarian cancer: referral source for genetic assessment and communication regarding assessment with nongenetic clinicians in the community setting." *Genetics in Medicine* 12.1: 25-31.
Reason: not relevant to PICO

Morgan, D., et al (2009). Cancer prevention and screening practices among women at risk for hereditary breast and ovarian cancer after genetic counseling in the community setting. *Familial Cancer* 8;4: 277-87.
Reason: Telephone Survey

Nelson, H. D et al (2005). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. [Review] [188 refs][Erratum appears in Ann Intern Med. 2005 Oct 4;143(7):547]. *Annals of Internal Medicine* 143;5:362-379
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Norquist, B et al (2011) Factors associated with genetic testing in BRCA1 and BRCA2 mutation carriers with advanced ovarian carcinoma. *Gynecologic Oncology Conference*[var.pagings], 2
Reason: Abstract Only

Oshima, K., et al (2011) Gene expression signature of TP53 but not its mutation status predicts response to sequential paclitaxel and 5-FU/epirubicin/cyclophosphamide in human breast cancer. *Cancer Letters* 307;2:149-157
Reason: Not relevant to PICO

Ozanne, E. M., et al.(2009) Identification and management of women at high risk for hereditary breast/ovarian cancer syndrome. *Breast Journal* 15;2: 155-62.
Reason: No Data

Palmero, E. I et al (2009) Population prevalence of hereditary breast cancer phenotypes and implementation of a genetic cancer risk assessment program in southern Brazil. *Genetics and Molecular Biology*.32;3:447-455
Reason: No carrier probability data

Panchal, S. M et al (2008) Selecting a BRCA risk assessment model for use in a familial cancer clinic. *BMC Medical Genetics* 9;116
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Parmigiani, G et al (2007) Validity of models for predicting BRCA1 and BRCA2 mutations. *Annals of Internal Medicine*.147;7:441-450)
Reason: Not relevant to PICO

Patenaude, A. F., et al. (2006) "Sharing BRCA1/2 test results with first-degree relatives: Factors predicting who women tell." *Journal of Clinical Oncology* 24.4: 700-06.
Reason: not relevant to PICO

Patel, A. N. G. (2010) Breast conservation therapy and brca status do not predict for poor outcomes in youngwomen with early-stage breast cancer. *International Journal of Radiation Oncology Biology Physics Conference*[var.pagings], S213.
Reason: Abstract Only

Petracci, E et al (2011) Risk factor modification and projections of absolute breast cancer risk. *Journal of the National Cancer Institute* 103;13:1037-1048
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Pierce, L. (2010) Local therapy options in BRCA1/2 carriers with operable breast cancer: The importance of adjuvant chemotherapy. *European Journal of Cancer*, Supplement Conference[var.pagings], 55
Reason: Abstract Only

Pierce, L. et al (2006). Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *Journal of Clinical Oncology* 24:16:2437-2443
Reason: Comparison not relevant to PICO

Plon, S. E et al (2011) Genetic testing and cancer risk management recommendations by physicians for at-risk relatives. *Genetics in Medicine* 13;2:148-154
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Quillin, J. M et al (2011) Genetic risk, perceived risk, and cancer worry in daughters of breast cancer patients. *Journal of Genetic Counseling* 20;2:157-164
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Rao, N. Y., et al.(2009) Evaluating the performance of models for predicting the BRCA germline mutations in Han Chinese familial breast cancer patients. *Breast Cancer Research & Treatment* 116;3: 563-70.
Reason:No threshold data

Rahko, E et al (2003) A mutant TP53 gene status is associated with a poor prognosis and anthracycline-resistance in breast cancer patients. *European Journal of Cancer* 39;4:447-453
Reason: Not relevant to PICO

Rolnick, S. J et al (2011) Barriers in Identification and Referral to Genetic Counseling for Familial Cancer Risk: The Perspective of Genetic Service Providers. *Journal of Genetic Counseling* 20;3:314-322
Reason: No carrier probability data

Rose, P. W et al (2001) Referral of patients with a family history of breast/ovarian cancer--GPs' knowledge and expectations. *Family Practice* 18;5:487-490
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Ruddy, K. J., et al.(2010) "Genetic testing in young women with breast cancer: results from a Web-based survey." *Annals of Oncology* 21.4: 741-47.
Reason: Not relevant to PICO.

Rueth, N. M et al (2011) Preoperative risk assessment among women undergoing bilateral prophylactic mastectomy for cancer risk reduction. *Annals of Surgical Oncology* 18;9:2515-2520
Reason: No carrier probability data

Sandhaus, L. M. S. (2001)"Reporting BRCA test results to primary care physicians." *Genetics in Medicine* 3.5: 327-34.
Reason: not relevant to PICO

Samphao, S et al (2009) Diagnosis of breast cancer in women age 40 and younger: delays in diagnosis result from underuse of genetic testing and breast imaging. *American Journal of Surgery* 198;4:538-543
Reason: No carrier probability data

Schlich-Bakker, K. J., H. F. ten Kroode, and M. G. Ausems. (2006) "A literature review of the psychological impact of genetic testing on breast cancer patients." *Patient Education and Counseling* 62.1: 13-20.
Reason: non systematic review

Schlich-Bakker, K. J., et al. (2007) "Barriers to participating in genetic counseling and BRCA testing during primary treatment for breast cancer." *Genetics in Medicine* 9.11 : 766-77.
Reason: intervention not relevant to PICO

Schlich-Bakker, K. J., et al. (2008) "BRCA1/2 mutation testing in breast cancer patients: a prospective study of the long-term psychological impact of approach during adjuvant radiotherapy." *Breast*

Cancer Research & Treatment 109.3: 507-14.
Reason: outcomes not relevant to PICO

Schneegans SM et al (2012) Validation of three BRCA 1/2 mutation-carrier probability models Myriad, BRCAPRO and BOADICEA in a population based series of 183 German families *Familial Cancer* 11;2:181-188
Reason: Outcomes not relevant to PICO

Schwartz, M. D et al (2009) Randomized trial of a decision aid for BRCA1/BRCA2 mutation carriers: impact on measures of decision making and satisfaction. *Health Psychology* 28;1:11-19
Reason: Not relevant to the current topic

Schlich-Bakker, K. J., et al. (2009) "Distress in couples approached for genetic counseling and BRCA1/2 testing during adjuvant radiotherapy." *Psycho-Oncology* 18.9: 965-73.
Reason: relates to same data as Schlich-Bakker 2006 plus data from partner of the participant.

Schwartz, M. D., et al. (2002) "Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample." *Journal of Clinical Oncology* 20.2: 514-20.
Reason: not relevant to PICO

Schwartz, M. D., et al. (2004) "Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients." *Journal of Clinical Oncology* 22.10: 1823-29.
Reason: Included in G1 – not relevant to G2

Schwartz, M. D., et al. (2005) "Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients." *Cancer Epidemiology, Biomarkers and Prevention* 14.4: 1003-07.
Reason: not relevant to PICO

Seynaeve, C et al (2010) activity of taxane chemotherapy for metastatic breast cancer (MBC) in BRCA1 and BRCA2 mutation carriers compared to sporadic breast cancer patients *Joural of Clinical Oncology* conference; var. pagings
Reason: Abstract Only

Seynaeve, C et al (2004) Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy. *European Journal of Cancer* 40;8:1150-1158.
Reason: Comparison not relevant to PICO

Shanley, S et al (2006) Acute chemotherapy-related toxicity is not increased in BRCA1 and BRCA2 mutation carriers treated for breast cancer in the United Kingdom. *Clinical Cancer Research* 12;23: 7033-7038
Reason: Comparison not relevant to PICO

Shanley, S et al (2006) Late toxicity is not increased in BRCA1/BRCA2 mutation carriers undergoing breast radiotherapy in the United Kingdom. *Clinical Cancer Research* 12;23:7025-7032
Reason: Comparison not relevant to PICO

Shannon, K. M et al (2002) Model-based predictions of BRCA1/2 mutation status in breast carcinoma patients treated at an academic medical center. Cancer 94;2:305-313
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Smith, A. W., et al. (2008)"Psychological distress and quality of life associated with genetic testing for breast cancer risk." *Psycho-Oncology* 17.8: 767-73.
Reason: not relevant to PICO

Spigel, D. R. (2004) "Early genetic counseling and testing for breast cancer patients and impact on surgical decision." *Journal of Clinical Outcomes Management* 11.7: 408-12.
Reason: commentary on Schwartz 2004

Stadler, Z. K. S. (2009) "Factors affecting surgical decision-making in patients undergoing BRCA1/2 testing at breast cancer diagnosis." *Cancer Research* Conference.var.pagings.
Reason: conference abstract

Tercyak, K. P et al (2007) Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. *Journal of Clinical Oncology* 25;3:285-291
Reason: Not relevant to PICO

Teller, P., et al.(2010) Validation of the pedigree assessment tool (PAT) in families with BRCA1 and BRCA2 mutations. *Annals of Surgical Oncology* 17;1: 240-46.
Reason:No threshold data

Tilburt, J. C et al (2011) Factors Influencing Cancer Risk Perception in High Risk Populations: A Systematic Review. *Hereditary Cancer in Clinical Practice* 9
Reason: No carrier probability data

Torrance, N., et al. (2006) "Genetic nurse counsellors can be an acceptable and cost-effective alternative to clinical geneticists for breast cancer risk genetic counselling. Evidence from two parallel randomised controlled equivalence trials." *British Journal of Cancer* 95.4: 435-44.
Reason: not relevant to PICO

Turner BC et al (1999) BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast conserving surgery *Journal of Clinical Oncology* 17;10:3017-3024
Reason: Not relevant to PICO

Walsh, T et al (2006) Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA* 295;12:1379-1388
Reason: Outcomes not relevant to PICO

Warner, E et al (1999) Hereditary breast cancer. Risk assessment of patients with a family history of breast cancer. *Canadian family physician Medecin de famille canadien*.45:104-112
Reason: No carrier probability data

Watson, M et al (1999) The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *British Journal of Cancer*.79;5-6:868-874
Reason: No carrier probability data

Weitzel, J. N et al (2003) Effect of Genetic Cancer Risk Assessment on Surgical Decisions at Breast Cancer Diagnosis. *Archives of Surgery* 138;12:1323-1329
Reason:Not relevant to current topic

White, D. B et al (2008). Too many referrals of low-risk women for BRCA1/2 genetic services by family physicians. *Cancer Epidemiology, Biomarkers & Prevention* 17;11:2980-2986
Reason:No carrier probability data

Williams, L et al (2008). Interactive patient decision aids for women facing genetic testing for familial breast cancer: a systematic web and literature review. [Review] [42 refs]. *Journal of Evaluation in Clinical Practice* 14;1:70-74
Reason: Not relevant to PICO, relates to information giving

Wilson, B. J., et al.(2005) Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions. *Health technology assessment (Winchester, England)*.9 ;3:1-126
Reason:No threshold data

Young, D et al (2006) Familial breast cancer: Management of 'lower risk' referrals. *British Journal of Cancer*.95;8:974-978
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

Vadaparampil, S. T., et al. "Experiences of genetic counseling for BRCA1/2 among recently diagnosed breast cancer patients: a qualitative inquiry." Journal of Psychosocial Oncology 26.4 (2008): 33-52.
Reason: intervention not relevant to PICO

van Harssel, J. J et al (2010). Efficiency of BRCAPRO and Myriad II mutation probability thresholds versus cancer history criteria alone for BRCA1/2 mutation detection. *Familial Cancer* 9;2:193-201
Reason: Not Relevant to PICO – relates to genetic testing threshold rather than carrier probability

van Riel, E., et al. (2010)"BRCA testing of breast cancer patients: medical specialists' referral patterns, knowledge and attitudes to genetic testing." *European Journal of Cancer Care* 19.3: 369-76.
Reason: Clinicians attitudes – outcomes not relevant to PICO

Veronesi, A. Familial breast cancer: Characteristics and outcome of BRCA 1-2 positive and negative cases. BMC Cancer 5 , 2005. Article Number, 70. 1970.
Reason: Outcomes not relevant to PICO

Vencken, P. (2011) Risk of primary (PBC) and contralateral (CBC) breast cancer after ovarian-cancer (OC) in BRCA1/2 mutation-carriers; is a prophylactic mastectomy justified? *International Journal of Gynecological Cancer Conference*[var.pagings], S87
Reason: Abstract Only

Vogl, F. D et al (2007) Risks of cancer due to a single BRCA1 mutation in an extended Utah kindred. *Familial Cancer* 6;1:63-71
Reason: No carrier probability data

Wevers, M. R., et al. (2011) "Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial." *BMC Cancer* 11: 6.
Reason: Article describes study protocol only – results of this trial may be relevant to guideline.

Wolpert, N., et al. (2000) "Prevalence of BRCA1 and BRCA2 mutations in male breast cancer patients in Canada... including commentary by Chappuis PO and Foulkes WD." *Clinical Breast Cancer* 1.1: 57-65.
Reason: not relevant to PICO

6 Surveillance and Strategies for Early Detection of Breast Cancer

6.1 Breast Awareness

No evidence was identified for the effectiveness of either clinical or self-breast examination as the sole screening modality in women with a family history of breast cancer and/or *BRCA*1/2 mutations.

A 2003 Cochrane Review which examined the evidence for regular self-examination or clinical examination for early detection of breast cancer (for women in general), concluded that trials did not suggest a beneficial effect of screening by breast examination, and may in some instances cause harm (Koster & Gotzsche 2003).

Furthermore, the Department of Health issued advice that clinical breast examination was not an appropriate screening technique in February 1998. The reference is PL/CMO/98/1.

6.1.1 Evidence Statement

There is a lack evidence for a high risk population that either clinical breast examination or self-examination is useful as the sole surveillance modality. (III)

6.2 Surveillance for women with no personal history of breast cancer

6.2.1 Review Question

What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?

6.2.2 Background

Women at increased risk of developing breast cancer due to their family history can opt to have their breasts removed or to have surveillance in order to detect a cancer when it is small and ideally before it has spread to other parts of the body. Population studies in women at normal risk of breast cancer have shown that early detection by mammography confers a survival advantage. This may also be the case for women at increased risk. There have been a number of international studies using MRI, Ultrasound, clinical breast examination and mammography which have shown that MRI is the most sensitive technique for detecting breast cancer especially in BRCA1 carriers. We do not know whether early detection in this high risk group confers a survival benefit. The risk of surveillance is that the test may be positive when no disease exists (false positive) resulting in additional tests being performed to confirm there is no disease as well as causing much worry for the woman. Some tests have higher false positive rates than others.
It is not known how often these surveillance tests should be carried out. Some researchers advocate every 6 months while most countries have suggested annually. It is not known at what age the tests should start and also at what age they should cease. Generally the tests begin 5 years before the youngest person in the family with breast cancer. Previously NICE has recommended stopping the test at 50 years. This may be too early for gene carriers. Some gene carriers opt to have their ovaries removed. This is known to reduce their risk of breast cancer by 50%. There may be other risk factors for developing breast cancer that have not been considered previously which add to the familial risk. No personal history means the woman has not had breast cancer.

6.2.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women with no personal history of breast cancer aged: 18-29 30-39 40-49 50-70 70+	Mammography • MRI • Ultrasound • Clinical Breast Examination • Any combination of tests at different timings and/or frequencies • No Screening	Each Other	• Sensitivity/Specificity/PPV /NPV in different age groups (versus histopathology or clinical follow-up)
Women with no personal history of breast cancer aged: 18-29 30-39 40-49	Mammography • MRI • Ultrasound • Clinical Breast Examination • Any combination of	Each Other	• Stage at Detection • Disease Specific Survival • Incidence of breast cancer • Incidence of Radiation Induced Cancer • Health Related Quality of

50-70 70+	tests at different timings and/or frequencies • No Screening		Life

6.2.4 Relative importance of these outcomes?

All outcomes were considered to be equally important for this topic. The topic was split into an A and B in order to allow for the evidence to be sifted for diagnostic studies to inform part A and clinical efficacy studies to inform part B.

6.2.5 How the information will be searched

What sources will be searched, e.g. will we look at Cinahl? (to be completed by reviewer/information specialist)

Are there any study design filters to be used (RCT, systematic review, diagnostic test).

Searches: *(To be Completed by subgroup lead)*	
Can we apply date limits to the search	2003
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filters applied
List useful search terms.	MRI, Breast cancer, mammography, familial risk, ultrasound, breast ultrasound, BRCA1 BRCA2, screening, surveillance, survival,

6.2.6 The review strategy

Any additional information to be added by subgroup lead

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced. Specific to this topic, there will be a single large search for this topic but the results will be sifted twice. First to identify and review diagnostic studies informing the sensitivity/specificity/PPV and NPV and secondly to identify and review clinical efficacy studies which will inform the second group of outcomes including disease specific survival, incidence of breast cancer etc.
List subgroups here and planned statistical analyses.	The subgroups for this topic are related to age and are outlined in the PICO table.

6.2.7 Search Results

Table: Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-current	1823	205	23/11/11
Premedline	2003-current	115	16	23/11/11
Embase	2003-current	4376	245	29/11/11
Cochrane Library	2003-current	48	10	29/11/11
Web of Science (SCI & SSCI) and ISI Proceedings	2003-current	3462	193	01/12/11

1 2001 study added 10/09/2012

Total References retrieved (after de-duplication): 401

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. exp Mammography/
25. (breast$ and screen$).ti.
26. (mammogra$ or echomammogra$).tw.
27. Ultrasonography, Mammary/
28. (ultraso$ or sonogra$ or echosonogra$).tw.
29. Magnetic Resonance Imaging/
30. "magnetic resonance imag$".tw.
31. MRI.tw.
32. ((non-invasive$ or noninvasive$) and (imag$ or diagnos$)).tw.
33. Mass Screening/
34. surveillance.tw.
35. Physical Examination/
36. Breast self-examination/
37. ("physical exam$" or "self exam$" or "self-exam$" or "clinical exam$" or "breast exam$").tw.
38. or/24-37
39. 23 and 38
40. limit 39 to yr="2003 -Current"

Notes:
A date limit of 2003 was applied.
No search filters were applied.

Update Searches

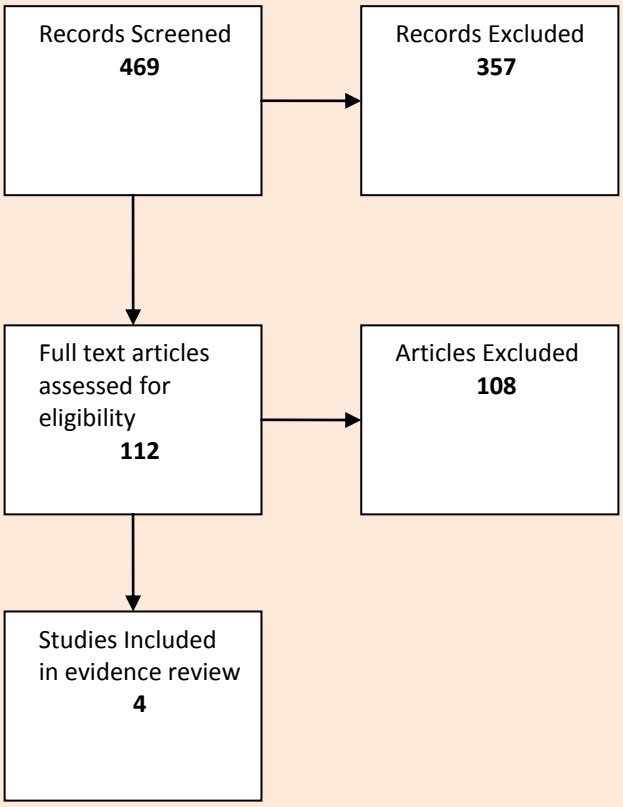
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	23/11/2011-17/07/2012	255	41	17/07/2012
Premedline	23/11/2011-17/07/2012	3	0	17/07/2012
Embase	11/2011-07/2012	121	22	17/07/2012
Cochrane Library	11/2011-07/2012	12	3	09/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	12/2011-07/2012	355	31	23/07/2012

Medline: 1 new references added 06/09/2012
Medline: 1 new reference added 10/09/2012
Embase: 1 new reference added 10/09/2012
Embase: 1 new reference added 17/09/2012
Embase: 1 new reference added 18/09/2012
Medline: 1 new reference added 24/09/2012

Total references retrieved after duplicates removed: 77

Part A – Diagnostic Outcomes

6.2.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=0)
Diagnostic Studies (n=3)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Qualitative Study (n=0)

6.2.9 Study Quality

Evidence about MRI, mammography, clinical breast examination and ultrasound for surveillance women at high familial risk of breast cancer or with a proven mutation was drawn from a systematic review (Warner et al, 2008) of 11 studies (Hagen et al., 2007; Hartman et al., 2004; Kriege et al., 2004; Kuhl et al., 2005; Leach et al., 2005; Lehman et al., 2005; Lehman et al., 2007; Sardanelli et al., 2007; Trecate et al., 2006; Warner et al., 2001; Warner et al., 2004) and three other studies (Riedl et al., 2007; Trop et al., 2010; Halapy et al., 2005).
Assessment of surveillance imaging was blinded in 12/14 of these studies; all were prospective. The MARIBS (Leach et al., 2005), MRISC (Kriege et al., 2004) and Halapy et al. (2005) studies excluded women with a personal history of breast cancer but approximately one third of those included in the other studies had a personal history of breast cancer. In all studies the reference standard for a positive surveillance test was biopsy and histopathology, for negative screening tests the reference standard was clinical and radiological follow up.

Table 6.1. Methodological quality of included studies

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?	Relevant clinical information?	Withdrawals explained?
MRISC trials (Kriege et al. 2003, 2004, 2006, 2006; Rijnsburger et al. 2007, 2010)*	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Kuhl et al. 2005*	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Leach et al (2005)* MARIBS	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Warner et al (2001)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Warner et al (2004)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Trecate et al (2006)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	?	Yes	Yes
Hartman et al (2004)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	?	Yes	Yes
Lehman et al (2005)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Lehman et al (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Sardinelli et al (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Hagen et al (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Riedl et al (2007)	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes

Trop et al (2010)	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Halapy et al 2005	No[a]	Yes[b]	Yes	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes

[a] Included only women over 50 years

[b] All breast cancers were histologically confirmed

[c] Only those screening positive received the reference test

* Included in Warner et al (2008) systematic review.

Table 6.2: Summary of Included Studies

Study	Country	Personal history of breast cancer	Age range (years)	Mutation carriers	Risk criteria (in those without proven mutation)	Index test	Comparator tests	Reference standard
Kuhl et al (2005)*	Germany	26%	≥ 30	8%	High familial risk (≥ 20% lifetime)	MRI	Mammography, US	Histopathology or for negative tests clinical / radiological follow-up
Kriege et al (2004)* MRISC	Netherlands	0%	19 to 72	19%	High familial risk (≥ 15% lifetime)	MRI	Mammography, US	Histopathology or for negative tests clinical / radiological follow-up
Leach et al (2005)* MARIBS	UK	0%	31 to 55	18%	High familial risk (≥ 0.9% annual)	MRI	Mammography	Histopathology or for negative tests clinical / radiological follow up
Warner et al (2001)*	Canada	28%	26 to 59	49%	High familial risk (≥ 25% lifetime)	MRI	CBE, US, mammography	Histopathology or for negative tests clinical / radiological follow up
Warner et al (2004)*	Canada	30%	26 to 65	100%	None	MRI	CBE, US, mammography	Histopathology or combination of other test results for negative tests
Trecate et al (2006)*	Italy	NR	23 to 81	NR	High familial risk (not specified)	MRI	CBE, US, mammography	Histopathology or for negative tests clinical / radiological follow up
Hartman et al (2004)*	USA	29%	≥ 25	59%	High familial risk (≥ 1% annual)	MRI	CBE, ductal lavage, mammography	Histopathology or for negative tests clinical / radiological follow up
Lehman et al (2005)*	USA, Canada	10%	≥ 25	NR	High familial risk (≥ 25% lifetime)	MRI	CBE, mammography	Histopathology or combination of other test results for negative tests
Lehman et al (2007)*	USA, Canada	NR	≥ 25	NR	High familial risk (≥ 20% lifetime)	MRI	CBE, mammography	Histopathology or combination of other

Study	Country	Personal history of breast cancer	Age range (years)	Mutation carriers	Risk criteria (in those without proven mutation)	Index test	Comparator tests	Reference standard
								test results for negative tests
Sardinelli et al (2007)*	Italy	44%	≥ 25	63%	High familial risk (not specified)	MRI	CBE, US, mammography	Histopathology or for negative tests clinical / radiological follow-up
Halapy et al (2005)	Canada	0%	50 to 69	NR	High familial risk (not specified)	Mammography	CBE	Histopathology or for negative tests clinical / radiological follow-up
Hagen et al (2007)*	Norway	NR	18 to 79	100%	None	MRI	mammography	Histopathology or for negative tests clinical / radiological follow-up
Riedl et al (2007)	Austria	28%	22 to 80	28%	Eligible for genetic testing (carrier probability NR)	MRI	US, mammography	Histopathology or for negative tests clinical / radiological follow-up
Trop et al (2010)	Canada	39%	21 to 75	78%	≥ 30% carrier probability	MRI	CBE, US, mammography	Histopathology or for negative tests clinical / radiological follow-up

Abbreviations: CBE, clinical breast examination; MRI, magnetic resonance imaging; NR, not reported; US, ultrasound.
* Included in Warner et al (2008) systematic review.

6.2.10 Evidence statements (Diagnostic Outcomes)

Moderate quality evidence suggests surveillance using MRI has better sensitivity for breast cancer than mammography, clinical breast examination or ultrasound. Surveillance with both MRI and mammography has better sensitivity than either test alone (Warner et al., 2008).
The Warner et al (2008) systematic review estimated breast cancer prevalence amongst high risk women undergoing surveillance as approximately 2%. Using their pooled sensitivities and specificities the results from 1000 combined MRI and mammography surveillance tests would include 17 true positives, 49 false positives, 931 true negatives and 3 false negatives.
Rijnsburger et al. (2010) analysed the relative sensitivity of mammography and MRI surveillance in three age groups: less than 40 years, 40 to 49 years and 50 or older. MRI had better sensitivity than mammography in all three groups: 61% versus 33%, 83% versus 39% and 67% versus 56% respectively.

Table 6.3: Diagnostic accuracy of surveillance mammography, MRI, ultrasound and clinical breast examination in women at high risk of breast cancer

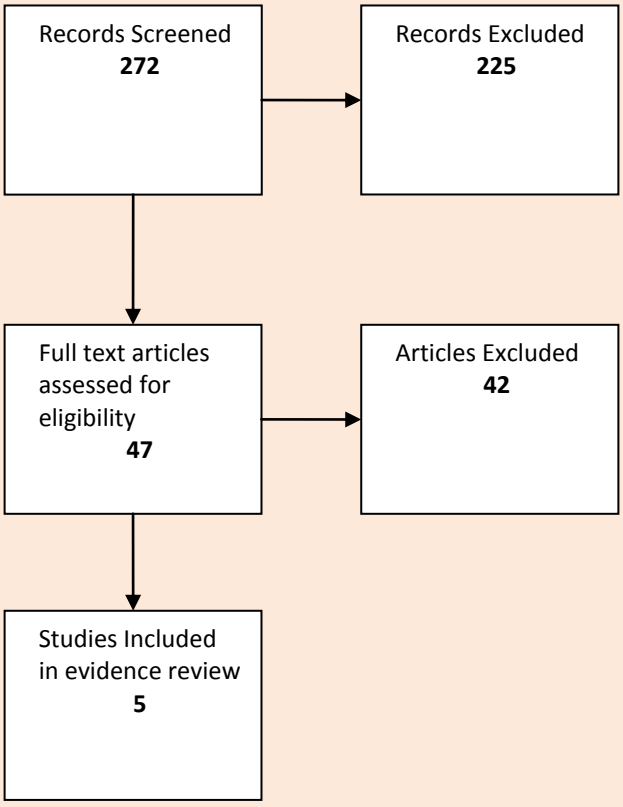
Test	Test threshold	Studies	Breast cancers diagnosed	Sensitivity	Specificity	PPV	NPV
Mammography	BI-RADS ≥ 3	(Kriege et al., 2004; Kriege et al., 2004; Leach et al., 2005; Lehman et al., 2007; Warner et al., 2004)	108 tumours / 6678 screens	39% (95% C.I. 37 to 41%)*	95% (95% C.I. 93 to 97%)*	15% (95% C.I. 8 to 26%)†	1.3% (95% C.I. 1.1 to 1.5%)†
Mammography	BI-RADS ≥ 4	(Kriege et al., 2004; Kuhl et al., 2005; Leach et al., 2005; Lehman et al., 2005; Sardanelli et al., 2007; Trecate et al., 2006; Warner et al., 2004)	178 tumours / 8818 screens	32% (95% C.I. 23 to 41%)*	99% (95% C.I. 98 to 99%)*	34% (95% C.I. 19 to 52%)†	1.4% (95% C.I. 1.2 to 1.6%)†
MRI	BI-RADS ≥ 3	(Hartman et al., 2004; Kriege et al., 2004; Leach et al., 2005; Lehman et al., 2007; Warner et al., 2004)	109 tumours / 6719 screens	77% (95% C.I. 70 to 84%)*	86% (95% C.I. 81 to 92%)*	8% (95% C.I. 6 to 11%)†	0.6% (95% C.I. 0.4 to 0.8%)†
MRI	BI-RADS ≥ 4	(Hartman et al., 2004; Kriege et al., 2004; Kuhl et al., 2005; Leach et al., 2005; Lehman et al., 2005; Sardanelli et al., 2007; Trecate et al., 2006; Warner et al., 2004)	178 tumours / 8857 screens	75% (95% C.I. 62 to 88%)*	96% (95% C.I. 95 to 97%)*	25% (95% C.I. 18 to 34%)†	0.4% (95% C.I. 0.2 to 0.9%)†
Mammography + MRI	BI-RADS ≥ 3	(Lehman et al., 2007; Warner et al., 2001; Warner et al., 2004)	63 tumours/ 2509 screens	94% (95% C.I. 90 to 97%)*	77% (95% C.I. 75 to 80%)*	8% (95% C.I. 7 to 9%)†	0.2% (95% C.I. 0.08 to 0.4%)†
Mammography + MRI	BI-RADS ≥ 4	(Kuhl et al., 2005; Leach et al., 2005; Lehman et al., 2007; Trecate et al., 2006; Warner et al., 2004)	115 tumours/ 4272 screens	84% (95% C.I. 70 to 97%)*	95% (95% C.I. 94 to 97%)*	25% (95% C.I. 18 to 33%)†	0.3% (95% C.I. 0.1 to 0.8%)†
Clinical Breast Examination	NR	(Halapy et al., 2005; Rijnsburger et al., 2010; Sardanelli et al., 2007; Trop et al., 2010; Warner et al., 2004)	157/12325 patients	9% to 50%	94% to 99%	4% to 81%	0.4% to 8.7%
Ultrasound	BI-RADS ≥ 4	(Riedl et al., 2007; Trecate et al., 2006; Trop et al., 2010; Warner et al., 2004)	116/2971 patients	32% to 60%	91% to 100%	10% to 100%	1.8% to 4.2%

Test	Test threshold	Studies	Breast cancers diagnosed	Sensitivity	Specificity	PPV	NPV
Mammography + Ultrasound	BI-RADS ≥ 4	(Kuhl et al., 2005)	43/529 patients	52%	89%	12%	1.4%

Abbreviations: BI-RADS, Breast Imaging, Reporting and Data System; NR, not reported; MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value.
*Results from separate univariate meta-analyses of sensitivity and specificity (Warner et al, 2008). †Assuming 2% pre-test probability of breast cancer (Warner et al, 2008).

Part B – Clinical Outcomes

6.2.11 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=3)
Qualitative Study (n=1)

6.2.12 Evidence statements (Clinical Outcomes)

Stage at Detection

Very low quality evidence from two studies suggests that invasive breast cancers diagnosed in mammography screened women aged 50 years or less with family history of breast cancer are significantly smaller than those diagnosed in unscreened women of similar age (Maurice et al 2006; Duffy et al, 2010). In these two studies 28 to 30% of invasive tumours diagnosed during screening were greater than 2 cm in diameter, this compared to 45 to 61% of tumours diagnosed in the unscreened comparison groups.

Very low quality evidence from two studies suggests women aged 50 or less with family history of breast cancer whose invasive breast cancer was diagnosed during screening were less likely to have positive nodes at diagnosis than unscreened women of similar age diagnosed with breast cancer (Maurice et al 2006; Duffy et al, 2010). In these two studies 32 to 34% women diagnosed with invasive breast cancer during screening had positive nodes, this compared to 47 to 53% of those diagnosed in the unscreened comparison groups.

Disease Specific Survival

Very low quality evidence suggests a disease specific survival benefit with mammographic surveillance in women aged less than 50 years with a family history of breast cancer.

In Maurice et al (2006) death from breast cancer was less likely in women aged less than 50 years with family history whose breast cancer was diagnosed during mammographic surveillance than in a control group of unscreened women of similar age who developed breast cancer (lead time adjusted HR 0.24 [95% CI 0.09 to 0.66]).

Duffy et al (2010) modelled death from breast cancer in a mammographic surveillance study in women with familial history aged less than 50 years and a control group from another study, using prognostic features at diagnosis and underlying risk. Projected ten year death from breast cancer was lower in the mammographic surveillance group than in the control group of unscreened women of similar age, RR 0.80 (95% CI 0.66 to 0.96).

In Maurice et al (2012) death from any cause was less likely in BRCA1/2 carriers aged between 28 and 77 years diagnosed with breast cancer during an intensive mammographic surveillance programme than in those diagnosed outside this programme (HR 0.44 [95% CI 0.25 to 0.77]). It was unclear, however, whether this estimate was adjusted for lead time bias.

Incidence of breast cancer, Incidence of Radiation Induced Breast Cancer

Low quality evidence, from case-control studies (Jansen et al, 2010), suggests that exposure to low dose radiation during screening mammography or chest X-ray is associated with an increased risk of breast cancer in women with a familial or genetic predisposition, OR 1.3 (95% C.I. 0.9 to 1.8). There was evidence of a dose-response relationship between low dose radiation and breast cancer in this population: exposure to low dose radiation before the age of 20 years (OR 2.0; 95% C.I. 1.3 to 3.1) and five or more exposures (OR 1.8; 95% C.I. 1.1 to 3.0).

Health Related Quality of Life (HRQOL)

Low quality evidence suggests that screening with biannual Clinical Breast Examination (CBE), annual mammography, annual Magnetic Resonance Imaging (MRI), and recommendations for monthly Breast Self-Examination (BSE) has no unfavourable impact on generic short-term HRQOL (Rijnsberger et al, 2004).

Rijnsberger et al (2004) recorded pain, discomfort and anxiety experienced by women at high risk of breast cancer during screening tests. The proportion of women who reported pain was 7%, 86% and 12% during CBE, mammography and MRI respectively; 9%, 69% and 45% of women experienced discomfort during CBE, mammography and MRI respectively; 22%, 28% and 37% of women experienced anxiety during CBE, mammography and MRI respectively.

GRADE Profile 6.1: what is the effectiveness of surveillance in women at increased risk of breast cancer but with no personal history

Quality assessment							No of patients		Effect		Qu
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surveillance mammography	No surveillance mammography	Relative (95% CI)	Absolute	
Size of tumour at diagnosis > 2cm (in women diagnosed with invasive breast cancer; Maurice et al 2006; Duffy et al, 2010)											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/130 (29.2%)	813/1531 (53.1%)	not pooled	not pooled	V L
Positive nodes at diagnosis (in women diagnosed with invasive breast cancer; Maurice et al 2006; Duffy et al, 2010).											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/123 (32.5%)	774/1521 (50.9%)	not pooled	not pooled	V L
Death from breast cancer (in women diagnosed with breast cancer, younger than 50 years; Maurice et al ,2006)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	4/62 (6.5%)	210/898 (23.4%)	HR 0.24 (0.09 to 0.66)	172 fewer per 1000 (from 73 more to 210 more)	V L
Death from any cause (in *BRCA1/2* carriers diagnosed with breast cancer within intensive versus population screening programmes; Maurice et al ,2012)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	4/45 (8.8%)	N.R./466	HR 0.44 (0.25 to 0.77)	NR	V L
Projected ten year breast cancer mortality (FH01 - Duffy et al, 2010)											
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	73/6710 (1.1%)	1461/106971 (1.4%)	RR 0.80 (0.66 to 0.96)	3 fewer per 1000 (from 1 fewer to 5 fewer)[3]	V L
Breast cancer following exposure to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposition (Jansen et al, 201											
7	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	5132 cases 11592 controls		OR 1.3 (0.9 to 1.8)	-	LO

Quality assessment							No of patients		Effect		Qu
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surveillance mammography	No surveillance mammography	Relative (95% CI)	Absolute	
Breast cancer following exposure before 20 years of age to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposi (Jansen et al, 2010)											
2	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	-[6]		OR 2.0 (1.3 to 3.1)	-	LO
Breast cancer following 5 or more exposures to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposition (Janse al, 2010)											
4	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	-[6]		OR 1.8 (1.1 to 3.0)	-	LO
Health related quality of life (Rijnsberger et al, 2004)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	334 women were screened (CBE, mammography and MRI) and their scores compared to a reference value from general population.		-	-	LO

[1] The screened and unscreened cohorts were drawn from different sources - so factors other than screening may contribute to differences in outcome.
[2] Survival outcomes were not measured directly but predicted using prognostic models.
[3] Duffey et al (2010) estimate that for every 10,000 screens (1000 women screened for ten years) there would be 2 breast cancer deaths prevented.
[4] Considerable heterogenity - one study (Andrieu et al 2006) reported a much greater effect size than the others.
[5] Some evidence of a dose-response effect - younger age at first exposure and 5 or more exposures to radiation had a greater odds ratio for breast cancer.
[6] total number of women in this subgroup not reported

6.2.13 Evidence tables

Part A

Citation: **MRISC (2010):** Kriege, M., et al. "Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition." Cancer 106.11 (2006a): 2318-26; Kriege, M., et al. "Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition." New England Journal of Medicine 351.5 (2004): 427-37; Kriege, M., et al. "MRI screening for breast cancer in women with high familial and genetic risk: First results of the Dutch MRI screening study (MRISC)." Journal of Clinical Oncology 21.23 (2003): 238S; Rijnsburger, A. J., et al. "BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study." Journal of Clinical Oncology 28.36 (2010): 5265-73. Kriege, M., et al. "Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer." Breast Cancer Research & Treatment 100.1 (2006b): 109-19. Rijnsburger, A. J., et al. "BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study." Journal of Clinical Oncology 28.36 (2010): 5265-73. Kriege, M., et al. "MRI screening for breast cancer in women with high familial and genetic risk: First results of the Dutch MRI screening study (MRISC)." Journal of Clinical Oncology 21.23 (2003): 238S.

Design: Prospective Cohort study
Country: The Netherlands
Aim: To determine whether previously reported increased diagnostic accuracy of magnetic resonance imaging (MRI) compared with mammography would be maintained during subsequent screening rounds.

Inclusion criteria

- Cumulative lifetime risk of breast cancer ≥ 15% because of a genetic or familial risk of breast cancer according to the tables of Claus
- Aged 25 – 70
- Women younger than 25 were included if they had a family history of breast cancer diagnosed before age 30
- Written informed consent

Exclusion criteria

- Symptoms suggestive of breast cancer
- Personal history of breast cancer

Population
2157 women with a genetic breast cancer risk enrolled between November 1999 and March 2006

Interventions

1) Annual mammography
2) Annual MRI

(Additional) Clinical Breast Examination (CBE) every 6 months

Outcomes
Sensitivity, specificity, positive predictive value

Results

Clinical Breast Examination

	Breast cancer +	Breast cancer -	
CBE +	**14**	**122**	136
CBE -	**54**	**5688**	5742
	68	5810	5878

Sensitivity: 20.6
Specificity: 97.9
Positive predictive value: 10.3
Negative predictive value: 99.1

Mammography

	Breast cancer +	Breast cancer -	
Mammography +	31	334	365
Mammography -	44	5844	5888
	75	6178	6253

Sensitivity: 41.3
Specificity: 94.6
Positive predictive value: 8.5
Negative predictive value: 99.3

MRI

	Breast cancer +	Breast cancer -	
MRI +	53	639	692
MRI -	22	5539	5561
	75	6178	6253

Sensitivity: 70.7
Specificity: 89.7
Positive predictive value: 7.7
Negative predictive value: 99.6

Age related sub-group analyse s

Mammography

	Sensitivity
>50	55.6
40-49	38.9
<40	33.3

MRI

	Sensitivity
>50	66.7

40-49	83.3
<40	61.1

General comments

- Data from the MRISC study
- Data was extracted from the most recent publication. Methodological details were taken from earlier publications. All publications were scrutinised for relevant sub-group analyses
- Patient flow and reasons for drop-out were fully reported
- Image assessments were blinded and scored according to BI-RADS classification
- Results according to screening round were presented by Kriege at al. 2006a; results according to risk group (moderate vs. high vs. mutation carriers) were presented by Kriege et al. 2004; Results according to whether the individual had a BRCA 1 vs. 2 mutation were presented by Rijnsburger et al. 2010; results according to age were presented by Kriege et al 2006b

References of Included Studies (For systematic reviews): Not applicable

Citation: Kuhl, C. K., et al. "Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer." Journal of Clinical Oncology 23.33 (2005): 8469-76

Design: Prospective cohort study
Country: Germany
Aim: To compare the effectiveness of mammography, breast ultrasound, and magnetic resonance imaging (MRI) for surveillance of women at increased familial risk for breast cancer (lifetime risk of 20% or more).

Inclusion criteria

- Clinically asymptomatic
- Met the criteria for high familial risk as defined by the Consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid, corresponding to a lifetime risk for breast cancer of at least 20% (families with two or more cases of breast cancer on the same side of the family, including at least two cases with onset before age 50 years, or with breast and ovarian cancer, irrespective of age; families with three or more cases of breast cancer on the same side of the family; families with at least one case of breast cancer diagnosed before age 35 years; and families with at least one case of male breast cancer)

Exclusion criteria

- Women with current clinical signs or symptoms of breast cancer
- Women who had undergone bilateral mastectomy
- Women who were diagnosed with metastatic disease

Population
529 asymptomatic women who met criteria for high familial risk. 390 had no personal history of breast cancer. Surveillance started at age 30 years or 5 years before the youngest family member affected with the disease; no upper age limit was defined

Interventions

- Mammography, ultrasound, MRI

Outcomes

- Sensitivity, specificity, positive predictive value

Results (for the sub-group of women with no personal history of breast cancer)

Mammography

	Breast cancer +	Breast cancer -	
Mammography +	**10**	**33**	43
Mammography -	**21**	**1112**	1133
	31	1145	1176

Sensitivity: 32.3
Specificity: 97.1
Positive predictive value: 23.3

Negative predictive value: 98.1

Ultrasound

	Breast cancer +	Breast cancer -	
US +	**12**	**103**	115
US -	**19**	**1042**	1061
	31	1145	1176

Sensitivity: 38.7
Specificity: 91
Positive predictive value: 10.4
Negative predictive value: 98.2

Mammography + ultrasound

	Breast cancer +	Breast cancer -	
Mammography & US +	**16**	**121**	137
Mammography & US -	**15**	**1024**	1039
	31	1145	1176

Sensitivity: 51.6
Specificity: 89.4
Positive predictive value: 11.7
Negative predictive value: 98.5

MRI

	Breast cancer +	Breast cancer -	
MRI +	**31**	**29**	60
MRI -	**0**	**1116**	1116
	31	1145	1176

Sensitivity: 100
Specificity: 97.5
Positive predictive value: 51.7
Negative predictive value: 100

Mammography + MRI

	Breast cancer	Breast cancer	

	+	-	
Mammography & MRI +	**31**	**42**	73
Mammography & MRI -	**0**	**1103**	1103
	31	1145	1176

Sensitivity: 100
Specificity: 96.3
Positive predictive value: 42.5
Negative predictive value: 100

General comments

- Additional ultrasonography and CBE
- In the first 2 years of the study, no mammogram was obtained in women younger than 30 years; similarly, in young women aged 30 to 39 years, no mammogram was obtained in the second surveillance round if the breast tissue had been dense at the baseline mammogram.
- Image assessments were blinded
- The authors concluded that mammography alone, and combined with breast ultrasound, seemed insufficient for early diagnosis of breast cancer in women at increased familial risk with or without documented *BRCA* mutation. If MRI is used for surveillance, diagnosis of intra-ductal and invasive familial or hereditary cancer is achieved with a significantly higher sensitivity and at a more favourable stage.

References of Included Studies (For systematic reviews): Not applicable

Citation: Leach, M. O., et al. "Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)." Lancet 365.9473 (2005): 1769-78.

Design: Prospective cohort study
Country: United Kingdom
Aim: To compare contrast enhanced magnetic resonance imaging (CEMRI) with mammography for screening

Inclusion criteria

- Aged 35–49 years
- Known carriers of a deleterious *BRCA1, BRCA2*, or *TP53* mutation (the latter were screened from age 25 years); they were a first degree relative of someone with a *BRCA1, BRCA2*, or *TP53* mutation; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome. The aim was to include women whose affected first degree relative(s) had at least a 60% chance of being a *BRCA1* or *BRCA2* mutation carrier, or women with an annual risk of breast cancer of at least 0·9%.

Exclusion criteria

- Symptoms indicative of breast cancer

Population
649 women aged 31–55 years (median 40) with a strong family history of breast cancer or a high probability of a *BRCA1*, *BRCA2*, or *TP53* mutation enrolled between August 1997 and May 2003

Interventions
Contrast enhanced MRI, mammography

Outcomes
Sensitivity, specificity, positive predictive value

Results

Contrast enhanced MRI

	Breast cancer +	Breast cancer -	
Mammography & MRI +	**27**	**344**	371
Mammography & MRI -	**8**	**1502**	1510
	35	1846	1881

Sensitivity: 77
Specificity: 81
Positive predictive value: 7
Negative predictive value: 99

Mammography

	Breast cancer +	Breast cancer -	
Mammography +	**14**	**121**	135
Mammography -	**21**	**1782**	1803
	35	1903	1938

Sensitivity: 40
Specificity: 93
Positive predictive value: 10
Negative predictive value: 99

General comments

- Image assessments were blinded
- There were no sub-group analyses of different age groups
- The authors concluded that CE MRI was more sensitive than mammography for cancer detection. Specificity for both procedures was acceptable. Annual screening, combining CE MRI and mammography was said to detect most tumours in this risk group.

References of Included Studies (For systematic reviews): Not applicable

Citation: Halapy, E., et al. "Accuracy of breast screening among women with and without a family history of breast and/or ovarian cancer." Breast Cancer Research & Treatment 90.3 (2005): 299-305.

Design: Prospective cohort study
Country: Canada
Aim: To compare interval cancer rates, sensitivity and specificity of breast cancer screening between women with moderate and strong family history and women without family history

Inclusion criteria

- Women considered to be at high risk of breast cancer due to factors such as having a family history of breast cancer (detailed criteria presented in an earlier publication)
- Residents of Ontario
- Age 50 or over

Exclusion criteria

- History of breast cancer
- Augmentation mammoplasty
- Acute breast cancer symptoms

Population
115460 women aged 50-69. 5788 women had a strong family history of breast cancer.

Interventions
Mammography, CBE

Outcomes
Sensitivity, specificity, positive predictive value

Results

Mammography

	Breast cancer +	Breast cancer -	
Mammography +	**29**	**320**	349
Mammography -	**9**	**5430**	5439
	38	5750	5788

Sensitivity: 76.3
Specificity: 94.6
Positive predictive value:
Negative predictive value:

CBE

	Breast cancer +	Breast cancer -	
CBE +	**15**	**343**	358

CBE -	**22**	**5369**	5391
	37	5712	5749

Sensitivity: 40.5
Specificity: 94
Positive predictive value:
Negative predictive value:

General comments

- Women who had only CBE were excluded
- Only the first screen was included for women screened twice during the two year study period

References of Included Studies (For systematic reviews): Not applicable

Citation: Riedl, C. C., et al. "Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer." Clinical Cancer Research 13.20 (2007): 6144-52.

Design: Prospective diagnostic accuracy study

Country: Austria

Study period: 1999 to 2006

Aim: To assess diagnostic accuracy of mammography, ultrasound and magnetic resonance imaging during annual surveillance of women at high risk of breast cancer.

Inclusion criteria
Women with proven BRCA1 or BRCA2 mutation, or those whose carrier probability was high enough to qualify for genetic testing at the study institution (probability threshold not reported but it was calculated using a modified Claus model).

Exclusion criteria
Pregnancy, or breast feeding. Confirmed non-carriers in a family with a proven mutation. Women who had bilateral mastectomy, women with metastatic disease, those with pacemakers. Women with clinical signs of breast cancer at their first visit were excluded until one year after treatment.

Population
327 women (93 with proven BRCA mutations). Age ranged from 22 to 80 years (mean 41 years). 91/327 (28%) of the women had a personal history of breast cancer. Women were observed for 1 to 7 years resulting in a total of 696 annual surveillance rounds (average of 2 screening rounds per patient).

Index and comparator tests Mammography, MRI and ultrasound. Tests were interpreted blind to other results. BI-RADS ≥ 4 was the threshold for a positive test (leading to biopsy).

Reference standard tests
Reference standard for BI-RADS ≥ 4 test results was biopsy and histopathology. For BI-RADS 3 results it was increased clinical/radiological follow up, for BI-RADS <3 it was normal clinical/radiological follow up.

Outcomes
Sensitivity, specificity

Results
Imaging tests were positive (BI-RADS ≥ 4) in 136 cases, the histopathology in these cases was 71 benign, 39 atypical ductal hyperplasia, 11 DCIS and 15 invasive cancer.

Mammography (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer +	Breast cancer -	
Mammography +	**12**	**17**	29
Mammography -	**12**	**631**	643
	24	648	672

Sn 50%, Sp 97%

Ultrasound (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer	Breast cancer	

	+	-	
US +	**10**	**20**	30
US -	**14**	**628**	642
	24	648	672

Sn 42%, 97%

MRI (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer +	Breast cancer -	
MRI +	**20**	**79**	99
MRI-	**4**	**569**	573
	24	648	672

Sn 86%, Sp 88%

General comments No adjustment made for multiple tests (average of 2) from the same patients included in analysis.

Citation: Trop, I., et al. "Multimodality breast cancer screening in women with a familial or genetic predisposition." Current Oncology 17.3 (2010): 28-36.

Design: Prospective diagnostic accuracy study
Country: Canada
Study period 2003 to 2007
Aim: To evalutate the diagnostic accuracy of mammography, ultrasonography and MRI as screening tests in women at high risk of breast cancer

Inclusion criteria Women with proven BRCA1 or BRCA2 mutations, or with at least a 30% carrier probability as calculated by BRCAPRO.

Exclusion criteria Prophylactic mastectomy, pregnant or lactating, allergy to gadolinium or contraindication for MRI.

Population 184 participants underwent 1 to 3 yearly screening rounds. Age ranged from 21 to 75 years (median 45 years). 71/184 (39%) had a personal history of breast cancer. 143/184 (78%) had BRCA1 or BRCA2 mutation.

Index and comparator tests Mammography, MRI and ultrasound. Tests were interpreted blind to other results. BI-RADS ≥ 4 was the threshold for a positive test (leading to biopsy).

Reference standard tests
Reference standard for BI-RADS ≥ 4 test results was biopsy and histopathology. For BI-RADS 3 results it was increased clinical/radiological follow up, for BI-RADS <3 it was normal clinical/radiological follow up.

Outcomes Sensitivity, Specificity

Results
Overall 12 cancers (DCIS or invasive cancer) were detected in the 184 participants.

Mammography (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer +	Breast cancer -	
Mammography +	**7**	**NR**	
Mammography -	**5**	**NR**	
	12		

Sn 58%, Sp 95%

Ultrasound (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer +	Breast cancer -	
US +	**5**	**NR**	
US -	**7**	**NR**	
	12		

Sn 42%, Sp 94%

MRI (BI-RADS ≥ 4) for DCIS or Invasive cancer

	Breast cancer +	Breast cancer -	
MRI +	**10**	**NR**	
MRI-	**2**	**NR**	
	12		

Sn 83%, Sp 84%

General comments

Citation: Warner, E., et al. "Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. [Review] [35 refs]." Annals of Internal Medicine 148.9 (2008): 671-79.

Design: Systematic review
Country: NA
Aim: To summarize the diagnostic accuracy and post-test probabilities associated with adding MRI to annual mammography screening of women at very high risk of breast cancer.

Inclusion criteria Prospective studies published after 1994 in which MRI and mammography were used to screen women at very high risk of breast cancer. English language publications only. Searches were done to September 2007.

Exclusion criteria Non-peer reviewed publications, studies which did not report sensitivity, specificity, PPV, NPV, tumour stage or survival.

Population
Women at high risk of breast cancer defined as having a known BRCA1 or BRCA2 mutation, or another gene associated with hereditary breast cancer; being an untested first-degree relative of a person with such a mutation; or having a family history consistent with hereditary breast cancer syndrome, atypical or lobular carcinoma in situ on previous biopsy or radiation therapy to the chest (before age 30 and at least 8 years previously).
Two studies (Kriege et al, 2004; Leach et al, 2005) included only women without a personal history of breast cancer. Approximately one third of the women in the remaining studies had a personal history of breast cancer.

Interventions Index tests were screening mammography and MRI (with or without additional tests such as clinical breast examination or ultrasound).
Reference standard test was typically biopsy plus hispathology for a positive screening test result or clinical/radiological follow-up for negative screening test result.

Outcomes
Sensitivity, specificity, positive predictive value, negative predictive value

Results
11 prospective non-randomised studies were included. See table above entitled “Diagnostic accuracy of screening mammography, MRI, ultrasound and clinical breast examination in women at high risk of breast cancer”.

General comments Univariate meta-analysis of diagnostic accuracy used. Bivariate analysis would have been more appropriate.

References of Included Studies (For systematic reviews):

1. Hagen, A. I., Kvistad, K. A., Maehle, L., Holmen, M. M., Aase, H., Styr, B. et al. (2007). Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast, 16, 367-374.
2. Hartman, A. R., Daniel, B. L., Kurian, A. W., Mills, M. A., Nowels, K. W., Dirbas, F. M. et al. (2004). Breast magnetic resonance image screening and ductal lavage in women at high genetic risk for breast carcinoma. Cancer, 100, 479-489.
3. Kriege, M., Brekelmans, C. T., Boetes, C., Besnard, P. E., Zonderland, H. M., Obdeijn, I. M. et al. (2004). Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. New England Journal of Medicine, 351, 427-437.

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5. Leach, M. O., Boggis, C. R., Dixon, A. K., Easton, D. F., Eeles, R. A., Evans, D. G. et al. (2005). Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS).[Erratum appears in Lancet. 2005 May 28-Jun 3;365(9474):1848]. Lancet, 365, 1769-1778.
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9. Trecate, G., Vergnaghi, D., Manoukian, S., Bergonzi, S., Scaperrotta, G., Marchesini, M. et al. (2006). MRI in the early detection of breast cancer in women with high genetic risk. Tumori, 92, 517-523.
10. Warner, E., Plewes, D. B., Hill, K. A., Causer, P. A., Zubovits, J. T., Jong, R. A. et al. (2004). Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA, 292, 1317-1325.
11. Warner, E., Plewes, D. B., Shumak, R. S., Catzavelos, P. A., Di Prospero, L. S., & Yaffe, M. J. (2001). Comparison of breast magnetic resonance imaging, mammography and ultrasound for surveillance of women at high risk for hereditary breast cancer. Journal of Clinical Oncology, 19, 3524-3531.

Part B

Citation: FH01 Duffy, S. W. (2010). Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: Tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. The Lancet Oncology, 11, 1127-1134.

Design: Observational study
Country: UK (a family history cohort from the Netherlands was also included for comparison)
Aim: To determine whether screening affects the disease stage and projected mortality of women younger than 50 years with a clinically significant family history of breast cancer.
Study period: 2003-2007 (for FH01 study), 1991-1997 (for UK Age Trial), 1980 to 2004 (for Dutch study)

Inclusion criteria
FH01 study: Women younger than 50 years old with a clinically significant family history of breast cancer.
UK Age trial control group: Women aged 39 to 41 randomized to usual care in a screening trial.
Dutch study: Women with invasive breast cancer with family history but BRCA1/2 negative, most of whom were unscreened,

Exclusion criteria
FH01 study: Inability to give written consent, pregnancy, previous history of breast cancer (including DCIS), bilateral prophylactic mastectomy, lack of BRCA1/2 mutation if a women's family had tested positive for a mutation .

Population
FH01 study: (N=6710; N=136 breast cancers diagnosed)
Age at diagnosis for women with breast cancer: 40 to 50 years.
UK Age trial: (N=106,971; N=809 breast cancers diagnosed)
Age at diagnosis for women with breast cancer: 40 to 49 years.
Dutch study: (N=238, all with invasive breast cancer)
Age at diagnosis for women with breast cancer: 25 to 77 years.

Interventions
Screening mammography (FH01 cohort only) – two view mammography every year for at least five years and of equivalent standard to that used in the NHS Breast Screening Programme.

Outcomes
For women diagnosed with cancer: invasive status, tumour size, node status and grade.
Predicted breast cancer mortality was calculated using a prognostic index.

Results

Invasive status	FH01 cohort	UK Age Trial control group	Dutch study (non BRCA cancer)
Invasive	96 (74%)	755 (93%)	NA
In situ	34 (26%)	54 (7%)	NA
Unknown	6	0	NA

Tumour size	FH01 cohort	UK Age Trial control group	Dutch study (non BRCA cancer)
≤2cm	61(70%)	397 (55%)	145 (63%)
>2cm	26 (30%)	321 (45%)	87 (38%)

Unknown	9	37	6

Invasive tumours were significantly smaller in the FH01 group than in the UK Age control group (p<0.01)

Node status	FH01 cohort	UK Age Trial control group	Dutch study (non BRCA cancer)
Negative	56 (68%)	306 (53%)	121 (52%)
Positive	26 (32%)	276 (47%)	111 (48%)
Unknown	14	173	6

Invasive tumours were significantly less likely to be node positive in the FH01 group than in the UK Age control group (p<0.01)

Grade	FH01 cohort	UK Age Trial control group	Dutch study (non BRCA cancer)
1	17 (19%)	53 (8%)	20 (11%)
2	31 (35%)	285 (43%)	56 (32%)
3	40 (45%)	324 (49%)	101 (57%)
Unknown	8	93	61

Invasive tumours were significantly more likely to be of more favourable histological grade in the FH01 group than in the UK Age control group (p<0.01)

	FH01 cohort	UK AgeTrial control group	
Risk corrected 10 year breast cancer mortality in patients with invasive tumours*	1.10%	1.38%	RR 0.80 (95% CI 0.66 to 0.96) in favour of FH01 cohort

*Mortality was predicted using Nottingham prognostic index score (using tumour size, node status and grade) for the three cohorts.

Authors estimated that 2 breast cancer deaths would be prevented for every 10,000 screens.

References of Included Studies (For systematic reviews): Authors performed a systematic review which identified evidence supporting the diagnostic accuracy of screening but little evidence about clinical outcome. References of included studies were not reported.

Citation: Goldfrank, D., Chuai, S., Bernstein, J. L., Ramon, Y. C., Lee, J. B., Alonso, M. C. et al. (2006). Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiology, Biomarkers & Prevention, 15, 2311-2313.

Design: Case-control study
Country: USA and Spain
Aim: To investigate the association between low-dose radiation exposure from mammograms and breast cancer incidence in BRCA mutation carriers.
Study period: 1995 to 2004

Inclusion criteria
Deleterious BRCA mutation carriers identified at Memorial Sloan Kettering Cancer Centre, New York or Hospital Sant Pau (Barcelona).

Exclusion criteria
none reported

Population
N=162; Cases N=34, Controls N=128
BRCA mutation: BRCA1 86/162 (53%), BRCA2 76/162 (47%)
Breast cancer status: affected 34/162 (21%), unaffected 128/162 (79%)
Age at ascertainment: median 43 years (range 25 to 73 years)

Interventions
Mammograms before diagnosis (for affected women) or before enrollment (for unaffected women). Before undergoing genetic testing women were asked about age at first mammogram, lifetime number of mammograms and number of mammograms in the preceding year

Outcomes
Incidence of breast cancer

Results
Logistic regression, adjusted for age diagnosis (cases) or questionnaire (controls), showed no significant association between number of mammograms received and breast cancer status, OR=0.94 (95%CI 0.88 to 1.00; p=0.06). Subgroup analyses by BRCA mutation (BRCA1 or BRCA2) and by age at diagnosis (>40 years or < 40 years) also showed no significant association.

A second analysis assessed the association between the lifetime total number of mammograms and breast cancer. There was no significant association between total mammogram exposure and breast cancer in the group as a whole (OR=1.04; 95% CI 0.99 to 1.09). In the subgroup of BRCA1 carriers, however, lifetime mammogram exposure was significantly associated with breast cancer, OR=1.08 (95% CI 1.01 to 1.16).

Comments Included in Jansen et al (2010) systematic review

Citation: Maurice, A., et al. "Screening younger women with a family history of breast cancer--does early detection improve outcome?" European Journal of Cancer 42.10 (2006): 1385-90.

Design: Observational study
Country: UK
Study period: 1991 to 2002 (follow up until 2004)
Aim: To estimate the benefits of mammographic screening of young women (<50 years) at increased risk of breast cancer due to family history.

Inclusion criteria
Women aged less than 50 with a family history of breast cancer and lifetime risk of at least 1 in 6 using Claus tables, screened at the Manchester family history clinic.
A cohort of unscreened women aged less than 50 years who presented symptomatically with breast cancer in the same period and to the same breast unit were also included for comparison.

Exclusion criteria

Population
Family history clinic group (FHC) (N=62 breast cancers detected during screening of 3016 patients)
Age at diagnosis: <40 years 23/62 (37%), 40 to 49 years 39/62 (63%)
Histology: invasive 43/62 (69%), *in situ* 19/62 (31%)

Surgical clinic group (SC) (N=1108, all with breast cancer)
Age at diagnosis: median 44 years
Histology: invasive 918/1108 (83%), *in situ* 82/1108 (7%), unknown 108/1108 (10%)

Interventions
Mammography and clinical breast examination screening at 12 to 18 month intervals started at presentation to the clinic, but not normally before the age of 35 years and never before 30 years.

Outcomes
Tumour size, histology & grade; nodal involvement; overall mortality; breast cancer mortality

Results

Tumour size	SC	FHC
<2cm	321(39%)	31(72%)
2-5cm	414(51%)	11(26%)
>5cm	78(10%)	1(2%)
Unknown	213	0

Node involvement	SC	FHC
0	441(47%)	27(66%)
1-4	312(34%)	13(32%)
>4	186(19%)	1(2%)
Unknown	97	2

	SC		FHC		
	n	N	n	N	
Death from breast cancer*	210	1108	4	62	Lead time adjusted HR 0.24 (95%CI 0.09 to 0.66) – in favour of the FHC group

*Minimum follow-up was two years, maximum follow-up was 13 years.

General comments
Unclear whether women with a personal history of breast cancer were included. Denominator for the FHC group was not the number of people screened but the number screened who developed breast cancer. Harms of screening not reported. Some of the women in the control group used may also have been in the control group of the UK Age trial.

Citation: Narod, S. A., Lubinski, J., Ghadirian, P., Lynch, H. T., Moller, P., Foulkes, W. D. et al. (2006). Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncology, 7, 402-406.

Design: Case control study
Country: International
Aim: To assess whether exposure to ionizing radiation through mammography screening was associated with risk of breast cancer in BRCA1 or BRCA2 carriers.
Study period: cases were diagnosed between 1952 to 2005, although participants were asked to recall any screening mammography before this period.

Inclusion criteria
Women with deleterious BRCA mutations identified through an international registry held at the Centre for Research on Women's Health, University of Toronto.

Exclusion criteria:
Diagnosis with ovarian or other cancer before breast cancer, prophylactic mastectomy or missing data for important variables.

Population
Cases and controls were matched for year of birth, BRCA mutation (BRCA1 or BRCA2), and country of residence.
Women with invasive breast cancer (cases) (N=1600)
Age (years): median 47.3 years (range 21.4 to 83.2)
Mutation: BRCA1 79%, BRCA2 21%
Bilateral oophorectomy: 3%
Family history of breast cancer: 57%
Nulliparous: 16%

Women without invasive breast cancer (controls) (N=1600)
Age (years): median 46.7 years (range 21.4 to 83.2)
Mutation: BRCA1 79%, BRCA2 21%
Bilateral oophorectomy: 5%
Family history of breast cancer: 59%
Nulliparous: 18%

Interventions
Mammography: 661 (41%0 of cases and 729 (46%) of controls had at least one mammography procedure. Analysis was stratified by age at first mammography.Subgroup analyses were done for women with BRCA1 mutations, women with BRCA2 mutations, cases diagnosed at age ≤ 40 years, cases diagnosed at age ≥ 40 years, cases not identified by mammography

Outcomes
Invasive epithelial breast cancer.

Results

	Cases	Controls
No Mammography	684	769
Mammography	661	729

Unadjusted OR=1.02 [95%CI 0.88 to 1.18]

Adjusting for parity, oral-contraceptive use, ethnic origin and bilateral oophrorectomy there was no association between ever having a screening mammography and odds of breast cancer, OR=1.03 (95%CI 0.85 to 1.25). Subgroup analyses according to for women with BRCA1 mutations, women with BRCA2 mutations, cases diagnosed at age ≤ 40 years, cases diagnosed at age ≥ 40 years, cases not identified by mammography did not show an association between mammography and odds of breast cancer. In the subgroup of women diagnosed at age ≤ 40 years, initiation of mammography in the thirties was significantly associated with breast cancer (OR 1.56, 95%CI 1.07 to 2.27), however this was only one of 24 such comparisons and the result may be due to chance. In this subgroup initiation of mammography before the age of 30 was not significantly associated with breast cancer.
Comments Included in Jansen et al (2010) systematic review

Citation: Rijnsburger, A. J., et al. "Impact of screening for breast cancer in high-risk women on health-related quality of life." British Journal of Cancer 91.1 (2004): 69-76.

Design: Prospective observational study
Country: The Netherlands
Aim: To examine the short-term effects of screening for breast cancer in high-risk women on generic health-related quality of life and distress.

Inclusion criteria

- Women at increased risk for breast cancer due to a familial or genetic predisposition (described more fully by Kriege et al, 2001)
- Women who were already under intensive surveillance/ women attending for the first time

Exclusion criteria

- Symptoms of breast cancer
- Previous breast cancer

Population
334 participants in the MRISC study

Interventions

- Participants visited the family cancer clinic twice a year for surveillance, consisting of biannual CBE and annual mammography and MRI. All women got instructions for monthly BSE.

Outcomes

- Health Related Quality of Life (HRQOL) measured by the SF-36, EQ5D, somatic subcscale SCL-90 at T0 (2 months prior to screening), T1 (on the day of scheduled screening) and T2 (1 week (in the case of CBE alone) or 4 weeks (in the case of CBE in combination with mammography and MRI)

Results

- The mean age at entry in the study was 40.9 years
- The mean number of years already adhering to regular surveillance was 5.4 years
- 12% of women reported MRI to be painful
- There was no significant change over time
- The study population showed significantly better HRQOL scores than age/sex matched controls

	T0 (n=326)	T1 (n=316)	T2 (n=288)	Reference scores SF-36: Dutch general population	Reference scores SF-36: USA general population	Reference scores EQ-5D and SOM scale

SF36 (score 100 – 0)						
Physical functioning	89.9		89.4	86.3	86.1	
Role – physical	85.7		84.1	77.6	82.8	
Bodily pain	82.4		83.0	72.8	75.0	
General health perceptions	76.4		77.3	72.2	72.7	
Vitality	67.1		68.9	64.8	59.3	
Social functioning	87.7		87.9	83.5	83.0	
Role – emotional	85.2		88.1	80.1	81.2	
Mental health	76.8		77.7	74.4	73.4	
SF36 summary scores						
Physical component summary	52.5		52.3	50.0	50.7	
Mental component summary	51.2		52.2	50.1	49.1	
EQ-5D						
Utility score (score 1-0)	0.88		0.88			0.85
VAS (self-rated health today) (score 100-0)	81.9	79.0	80.7			86.9
Somatic sub-scale SCL-90 (score 12-60)	17.5		17.1			18.7

Rijnsberger et al (2004) recorded pain, discomfort and anxiety experienced during screening tests. The proportion of patients who reported pain was 7%, 86% and 12% during CBE, mammography and MRI respectively; 9%, 69% and 45% of patients experienced discomfort during CBE, mammography and MRI respectively; 22%, 28% and 37% of patients experienced anxiety during CBE, mammography and MRI respectively

General comments

HRQOL data from the Dutch magnetic resonance imaging (MRI) screening (MRISC) study

This was interim data. The study was ongoing at the time of publication.

Response rates were high (T0: 98.5%; T1: 96.6%; T2: 94.4%).

The study population showed significantly better generic health-related quality of life scores compared to age/sex adjusted reference scores from the general population.

Neither generic health-related quality of life scores nor distress scores among the study sample showed significant changes over time. The impact of the screening process on generic health status did not differ between risk categories.

The authors concluded that screening for breast cancer in high-risk women does not have an unfavourable impact on short-term generic health-related quality of life and general distress.

In this study, high-risk women who opted for regular breast cancer screening had a better health status than women from the general population.

References of Included Studies (For systematic reviews): Not applicable

Citation: Jansen-van der Weide MC, Greuter, M. J., Jansen, L., Oosterwijk, J. C., Pijnappel, R. M., & de Bock, G. H. (2010). Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. Eur Radiol., 20, 2547-2556.

Design: Systematic review
Country: NA
Aim: To investigate how low dose radiation affects breast cancer risk in women with a genetic/familial predisposition to breast cancer.
Study period: literature search included studies published between 1989 and 2009

Inclusion criteria
Studies including women with a familial or genetic predisposition to breast cancer, some of whom had been exposed to low dose radiation (mammography or chest X-ray), with a quantification of the effect of low-dose radiation in terms of relative risk or odds-ratio, published in peer reviewed journals.

Exclusion criteria
Studies with high dose radiation (radiotherapy), animal or cell level studies and theoretical model studies.

Population
7 studies were included: five of the effect of mammography/chest X-ray on breast cancer risk in women with BRCA1/2 mutation, a CHEK2*1100delC mutation or other mutations in DNA repair genes. Two studies were in women with increased familial risk (breast or ovarian cancer amongst first, second or third degree relatives).

Interventions
Mammography or chest x-ray, exposed patients received a cumulative dose ranging from 0.3 to 33 mSv.

Outcomes
breast cancer

Results
Pooled odds ratios showed an increased risk of breast cancer among high risk women due to low dose radiation exposure, OR=1.3 (95% C.I. 0.9 to 1.8). There was evidence of a dose-response relationship between low dose radiation and breast cancer in this population: exposure to low dose radiation before the age of 20 years (OR 2.0; 95% C.I. 1.3 to 3.1) and five or more exposures (OR 1.8; 95% C.I. 1.1 to 3.0).

References of Included Studies (For systematic reviews):

1. Andrieu, N., Easton, D. F., Chang-Claude, J., Rookus, M. A., Brohet, R., Cardis, E. et al. (2006). Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol, 24, 3361-3366.

2. Bernstein, J. L., Teraoka, S. N., John, E. M., Andrulis, I. L., Knight, J. A., Lapinski, R. et al. (2006). The CHEK2*1100delC allelic variant and risk of breast cancer: screening results from the Breast Cancer Family Registry. Cancer Epidemiol.Biomarkers Prev, 15, 348-352.

3. Goldfrank, D., Chuai, S., Bernstein, J. L., Ramon, Y. C., Lee, J. B., Alonso, M. C. et al. (2006). Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiology, Biomarkers & Prevention, 15, 2311-2313.

4. John, E. M., Phipps, A. I., Knight, J. A., Milne, R. L., Dite, G. S., Hopper, J. L. et al. (2007). Medical radiation exposure and breast cancer risk: findings from the Breast Cancer Family Registry. Int J Cancer, 121, 386-

394.

5. Ma, H., Hill, C. K., Bernstein, L., & Ursin, G. (2008). Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Research & Treatment, 109, 77-90.

6. Millikan, R. C., Player, J. S., Decotret, A. R., Tse, C. K., & Keku, T. (2005). Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. Cancer Epidemiol.Biomarkers Prev, 14, 2326-2334.

7. Narod, S. A., Lubinski, J., Ghadirian, P., Lynch, H. T., Moller, P., Foulkes, W. D. et al. (2006). Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncology, 7, 402-406.

Citation: Maurice, A., Evans, D. G., Affen, J., Greenhalgh, R., Duffy, S. W., Howell, A. et al. (2012). Surveillance of women at increased risk of breast cancer using mammography and clinical breast examination: further evidence of benefit. International Journal of Cancer, 131, 417-425.

Design: Retrospective cohort study
Country: UK
Aim:To assess the effectiveness of a surveillance program for women with a significant family history of breast cancer
Study period: 1987 to 2008

Inclusion criteria
Women at 1/6 or greater lifetime risk of breast cancer counseled at the Manchester Family History Clinic and selected for annual surveillance between the ages of 35 and 50 years.
A group of women with BRCA1/2 mutations diagnosed with breast cancer but not included in the surveillance programme were also included to estimate the effectiveness of screening. These women were identified from a database at the regional genetics centre and the records of breast units where the diagnosis was made.

Exclusion criteria
Cases were excluded from the analysis if their breast cancers were diagnosed incidentally at the time

Population
7475 women in the screened group. Unclear how many were included in the comparison group not in the screening programme.

Interventions
Mammography and CBE, annually from 35 to 50. Women with ¼ lifetime risk were offered 18 monthly screening in addition to the National Screening Programme between the ages of 51 and 60 years. Screening of women below 35 was offered 5 years before the youngest affected family member but never before the age of 30 years.

Outcomes
Breast cancer (prevalent, incident and interval cancers), overall survival

Results
Breast cancers detected within the intensive surveillance programme

Age at diagnosis (years)	Prevalence	Incidence	Interval
<30	1	1	0
30 – 40	9	14	10
40 -50	11	42	19
>50	5	39	14

Overall survival of BRCA1/2 carriers diagnosed with breast cancer within the intensive surveillance program compared with BRCA1/2 carriers diagnosed with breast cancer but not in the intensive programme (i.e. population screening programme only), HR 0.44 (95%C.I. 0.25 to 0.77). For BRCA1 carriers HR 0.54 (0.24 to 1.20) and for BRCA2 carriers HR 0.36 (95% C.I. 0.17 to 0.79).

Death from any cause in BRCA1/2 carriers diagnosed with

Screening group	n	N
Intensive	4	45
Population only	?	466

Comments Unclear how lead time bias was accounted for when comparing survival of women with screen detected cancers and those that presented symptomatically.

6.3 Surveillance for people with a personal history and a family history of breast cancer

6.3.1 Review Question

What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk reducing mastectomy?

6.3.2 Background

Women who have primary breast cancer are at an increased risk of developing breast cancer in the remaining breast tissue with those women with a familial history at a much higher risk. For this reason women who develop breast cancer and have a familial history may be offered a risk reducing mastectomy. Some may not be offered this and others may choose not to have this done. For those women who have breast tissue remaining it is not clear what surveillance should be offered to them. At present all women are offered mammography annually or biennially for between 3-5 years and some for longer than this. It is known that detecting a second event at an early stage compared to a late stage does confer a survival advantage. It is not known whether this is also the same for women at familial risk.

It is not known whether offering mammography surveillance confers a survival advantage to all women or to those at a familial risk. It is likely that this is the case as mammography is able to detect tumours at an earlier stage than no surveillance. It is not known how frequently mammography should be undertaken. It is known that MRI is more sensitive than mammography and it may be that in some groups (BRCA1 carriers) that MRI may be more appropriate than mammography.

Women with a breast cancer may have undertaken other risk reducing options such as oophorectomy or medical oophorectomy or other drugs to reduce their risk.

Digital mammography is known to be more sensitive for the detection of breast cancer in pre menopausal women or in those women with dense breasts.

6.3.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with a personal history of breast cancer and a familial risk aged: 18-29 30-39 40-49 50-70 70 +	• Mammography • MRI • Ultrasound • Clinical Breast Exam • Any combinations of tests at different frequencies/timings • No screenings	Each Other	• Sensitivity/specificity/ PPV/NPV in the different age groups (versus histopathology or clinical follow-up)
Patients with a personal history of	• Mammography • MRI	Each Other	• Early detection of cancer/stage at

breast cancer and a familial risk aged: 18-29 30-39 40-49 50-70 70 +	• Ultrasound • Clinical Breast Exam • Any combinations of tests at different frequencies/timings • No screenings		detection • Overall Survival • Incidence • Radiation induced cancer • Interval Cancers • Health related quality of life

The outcomes considered to be important for this topic were both diagnostic and clinical and therefore was decided to split the topic into a part A and B for the purposes of sifting the relevant evidence. A single large search will be conducted for the topic however the evidence will be sifted twice, once to identify the diagnostic studies which will inform part A and second to identify the clinical efficacy studies which will inform part B.

6.3.4 Relative Importance of these outcomes

The GDG considered all outcomes to be of equal importance to the topic.

6.3.5 How the information will be searched

Searches:	
Can we apply date limits to the search	1970 This topic forms part of the new short guideline. The type of date limits we would be looking for here will relate to when surveillance techniques became available. For example there would be little point in doing a search for MRI as far back as 1965 if it only became available in 1990.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filters to be applied to searches but sifting and reporting of evidence to be split into diagnostic efficacy and clinical efficacy
List useful search terms.	Breast cancer, Recurrence, second primary, risk reducing oophorectomy, MRI, Ultrasound, mammography, digital mammography, clinical breast examination,

6.3.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies

	considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced. Specific to this topic, there will be a single large search for this topic but the results will be sifted twice. First to identify and review diagnostic studies informing the sensitivity/specificity/PPV and NPV and secondly to identify and review clinical efficacy studies which will inform the second group of outcomes including disease specific survival, incidence of breast cancer etc.
List subgroups here and planned statistical analyses.	Diagnostic efficacy outcomes Clinical efficacy outcomes

6.3.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1970-current	1520	59	15/11/2011
Premedline	1970-current	69	1	15/11/2011
Embase	1970-current	2341	33	16/11/2011
Cochrane Library	1970-current	54	7	21/11/2011
Web of Science (SCI & SSCI) and ISI Proceedings	1970-current	2523	27	16/11/2011

Total References retrieved (after de-duplication): 109

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. or/9-18
20. 8 and 19
21. Neoplasms, Second Primary/
22. Neoplasm Recurrence, Local/
23. 21 or 22
24. exp Breast Neoplasms/
25. exp "Neoplasms, Ductal, Lobular, and Medullary"/
26. 24 or 25
27. 23 and 26
28. (breast$ adj3 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
29. (mammar$ adj3 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
30. 28 or 29
31. ("second primar$" or secondary or recurren$ or metachronous or ipsilateral or history).tw.
32. 30 and 31
33. 27 or 32
34. 20 and 33
35. exp Mammography/
36. (breast$ and screen$).ti.
37. mammogra$.tw.
38. Ultrasonography, Mammary/
39. (ultraso$ or sonogra$ or echosonogra$).tw.
40. Magnetic Resonance Imaging/
41. "magnetic resonance imag$".tw.
42. MRI.tw.
43. ((non-invasive$ or noninvasive$) and (imag$ or diagnos$)).tw.
44. Mass Screening/
45. surveillance.tw.
46. Physical Examination/
47. Breast self-examination/
48. ("physical exam$" or "self exam$" or "self-exam$" or "clinical exam$" or "breast exam$").tw.
49. or/35-48

50. 34 and 49

Notes:

A date limit of 1970 was applied by advice of the GDG, as before 1970 it is unlikely surveillance studies were published.

No search filters were applied.

Update Searches:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	21/11/2011-17/07/2012	88	20	17/07/2012
Premedline	21/11/2011-17/07/2012	2	1	17/07/2012
Embase	11/2011-07/2012	94	18	17/07/2012
Cochrane Library	11/2011-07/2012	12	2	09/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	11/2011-07/2012	142	9	23/07/2012

Embase: 1 new reference added 17/09/2012

Embase: 1 new reference added 18/09/2012

Total references retrieved after duplicates removed: 42

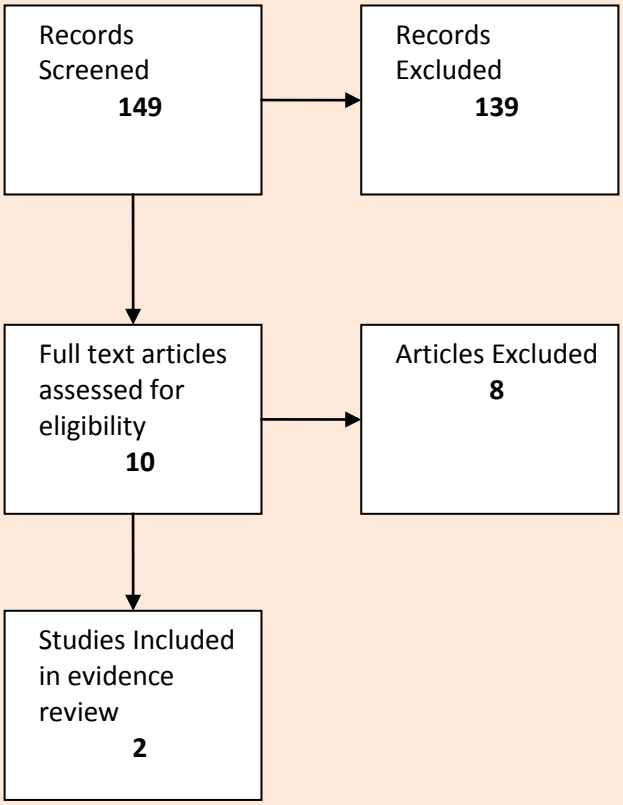
Table 6.4: Summary of included studies (diagnostic and clinical outcomes)

Study	Study Type	Population	Aim	Intervention	Comparison	Outcome
Elmore et al (2010)	Retrospective Case Series	N=141 78 patients undergoing surveillance for both breasts following breast conserving therapy 63 patients undergoing surveillance of contralateral breast and ipsilateral chest wall following mastectomy	To determine factors predicting the use of MRI surveillance in women treated for previous breast cancer and the incidence of in breast recurrence and/or new cancers indentified by MRI	Breast contrast enhanced MRI	None	Factors predictive of MRI Incidence of breast cancer recurrence Incidence of new breast cancer
Robertson et al (2011)	Systematic review	N=9 studies with a total of 3724 patients	To determine the test performance of surveillance mammography, alone or in combination with other tests in detecting ipsilateral breast cancer recurrence and/or metachronous contralateral breast cancer in women undergoing routine surveillance To compare surveillance mammogrpahy performance with alternative tests, alone or in combination, in women with a previous diagnostic test result indicating suspected ipsilateral breast tumour recurrence	Unltrasound MRI Specialist led clinic exam Unstructured primary care follow-up	Each Other	Test performance Adverse Effects Acceptability of tests Reliability of tests Radiological/operator expertise Interpretability/readability of tests

			and/or metachronous contralateral breast cancer			
Sardanelli et al (2011)	Prospective, non-randomised study	N=501	To prospectively compare clinical breast exam, mammography, ultrasonography and MRI in the surveillance of women at high risk of inherited breast cancer including women with a previous breast cancer history	Annual evaluation with clinical breast exam, mammograpy, ultrasonography and MRI	Each other	Breast cancer incidence, screen detected and interval cancers Diagnostic performance of screening modalities
Houssami et al (2011)	Retrospective Case Series	N=713191 screens (no details on the number of women this includes)	To evaluate mammography screening outcomes in women with a personal history of breast cancer and who have an increased risk of recurrent or new breast cancer as compared with women with no personal history	Mammography screening	None	Number of screens Number of cancers detected Cancer detection rate Recall to assessment rate Positive predictive value for recall Proportion of screens detecting cancer which required multiple reads

Diagnostic Outcomes

6.3.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=1)
Qualitative Study (n=0)

6.3.9 Study quality (Diagnostic Outcomes)

Evidence about the surveillance needs of women with a personal history and familial risk of breast cancer drawn from two publications: a systematic review of eight studies (Robertson et al, 2011) and a primary study (Sardanelli at al, 2011).

The nine studies included in Roberston et al (2011) was considered to be of moderate quality (using QUADAS criteria). The main limitations were: unclear time between index and reference tests, lack of blinding for both index and reference tests and partial verification bias. No meta-analysis was done in the review due to heterogeneity across the studies.

Sardanelli et al (2011) included asymptomatic patients at high risk for breast cancer and who were proven BRCA1/2 carriers or who were untested first degree relatives of BRCA1/2 carriers or who had a strong family history of breast or ovarian cancer and also included women with a personal history of breast cancer provided they had not undergone bilateral total mastectomy. The study did not however present the diagnostic outcomes by subgroup and therefore caution should be used when interpreting the results as they also include women with no personal history. This study was not considered high quality due to the unrepresentative spectrum of patients and lack of blinding of index and reference tests.

Both studies assessed the diagnostic performance of a number of interventions including clinical breast exam, mammography, ultrasonography, MRI as well as a number of different combinations of interventions.

Robertson et al (2011) reported on the diagnostic performance of all surveillance methodologies for detecting ipsilateral and contralateral breast cancer separately. Diagnostic performance results were also reported separately comparing patients undergoing routine surveillance with patients undergoing non-routine surveillance where possible.

Sardanelli et al (2011) reported diagnostic performance of the different surveillance methods for women <50 years of age compared and women ≥50 years separately where available.

Table 6.5: Sensitivities, specificities, positive likelihood ratios and negative likelihood ratios for interventions and combinations of interventions for both contralateral and ipsilateral breast cancer occurrences (reported as ranges).

	No of studies	Incidence Rate (screen detected and interval cancers)	Sensitivity (range)	Specificity (range)	+LR (range)	-LR (range)
Clinical breast examination	5* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	0%-89%	49%-99.3%	1.0-26.4	0.2-0.83
Mammography	6* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	50%-83%	50%-99%	1.3-52.3	0.3-0.7
Ultrasonography	3* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	43%-87%	31%-98.4%	0.6-33	0.2-1.8
MRI	7* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	86%-100%	50%-96.7%	1.3-27.6	0.09-0.7
Mammography+ultrasonography	2 (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	62%-95%	97.6%-99%	26-61.5	0.05-0.38
MRI+mammography	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	93.2%	96.3%	25.4	0.07
MRI+ultrasonography	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	93.3%	96%	23.6	0.07
Clinical Exam +	1* (Sardanelli,	3.3% (95% 2.4%-4.3%)	100%	67%	3.0	Not

mammography	2011)	taken from Sardanelli, 2011)				Reported
Mammography + Clinical Exam + Ultrasound	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	64%	84%	3.9	0.4
Mammography + Clinical Exam +Ultrasound +MRI	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	100%	89%	8.9	Not Reported

***Total number of individual studies from the systematic reviews which reported results for each imaging modality or combination of modalities

Table 6.6: Sensitivities, specificities, positive likelihood ratios and negative likelihood ratios for Mammography, ultrasonography and MRI by age (taken from Sardanelli et al, 2011).

	Sensitivity (%)	Specificity (%)	+LR	-LR
Women <50 (941 rounds)				
Mammography	10/22	628/636	36.1 (13.0-100.4)	0.55 (0.27-1.13)
	45.5 (24.4-67.8)	98.7 (97.5-99.5)		
Ultrasonography	9/21	620/630	27.0 (9.9-73.4)	0.58 (0.28-1.19)
	42.9 (21.8-66.0)	98.4 (97.1-99.2)		
MRI	16/18	595/616	26.1 (11.7-58.1)	0.12 (0.03-0.50)
	88.9 (65.3-98.6)	96.6 (94.8-97.9)		
Women ≥50 (651 rounds)				
Mammography	15/28	407/409	109.6 (23.9-503.1)	0.47 (0.24-0.91)
	53.6 (33.9-72.5)	99.5 (98.2-99.9)		
Ultrasonography	17/29	380/386	37.7 (13.8-103.0)	0.42 (0.21-0.84)
	58.6 (38.9-76.5)	98.4 (96.6-99.4)		
MRI	26/28	371/383	29.6 (13.5-64.9)	0.07 (0.02-0.31)
	92.9 (76.5-99.1)	96.9 (94.6-98.4)		

6.3.10 Evidence Statements (Diagnostic outcomes)

Moderate quality evidence (Robertson et al, 2011) suggests that MRI has the optimal combination of sensitivity and specificity for the detection of ipsilateral breast tumour recurrence in patients undergoing routine surveillance and non-routine surveillance following breast conserving surgery.

Moderate quality evidence (Robertson et al, 2011) suggests that MRI has higher sensitivity and specificity for the detection of ipsilateral breast tumour recurrence in patients undergoing surveillance following breast conserving surgery. In this review combined surveillance mammography, clinical exam, ultrasound and MRI had the highest sensitivity (100%) for the detection of metachronous contralateral breast cancer in surveillance following breast conserving surgery (Robertson et al, 2011).

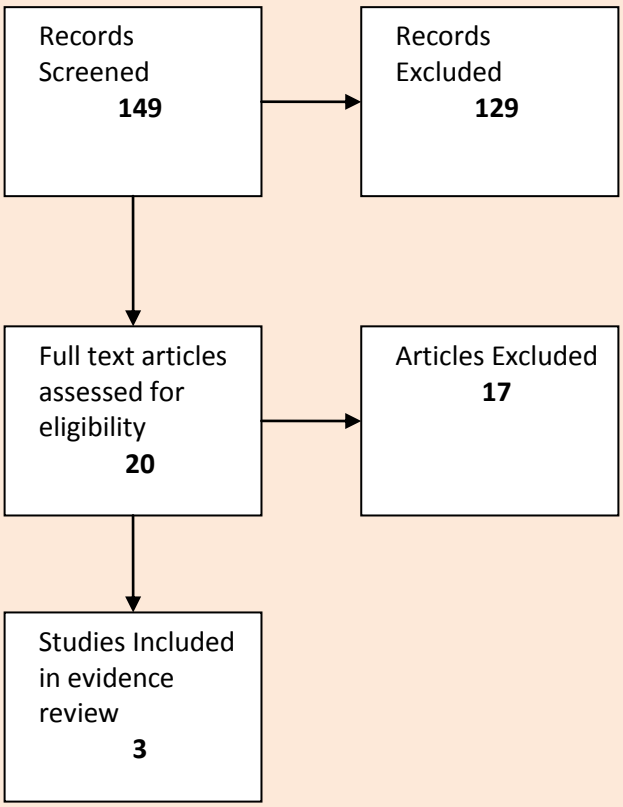
For patients undergoing routine surveillance following mastectomy moderate quality evidence (Roberston et al, 2011) suggests MRI has higher sensitivity than mammography or clinical examination for the detection of ipsilateral breast tumour recurrence. In these patients combined surveillance mammography and ultrasound had the highest sensitivity (95%) and specificity (99%) for the detection of metachronous contralateral breast cancer.

Moderate quality evidence from a surveillance study including women with and without a personal history f breast cancer (Sardanelli et al, 2011), suggests that MRI is more sensitive than mammography, ultrasonography, CBE or combined mammography and ultrasonography.

Moderate quality evidence, from a surveillance study including women with and without a personal history f breast cancer (Sardanelli et al, 2011), suggests no significant different in the sensitivity of MRI + Mammography, MRI + ultrasonography, MRI + Mammography + Ultrasonography or MRI

Clinical Outcomes

6.3.11 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=)
Prospective cross sectional study (n=0)
Case Series Studies (n=3)
Qualitative Study (n=0)

6.3.12 Evidence Statements (Clinical Outcomes)

No evidence was found about the relative effect of surveillance MRI, mammography, ultrasound, clinical breast examination and no surveillance on stage at detection, overall survival, radiation induced cancer or health related quality of life.

Very low to low quality evidence (Elmore et al, 2010: GRADE Profile 6.1)suggests a new breast cancer will be detected on approximately 1% of surveillance tests in women with a personal history of breast cancer and a familial risk.

Low quality evidence (Houssami et l, 2011: GRADE Profile 6.1)) reported a cancer detection rate of 95.5/10,000 screens (95% CI, 78.3-112.7) for screening with mammography.

Although Sardanelli et al (2010) reported clinical outcomes as well as diagnostic outcomes, the results for clinical outcomes are reported for all interventions combined and not for individual outcomes and therefore there is a question mark over usefulness of the clinical data from this study in supporting the drafting of recommendations.

GRADE Profile 6.1: What is the effectiveness of specific surveillance methodologies for people with a personal history of breast cancer and a familial risk, who have not undergone a risk reducing mastectomy?

Quality assessment						Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	
Incidence of breast cancer recurrence[9] (follow-up 18-54 months[1]) Elmore et al (2010)						
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	VERY LOW
Incidence of new breast cancer (follow-up 18-54 months[1]) Elmore et al (2010)						
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	VERY LOW
Interval and screen detected cancers (follow-up 12-96 months) Sardanelli et al (2011)						
1	observational studies	serious[4]	no serious inconsistency	serious[5]	no serious imprecision[6]	VERY LOW
Cancer Detection Rates (Houssami et al, 2011)						
1	observational studies	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	LOW

[1] Not clear from the study though patients are drawn from a three year period and it appears that 1st surveillance spanned and 18 month period following treatment which would give a minimum follow-up of 18 months and maximum follow-up of 54 months.

[2] This study is a retrospective study with a high risk of bias based on Review Manager assessment of study quality

[3] Small numbers included in the study over a three year period (n=141)

[4] None randomised, open label study

[5] Not all included women will have a personal history however all included women have a high risk of inherited breast cancer and the study reported a significant difference in the incidence rate per woman-year between women with a personal history of breast cancer and women without (p=0.045).

[6] N=501 patients included

[7] Unclear whether including only women with a personal history and a high risk of inherited breast cancer would change the result and if so, in which direction.

[9]Stated as an outcome yet not clearly reported
[10]Retrospective observational study, no information given on exclusion criteria and no details on follow up times

Three studies, addressing the surveillance needs of women with a personal history and familial risk of breast cancer and specifically reporting clinical outcomes were identified (Elmore, 2010, Sardanelli, 2011 and Houssami, 2011).

Elmore et al (2010) is a retrospective audit with a small number of patients and included a patient population which could be considered to be indirectly related to the topic in that all patients had a personal history of breast cancer and although family history was assessed, it was a means to determining GAIL score in order to determine whether GAIL score was predictive of MRI use and it is therefore possible that some patients with a familial risk and a personal history may not have received MRI scans.

Sardanelli et al (2011) is a large prospective, multicentre, non randomised study which reported both clinical and diagnostic outcomes; only the clinical outcomes are relevant to this section. The results for clinical outcomes are reported for all interventions combined and not for individual outcomes and therefore there is a question mark over usefulness of the clinical data from this study in supporting the drafting of recommendations.

Houssami et al (2011) is a retrospective study comparing screening outcomes in women with a personal history of breast cancer with women with no personal history. Screening detected 118 breast cancers in women witha personal history for a cancer detection rate of 95.5/10,000 screens (95% CI, 78.3-112.7).

The quality of data available to inform individual outcomes of interest has been evaluated and found to be of a very low quality as assessed using GRADE methodology (GRADE profile 6.1).

Therefore the evidence for this topic should be interpreted with caution when developing recommendations

6.3.13 Evidence Tables

Citation: Elmore L et al (2010) Breast MRI surveillance in women with prior curative-intent therapy for breast cancer *Journal of Surgical Research* 163;1:58-62

Design: Retrospective Study

Country: USA

Setting: Follow up/Surveillance

Aim: to determine factors predicting the use of MRI surveillance in women treated for previous breast cancer and the incidence of in-breast recurrence and/or new cancers identified by MRI

Inclusion criteria
All consecutive patients diagnosed with stage 0-III invasive breast cancer and who underwent curative-intent treatment and subsequently breast contrast enhanced MRI for surveillance following treatment.

Exclusion criteria
None given

Sample Size
None calculated

Randomisation Method
Not Applicable

Population
N=141
N=78 patients undergoing surveillance for both breasts following breast conserving therapy
N=63 patients undergoing surveillance of contralateral breast and ipsilateral chest wall following mastectomy

Study Duration
January 2005 – December 2008

Interventions
Breast contrast enhanced MRI

Outcomes
Factors predictive of MRI
Incidence of breast cancer recurrence
Incidence of new breast cancer

Results

- 141 patients underwent a total of 202 MRI
- N=94 women underwent one MRI; 37 women had two, 7 had three, 2 had 4 and one women had five MRI scans.
- N=125 required no further imaging
- N=16 required 2nd look ultrasound with 6 requiring biopsy of suspicious lesions
- 2/6 lesions were invasive breast cancers and were not seen on routine imaging.

- 14/16 (88%) of reimaging occurred within 18 months of treatment following first surveillance MRI and both cancers were found during the 1st surveillance (13 months and 15 months respectively).
- Routine imaging did not reveal any additional cancers during the study period (211 mammograms were carried out in 141 patients)
- The rate of new cancer detection on surveillance MRI was 0.9% (2/202 imaging procedures) or 1.4% (2/141 patients) during the study period
- Patient age, GAIL score, tumour stage, grade, histology, receptor status and surgical treatment were not predictive of MRI use (p>0.05).

General comments

Poor quality study with small numbers of patients. The population is indirectly relevant to the topic in that all of the included patients had a personal history the family histories were assessed as a means to determining GAIL score in order to assess whether GAIL score was predictive of MRI use, however not all patients included in the cohort may have a familial risk and it is not clear from study whether this is the case. Not a comparative study, no suitable checklist for assessing the study quality.

Citation: Robertson C et al (2011) Surveillance mammography for detecting ipsilateral breast tumour recurrence and metachronous contralateral breast cancer: a systematic review *European Radiology* 21;2484:2491

Design: Systematic Review

Country: UK

Setting: Follow-up

Aim: To determine the test performance of surveillance mammography, alone or in combination with other tests in detecting ipsilateral breast cancer recurrence and/or metachronous contralateral breast cancer in women undergoing routine surveillance

To compare surveillance mammography performance with alternative tests, alone or in combination, in women with a previous diagnostic test result indicating suspected ipsilateral breast tumour recurrence and/or metachronous contralateral breast cancer.

Inclusion criteria
Randomised controlled trials of surveillance mammography and diagnostic cohort studies of surveillance mammography or other comparator tests carried out in women previously treated for primary breast cancer and who do not have detectable metastasis at the time of initial treatment.

Indirect comparisons by comparing cohort studies analysing results of at least 100 women receiving surveillance mammography, a comparator test or a combination of tests with the reference standard in the same population.

Studies assessing test performance for routine and non-routine surveillance patients

Studies reporting absolute numbers of true positives, true negatives, false positives and false negatives or provide enough information to enable their calculation.
Studies also have to include a per-patient analysis.

Exclusion criteria
Case reports
Studies investigating technical aspects of a test

Sample Size
Not calculated

Randomisation Method
Not Applicable

Population
N=9 studies included representing a total of 3724 patients

Study Duration
Searches were conducted from 1990 to March 2009

The earliest included study took place in 1995 and the latest in 2009
Earliest participant enrolment given was 1992 and latest was 2003 (n=5 studies)

Interventions

Comparator tests included ultrasound, MRI, specialist led clinic exam and unstructured primary care follow-up

Reference Standard: histopathological assessment for positive tests and a period of follow-up for negative tests.

Outcomes

- Test performance in diagnosing ipsilateral and/or metachronous contralateral breast tumour recurrence in women undergoing routine surveillance.
- Test performance in diagnosing ipsilateral and/or metachronous contralateral breast tumour recurrence in women undergoing non-routine surveillance.

Other outcomes if reported:

- Adverse effects (defined as physical harms) of mammography and other tests
- Acceptability of tests
- Reliability of tests
- Radiological/Operator expertise
- Interpretability/readability of the tests

Sensitivity, specificity, positive predictive likelihood ratio and negative predictive likelihood ratio

Results

- No meta-analysis was conducted due to heterogeneity across the included studies.

- None of the included studies reached the criteria to be classed as higher quality.
- In 8 studies, it was unclear whether the time between positive test result and histopathological reference standard was short enough to avoid improvement or progression (disease progression bias).
- All studies were considered to have had appropriate follow-up time intervals for confirming negative test results and therefore were judged to be at low risk of disease progression bias for negative results.
- In one study (Shin, 2005) there is a risk of partial verification bias as it is unclear whether all patients with a negative result received follow-up.
- One study (Drew, 1998) was considered to be at risk of partial verification bias due to the fact that only patients with a positive MRI result were referred for reference standard verification.

- Median age = 53 years (range 22-82)
- Reported follow-up of test negatives = 5-32 months

Test	Study	Primary Surgical treatment	Reported sensitivity %	Reported Specificity %	+LR	-LR	Diagnostic OR (95% CI)
Surveillance Mammography	Bone (1995)	Mastectomy	64	97	22.2	0.4	60.3 (10.2-358.1)
	Drew (1998)	Breast Conserving Surgery	67	85	4.6	0.4	11.7 (2.6-52.4)
MRI	Bone (1995)	Mastectomy	86	Not Reported			
	Drew (1998)	Breast Conserving Surgery	100	93	14.3		
Clinical Exam	Bone (1995)	Mastectomy	50	Not Reported			

	Drew (1998)	Breast Conserving Surgery	89	76	3.7	0.2	25.4 (3.0-213.9)
Combined clinical exam and surveillance mammography	Drew (1998)	Breast Conserving Surgery	100	67	3.0		

Sensitivity, specificity, likelihood and diagnostic odds ratio for detecting ipsilateral breast tumour recurrence in patients undergoing routine surveillance (2 studies with a total of 188 patients)

Test	Study	Primary Surgical Treatment	Reported Sensitivity %	Reported Specificity (%)	+LR	-LR	Diagnostic OR (95% CI)
Surveillance Mammography	Belli (2002)	Breast Conservation	71	63	1.9	0.5	4.2 (2.6-52.4)
	Mumtaz (1997)	Breast Conservation	50	75	2.0	0.7	3 (0.6-14.0)
	Ternier (2006)	Breast Conservation	83	57	1.9	0.3	6.3 (2.5-15.6)
Ultrasound	Belli (2002)	Breast Conservation	43	31	0.6	1.8	0.3 (0.1-2.1)
	Ternier (2006)	Breast Conservation	87	73	3.2	0.2	17 (6.2-46.5)
MRI	Belli (2002)	Breast Conservation	100	94	16.0	IC	IC
	Mumtaz (1997)	Breast Conservation	93	88	7.4	0.1	91 (7.4-1126.9)
	Rieber (1997)	Breast Conservation	100	96	24.2	IC	IC
Clinical Examination	Belli (2002)	Breast Conservation	43	56	1.0	1.0	1.0 (0.2-5.8)
	Ternier (2006)	Breast Conservation	62	49	1.2	0.8	1.5 (0.7-3.4)

Sensitivity, specificity, likelihood and diagnostic odds ratio for detecting ipsilateral breast tumour recurrence in patients undergoing non-routine surveillance (4 studies with a total of patients)

Test	Study	Primary Surgical Treatment	Reported Sensitivity %	Reported Specificity (%)	+LR	-LR	Diagnostic OR (95% CI)
Surveillance Mammography	Bone (1995)	Mastectomy	67	50	1.3	0.7	2.0 (0.1-78.2)
MRI	Bone (1995)	Mastectomy	67	50	1.3	0.7	2.0 (0.1-78.2)
	Viehweg (2004)	Breast Conservation	91	90	9.4	0.1	93.1 (11.0-786.2)
Clinical Exam	Bone (1995)	Mastectomy	0	50			
Combined surveillance mammography and ultrasound	Kim (2009)	Mastectomy	95	99	61.5	0.05	1149.2 (148.0-8937.8)
		Breast Conservation					
Combined surveillance mammography, clinical exam and ultrasound	Viehweg (2004)	Breast Conservation	64	84	3.9	0.4	8.9 (2.4-33.0)
Combined surveillance	Viehweg (2004)	Breast Conservation	100	89	8.9	IC	IC

mammography, clinical examination, ultrasound and MRI							

Sensitivity, specificity, likelihood ratio and diagnostic odds ratio for detecting metachronous contralateral breast cancer in routine surveillance patients

- No study reported diagnostic accuracy of the tests for diagnosing metachronous contralateral breast cancer in non-routine surveillance.
- One study (Shin, 2005) reported on overall test performance of ultrasound for diagnosing both ipsilateral and metachronous contralateral breast cancer in routine surveillance. A sensitivity of 71%, specificity of 98%, +LR of 41.4, -LR of 0.3 and DOR=138.25 (95% CI, 61.26-312.04).
- None of the included studies reported on any of the other outcomes of interest.

General comments

There was no attempt to mix or compare the performance of tests used for non-routine adjunct imaging and tests used for routine surveillance as it is not known whether the accuracy of the tests differ due to the fact that a test operator is primed to evaluate a suspicious finding in the non-routine surveillance patients.

There was no attempt to mix or compare data on test performance for the detection of ipsilateral breast tumour recurrence and metachronous contralateral breast cancer due to anatomical differences between the treated and untreated breast.

Study quality was assessed using and adapted version of QUADAS with higher quality studies defined as those which included a representative patient spectrum and without partial verification bias. (i.e. whether the whole population received reference standard verification or not).

References for included studies

Bone B et al (1995) Contrast enhanced MR imaging of patients of the breast in patients with breast implants after cancer surgery *Acta Radiol*36:111-116

Kim MJ et al (2009) Sonographic surveillance for the detection of contralateral metachronous breast cancer in an Asian population *AJR Am J Roentgenol* 192;221-228

Belli P et al (2002) Role of magnetic resonance imaging in the diagnosis of recurrence after breast conserving surgery *Rays* 27:241-257

Drew PR et al (1998)Routine screening for local recurrence following breast conserving therapy for cancer with dynamic contrast enhanced magnetic resonance imaging of the breast *Ann Surg Oncol* 5:265-270

Mumtaz H et al (1997) Comparison of magnetic resonance imaging and conventional triple assessment in locally recurrent breast cancer *Br J Surg* 84;1147-1151

Rieber A et al (1997) Value of MR mammography in the detection and exclusion of recurrent breast carcinoma *J Comput Assist Tomogr* 21:780-784

Viehweg P et al (2004) MR imaging of the contralateral breast in patients after breast conserving surgery *Eur Radiol* 14:402-408

Shin JH et al (2005) Ultrasonographic detection of occult cancer in patients after surgical therapy for breast cancer *J Ultrasound Med* 24;643-649

Ternier F et al (2006) Computed tomography in suspected local breast cancer recurrence *Breast Cancer Res Treat* 100;247-254

Citation: Sardanelli F et al (2011) Multicentre surveillance of women at high genetic breast cancer risk using mammography, ultrasonography and contrast enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results *Investigative Radiology*

Design: Prospective, non randomised, multicentre study (18 centres in 14 towns)

Country: Italy

Setting: Surveillance/follow-up

Aim: to prospectively compare clinical breast examination (CBE), mammography, ultrasonography and MRI in the surveillance of women at high risk of inherited breast cancer including women with a previous history of breast cancer.

Inclusion criteria
Asymptomatic patients at high risk for breast cancer ≥25 years of age who were
Proven carriers of BRCA1/2 mutations
Untested first degree relatives of BRCA1/2 carriers
Strong family history of breast/ovarian cancer with 3 or more events in first or second degree relatives in either the maternal or paternal line
Anyone <25years only if there was early onset breast cancer in the patient or close relative

Exclusion criteria
Women with a personal history of breast cancer who had undergone bilateral total mastectomy
Pregnancy
Breast feeding
Current chemotherapy
Terminal illness
Contraindications to MRI or gadolinium based contrast agent administration

Sample Size
No details

Randomisation Method
Not applicable

Population
N=501 undergoing at least one round of surveillance

Study Duration
Junne 200-January 2007

Interventions
Full details were published in a preliminary assessment.
Annual evaluation with clinical breast exam, mammography, ultrasonography and MRI for at least 2 rounds
After 2 rounds, at least 1 year follow-up with CBE, mammography, ultrasonography and optional MRI with local investigators free to offer further surveillance to enrolled women at their discretion.

Outcomes
Breast Cancer Incidence, screen detected and interval cancers
Diagnostic Performance of screening modalities

Results

501 women underwent assessment in the first round
425 (85%) women underwent assessment in the second round
336 (67%) underwent 3rd round assessment
228 (46%) underwent 4th round assessment

Reasons include: voluntary withdrawal or loss to follow-up, prophylactic bilateral mastectomy, screen detected or interval cancer, other diseases or onset/evolution of concurrent ovarian cancer.

52 patients were found to have breast cancer, 49 of whom were screen detected and 3 were interval cancers
A 3.3% (95% CI, 2.4%-4.3%) overall incidence rate per woman-year analysis was observed with a significant age trend (p=0.003), increasing from;

- 0 of 86 (0.0%) in women under 30 years
- 9 of 389 (2.3%) for women aged 30-39 years
- 12 of 466 (2.6%) for women aged 40-49 years
- 17 of 375 (4.5%) for women aged 50-59 years
- 11 of 223 (4.9%) for women aged 60- 69 years
- 3 of 53 (5.7%) for women aged over 69 years

A significant difference between incidence for women under 50 and women aged over 50 years was observed:

- 21/941 (2.2%. 95% CI, 1.4%-3.4%) versus 31/651, (4.8%, 95% CI, 3.3%-6.7%) p=0.005

No significant difference between was observed between women with proven (or first degree relatives of) BRCA1 mutation carriers, proven (or first degree relatives of) BRCA2 mutation carriers, and women enrolled only on the basis of family history

- 21/566 (3.7%, 95% CI, 2.3%-5.6%); 10/477 (2.1%, 95% CI, 1.0%-3.8%) and 21/549 (3.8%, 95% CI, 2.4%-5.8%) respectively (p=0.227).

A significant difference was observed between women with a personal history of breast cancer and women without:

- 29/674 (4.3%, 95% CI 2.9%-6.1%) versus 23/918 (2.5%, 95% CI, 1.6%-3.7%); p=0.045

Overall detection rate per year-woman was 49/1592 (3.1%, 95% CI2.3%-4.0%)
Overall incidence of interval cancers per year-woman was 3/1592 (0.2%, 95% CI, 0.0%-0.5%)

A total of 50 cancers were studied with mammography; 17 were diagnosed and 14 were not diagnosed using film screen mammography (sensitivity 17/31, 55%) and 8 were diagnosed and 11 were not diagnosed using digital mammography (sensitivity 8/19, 42%) p=0.560.

Sensitivity of MRI was significantly higher compared with mammography, ultrasonography, CBE or a combined mammography and ultrasonography (p<0.001):

- MRI=91%
- Mammography=50%
- Ultrasonography=52%
- CBE=18%
- Combined mammography and ultrasonography=63%

No significant difference in the sensitivity of MRI plus mammography, MRI plus ultrasonography, MRI plus mammography plus ultrasonography or MRI alone was observed (no p value given)

- MRI plus mammography=93%
- MRI plus ultrasonography=93%
- MRI plus mammography plus ultrasonography=93%
- MRI alone=91%

Specificities ranged from 96% to 99%
Positive predictive values ranged from 53% to 71%
Positive likelihood ratios ranged from 23.6 to 52.3
Negative predictive values ranged from 96% to 100% (no significant differences)
Negative likelihood ratios differed significantly for MRI versus ultrasonography, mammography or CBE ($p<0.05$)

- MRI=0.09
- Ultrasonography=0.49
- Mammography=0.5
- CBE=0.83

Of all 52 cancers, 16 (31%) were diagnosed by MRI alone:

- 8/21 (38%) in women below 50 years of age and 8/31 (26%) in women older than 50 years of age (p=0.155).

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Overall (1592 rounds)						
Clinical breast examination	9/51 17.6 (8.4-30.9)	1040/1047 99.3 (98.6-99.7)	9/16 56.3 (29.9-80.2)	1040/1082 96.1 (94.8-97.2)	26.4 (9.5-73.7)	0.83 (0.55-1.26)
Mammography	25/50 50.0 (35.5-64.5)	1035/1045 99.0 (98.2-99.5)	25/35 71.4 (53.7-85.4)	1035/1060 97.6 (96.5-98.5)	52.3 (23.8-114.7)	0.50 (0.31-0.82)
Ultrasonography	26/50 52.0 (37.4-66.3)	1000/1016 98.4 (97.5-99.1)	26/42 61.9 (45.6-76.4)	1000/1024 97.7 (96.5-98.5)	33.0 (16.7-65.5)	0.49 (0.30-0.80)
MRI	42/46 91.3 (79.2-97.6)	966/999 96.7 (95.4-97.7)	42/75 56.0 (44.1-67.5)	966/970 99.6 (98.9-99.9	27.6 (16.1-47.6)	0.09 (0.03-0.25)
Mammography+ultrasonography	30/48 62.5 (47.4-76.0)	975/999 97.6 (96.4-98.5)	30/54 55.6 (41.4-69.1)	975/993 98.2 (97.2-98.9)	26.0 (14.1-47.9)	0.38 (0.22-0.67)
MRI+mammography	41/44 93.2 (81.3-98.6)	944/980 96.3 (95.0-97.4)	41/77 53.2 (41.5-64.7)	944/947 99.7 (99.1-99.9)	25.4 (14.8-43.5)	0.07 (0.02-0.23)
MRI+ultrasonography	42/45 93.3 (81.7-98.6)	923/961 96.0 (94.6-97.2)	42/80 52.5 (41.0-63.8)	923/926 99.7 (99.1-99.9)	23.6 (13.9-40.1)	0.07 (0.02-0.22)
Women <50 (941 rounds)						
Mammography	10/22 45.5 (24.4-67.8)	628/636 98.7 (97.5-99.5)	10/18 55.6 (30.8-	628/640 98.1 (96.7-99.0)	36.1 (13.0-100.4)	0.55 (0.27-1.13)

			78.5)			
Ultrasonography	9/21 42.9 (21.8-66.0)	620/630 98.4 (97.1-99.2)	9/19 47.4 (24.4-71.1)	620/632 98.1 (96.7-99.0)	27.0 (9.9-73.4)	0.58 (0.28-1.19)
MRI	16/18 88.9 (65.3-98.6)	595/616 96.6 (94.8-97.9)	16/37 43.2 (27.1-60.5)	595/597 99.7 (98.8-1.00)	26.1 (11.7-58.1)	0.12 (0.03-0.50)
Women ≥50 (651 rounds)						
Mammography	15/28 53.6 (33.9-72.5)	407/409 99.5 (98.2-99.9)	15/17 88.2 (63.6-98.5)	407/420 96.9 (94.8-98.3)	109.6 (23.9-503.1)	0.47 (0.24-0.91)
Ultrasonography	17/29 58.6 (38.9-76.5)	380/386 98.4 (96.6-99.4)	17/23 73.9 (51.6-89.8)	380/392 96.9 (94.7-98.4)	37.7 (13.8-103.0)	0.42 (0.21-0.84)
MRI	26/28 92.9 (76.5-99.1)	371/383 96.9 (94.6-98.4)	26/38 68.4 (51.3-82.5)	371/373 99.5 (98.1-99.9)	29.6 (13.5-64.9)	0.07 (0.02-0.31)

ROC Curve analysis (Curves provided in the paper)

Modality	AUC (95% CI)	SE	Difference (95% CI)	SE	Z	P
Mammography	0.83 (0.76-0.90)	0.038	0.01 (-0.08-0.08)	0.038	0.37	0.715
Ultrasonography	0.82 (0.74-0.89)	0.038				
MRI	0.97 (0.94-1)	0.014	0.14 (0.07-0.22)	0.039	3.89	0.0002
Mammography	0.83 (0.78-0.9)	0.036				
MRI	0.97 (0.94-1)	0.014	0.16 (0.08-0.23)	0.040	3.92	<0.0001
Ultrasonography	0.82 (0.74-0.89)	0.037				
MRI	0.97 (0.94-1)	0.014	0.19 (0.03-0.17)	0.036	2.90	0.0037
Mammography + Ultrasonography	0.87 (0.80-0.93)	0.034				
MRI	0.97 (0.94-1)	0.014	-0.01 (-0.03-0.01)	0.09	-1.21	0.2256
MRI + Mammography	0.98 (0.97-0.008)	0.006				
MRI	0.97 (0.94-1)	0.014	-0.01 (-.03-0.01)	0.008	-1.07	0.2827
MRI + Ultrasonography	0.98 (0.97-0.99)	0.007				
MRI	0.97 (0.94-1)	0.014	-0.01 (-0.02-0.01)	-0.97	-0.97	0.3344
MRI +Mammography + Ultrasonography	0.98 (0.96-0.99)	0.007				

General comments

Citation: Houssami et al (2011) Breast screen based mammography screening in women with a personal history of breast cancer, Western Australia study *Medical Journal of Australia* 195;8:460-464

Design: Retrospective case series

Country: Australia

Setting: Follow up

Aim: to evaluate mammography screening outcomes in women with a personal history of breast cancer and who have an increased risk of recurrent or new breast cancer as compared with women with no personal history

Inclusion criteria
All screening mammograms for women reporting a personal history of breast cancer
Screening mammograms in women with no personal history for comparison

Exclusion criteria
None given

Sample Size
No details

Randomisation Method
Not applicable

Population
N=713191 screens

- N=12358 in women with personal history
- N=700833 in women with no personal history

Study Duration
Screening occurred between January 1997 and December 2006

Interventions
Mammography Screening

Outcomes
Number of screens
Number of breast cancers detected
Cancer detection rate
Recall to assessment rates
Positive predictive value for recall
Proportion of screens detecting cancer that required multiple reads

Results
Screening detected 118 breast cancers in women with a personal history for a cancer detection rate of 95.5/10,000 screens (95% CI, 78.3-112.7)

Cancer detection rates

Initial Screening exams		
40-49 years	9	559 (259-1035)
50-69 years	51	664.9 (482.4-847.4)

≥70 years	20	760.5 (427.2-1093.7)
All age groups	80	671.7 (524.5-818.9)
Repeat Screening exam (incident screening)		
40-49 years	24	567.4 (340.4-794.4)
50-69 years	303	350.9 (268.9-390.5)
≥70 years	69	327 (249.9-404.2)
All age groups	396	354.6 (319.7-389.5)
All screening exams		
40-49 years	33	565.1 (372.3-757.9)
50-69 years	354	376.6 (337.3-415.8)
≥70 years	89	375.1 (297.1-453)
All age groups	476	385.2 (350.6-419.8)

Rates of recall to assessment in women with a personal history of breast cancer

Positive predictive value for recall in women with a previous history of breast cancer was 24.8% (95% CI, 10.9%-11.6%).
The rate of screens requiring three or more reads was 36.4/10000 screens (95% CI 25.8-47.1)

General comments

The study compared results between women with a personal history of breast cancer and women without a personal history. This comparison was not relevant to the topic and therefore only the results relating to women with a personal history of breast cancer are presented here.

6.4 References (2013)

Duffy, S. W. et al (2010). Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: Tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. *The Lancet Oncology*, 11;1127-1134.

Elmore L et al (2010) Breast MRI surveillance in women with prior curative-intent therapy for breast cancer *Journal of Surgical Research* 163;1:58-62

Halapy, E., et al. (2005) "Accuracy of breast screening among women with and without a family history of breast and/or ovarian cancer." *Breast Cancer Research & Treatment* 90;3:299-305

Houssami et al (2011) Breast screen based mammography screening in women with a personal history of breast cancer, Western Australia study *Medical Journal of Australia* 195;8:460-464

Jansen-van der Weide MC, Greuter, M. J., Jansen, L., Oosterwijk, J. C., Pijnappel, R. M., & de Bock, G. H. (2010). Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. *Eur Radiol*., 20;2547-2556.

Kuhl, C. K., et al. (2005) "Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer." *Journal of Clinical Oncology* 23;.33 :8469-76

Leach, M. O., et al. (2005) "Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)." *Lancet* 365;9473:1769-78.

Maurice, A., Evans, D. G., Affen, J., Greenhalgh, R., Duffy, S. W., Howell, A. et al. (2012). “Surveillance of women at increased risk of breast cancer using mammography and clinical breast examination: further evidence of benefit.” *International Journal of Cancer*, 131;417-425.

Maurice, A., et al. (2006) "Screening younger women with a family history of breast cancer--does early detection improve outcome?" *European Journal of Cancer* 42;10:1385-90.

Riedl, C. C., et al. (2007) "Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer." *Clinical Cancer Research* 13;20: 6144-52.

Rijnsburger, A. J., et al. (2004) "Impact of screening for breast cancer in high-risk women on health-related quality of life." *British Journal of Cancer* 91;1:69-76.

Robertson C et al (2011) Surveillance mammography for detecting ipsilateral breast tumour recurrence and metachronous contralateral breast cancer: a systematic review *European Radiology* 21;2484:2491

Sardanelli F et al (2011) Multicentre surveillance of women at high genetic breast cancer risk using mammography, ultrasonography and contrast enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results *Investigative Radiology*

Trop, I., et al. (2010) "Multimodality breast cancer screening in women with a familial or genetic predisposition." *Current Oncology* 17;3: 28-36.

Warner, E., et al. (2008) "Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. [Review] [35 refs]." *Annals of Internal Medicine* 148;9: 671-79.

Excluded Studies

Abraham, L., et al (2009) “Accuracy of self-reported breast cancer among women undergoing mammography.” *Breast Cancer Research & Treatment* 118;3:583-592.
Reason: No comparator

Banks, E., et al. (2004) "Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study." *British Medical Journal* 329;7464: 477-79.
Reason: Screening of general population. High risk women were not reported as a sub-group

Beattie, M. (2005) "The addition of MRI greatly improved the sensitivity of screening for early breast cancer in mutation carriers." *Evidence-based Obstetrics and Gynecology* 7;2: 100-02.
Reason: Appraisal of Warner et al (2004) and MRISC studies

Bennett, I. C., et al. (2010) "Outcomes of multimodality breast screening for women at increased risk of familial breast cancer." *World Journal of Surgery* 34;5:979-86.
Reason:Non-comparative study

Bermejo-Perez, M. J., et al. (2008) "Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review. [Review] [42 refs]." *British Journal of Radiology* 81;963:172-79.
Reason: Narrative review of cancer surveillance based on imaging techniques for BRCA1/2 carriers specifically. Studies including individuals without a BRCA 1/2 mutation were excluded unless results from the sub-group could be extrapolated.

Bolt, S., et al. (2008) "A review of breast cancers found in the Welsh Family History screening programme." *Breast Cancer Research* 10
Reason: Abstract of a poster presentation. Includes insufficient data to allow inclusion.

Bosse, K. (2010) "The value of breast ultrasound in BRCA1 and BRCA2 mutation carriers." *Archives of Gynecology and Obstetrics* Conference.Deutsche Gesellschaft fur Gynakologie und Geburtshilfe, DGGG Munich-S46.
Reason: Abstract. Includes insufficient data to allow inclusion.

Brandt, A., et al. (2010) "Breast cancer risk in women who fulfill high-risk criteria: at what age should surveillance start?" *Breast Cancer Research & Treatment* 121;1:133-41.
Reason: Non-comparative study

Clements, A., et al (2008). 'More positive about mammography' - reactions of women to a false positive recall: a qualitative study of women at risk of familial breast cancer. *Breast Cancer Research* 10:S45-S46
Reason: Abstract Only

Coolen, A. (2011) "False-negative tests in breast cancer management." *Netherlands Journal of Medicine* 69;7: 324-29.
Reason: Non-systematic review of false negative tests in breast cancer management.

Cortesi, L. Turchetti. (2006) "Breast cancer screening in women at increased risk according to different family histories: An update of the Modena Study Group experience." *BMC Cancer* 6;210.
Reason: No personal history/outcomes not relevant to PICO

De Bock, G. (2010) "The effectiveness of breast cancer screening with MRI and mammography in women with a BRCA1/2 mutation." *European Journal of Cancer, Supplement* Conference.var.pagings:240.
Reason: Study of the efficacy screening in the prevention of breast cancer recurrence.

de Gonzalez, A., et al.(2009) "Estimated Risk of Radiation-Induced Breast Cancer From Mammographic Screening for Young BRCA Mutation Carriers." *Journal of the National Cancer Institute* 101;3:205-09.
Reason: Non-comparative study

Dent, R., et al. (2007) "Screening for hereditary breast cancer. [Review] [65 refs]." *Seminars in Oncology* 34;5: 392-400.
Reason: Non-systematic narrative review of screening for women with hereditary breast cancer.

Dorval, M., et al (2011) Breast and ovarian cancer screening of non-carriers from BRCA1/2 mutation-positive families: 2-year follow-up of cohorts from France and Quebec. *European Journal of Human Genetics* 19;5:494-499
Reason: No personal history

Edwards, S., et al (2011) "Knowledge of Breast Screening and Compliance with Annual Screening in Women with A Family History of Breast Cancer." *American Journal of Epidemiology* 173;S304.
Reason: Abstract Only

Elmore, L., et al.(2010) "Use of breast MRI surveillance in women at high risk for breast cancer: a single-institutional experience." *Annals of Surgical Oncology* 17;Suppl 3:263-67.
Reason: Non-comparative study

Fries, M. H., et al.(2004) "Outcome of five years of accelerated surveillance in patients at high risk for inherited breast/ovarian cancer: report of a phase II trial." *Military Medicine* 169;6: 411-16.
Reason: Non-comparative study

Gilbert, F. J. and F. J. Gilbert. (2005) "Should we use MRI to screen women at high-risk of breast cancer?" *Cancer Imaging* 5;1:32-38.
Reason: Non-systematic narrative review of breast cancer screening using MRI.

Gorecka-Szyld, B.(2005) "Mammographic and sonomammographic patterns of breast cancer in women belonging to a genetically confirmed risk group with a detected BRCA1 gene mutation." *Polish Journal of Radiology* 70;1:13.
Reason: Non-comparative study

Grann, V. R., et al. (2011) "Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers." *Breast Cancer Research & Treatment* 125;3: 837-47.
Reason: Simulated cohort of women.

Greuter, M. J. W. (2010) "The validation of a simulation model incorporating radiation risk for mammography breast cancer screening in women with a hereditary-increased breast cancer risk." *European Journal of Cancer* 46;3:495-504.
Reason: Simulation model of breast cancer screening

Gui, G. P., et al. (2006) "Clinical outcome and service implications of screening women at increased breast cancer risk from a family history." *European Journal of Surgical Oncology* 32;7:719-24.
Reason: Non-comparative study

Hermsen, B. B., et al. (2007) "No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study." *British Journal of Cancer* 96;9:1335-42.
Reason: Non-comparative study

Hoogerbrugge, N. (2008) "The impact of a false-positive MRI on the choice for mastectomy in BRCA mutation carriers is limited." *Annals of Oncology* 19;4:655-59.
Reason: Non-comparative study

Immonen-Raiha, P., et al (2005) “Mammographic screening reduces risk of breast carcinoma recurrence.” *Cancer* 103;3:474-482.
Reason: Protocol for screening unclear

Jansen-van der Weide, M. C. G. (2010) "Mammography screening and radiation-induced breast cancer among women with a familial or genetic predisposition: A meta-analysis." *European Journal of Cancer*, Supplement Conference.var.pagings:239.
Reason: Systematic review of radiation-induced breast cancer. Presented as an abstract only. Contained insufficient data to allow conclusion.

Ji, J., et al. (2007) "Risk for contralateral breast cancers in a population covered by mammography: effects of family history, age at diagnosis and histology." *Breast Cancer Research & Treatment* 105;2: 229-36.
Reason: Non-comparative study

Kaas, R., et al. (2008) "Stage of breast cancers found during the surveillance of women with a familial or hereditary risk." *European Journal of Surgical Oncology* 34;5:501-07.
Reason: Included women with a personal history of breast cancer

Khatcheressian, J. L., et al (2006) “American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting.” *Journal of Clinical Oncology* 24;31:5091-5097.
Reason: Not relevant to PICO

Kriege, M. (2005) "MRI screening for breast cancer in women with a familial or genetic predisposition." *Imaging Decisions MRI* 9;2:11-18.
Reason: Non-systematic review

Kuhl, C., et al.(2010) "Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial." *Journal of Clinical Oncology* 28;9: 1450-57.
Reason: Diagnostic accuracy outcomes included in Warner et al (2008)

Leach, M. O. and Martin O. Leach.(2009) "Breast cancer screening in women at high risk using MRI. [Review] [56 refs]." *NMR in Biomedicine* 22;1: 17-27.
Reason: Non-systematic narrative review of breast cancer screening using MRI.

Lee, J. M., et al. (2008) "Breast cancer screening in BRCA1 mutation carriers: effectiveness of MR imaging--Markov Monte Carlo decision analysis." *Radiology* 246;3:763-71.
Reason: Simulation model of breast cancer screening

Lehman, C. D. (2006) "Role of MRI in screening women at high risk for breast cancer." *Journal of Magnetic Resonance Imaging* 24;5:964-70.
Reason: Non-systematic review

Le-Petross, H. T. A. (2009) "Effectiveness of screening women at high risk for breast cancer with alternating mammography and MRI." *Cancer Research Conference*.var.pagings
Reason: Non-comparative study

Lemon, S. C., et al (2006) "Mammography screening after breast cancer diagnosis in a first degree female relative: age group differences (United States)." *Cancer Causes & Control* 17;8:1053-1065
Reason: Not relevant to PICO (predictive factors)

Licklider, D., et al (2004) "Outcome of five years of accelerated surveillance in patients at high risk for inherited breast/ovarian cancer: Report of a phase II trial." *Military Medicine* 169;6:411-416.
Reason: Phase II trial

Lim, Y., E. Hurley, and P. Riley. (2010) "Screening MRI in patients at high risk of breast carcinoma from the Manchester family history clinic: our initial 2-year experience." *Breast Cancer Research* 12
Reason: Abstract only. Includes insufficient data to allow inclusion.

Lord, S. J., et al. (2007) "A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. [Review] [30 refs]." *European Journal of Cancer* 43;13:1905-17.
Reason: Systematic review, includes the same studies as Warner et al (2008).

Mackay, J., et al (2001) "Development of a protocol for evaluation of mammographic surveillance services in women under 50 with a family history of breast cancer." *Journal of Epidemiology & Biostatistics* 6;5:365-369.
Reason: Protocol

Maurice, A., et al (2012)." Surveillance of women at increased risk of breast cancer using mammography and clinical breast examination: Further evidence of benefit." *International Journal*

of Cancer 131;2:417-425
Reason: Not post treatment surveillance

Moller, P., et al (2007) “Surveillance for familial breast cancer: Differences in outcome according to BRCA mutation status.” *International Journal of Cancer* 121;5:1017-1020.
Reason: Not follow-up following treatment

Randall, D., et al. (2009) "Annual or biennial mammography screening for women at a higher risk with a family history of breast cancer: prognostic indicators of screen-detected cancers in New South Wales, Australia." *Cancer Causes & Control* 20;5:559-66.
Reason: Included women with a personal history of breast cancer

Robertson, C., et al (2011).” The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews registry database analyses and economic evaluation.” *Health Technology Assessment* 15;34:v-322.
Reason: Population not relevant (included all patients and no subgroup analysis)

Salas, D., et al. (2011) "Effect of start age of breast cancer screening mammography on the risk of false-positive results." Preventive Medicine 53;1-2:76-81.
Reason: Non-comparative study

Saslow, D., et al (2007) “American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography.” CA: *A Cancer Journal for Clinicians* 57;2:75-89
Reason: Guidelines

Sardanelli, F., et al. (2007) "Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results." *Radiology* 242;3:698-715.
Reason: Included women with a personal history of breast cancer (included in topic I)

Sardanelli, F., et al. (2007) "Breast MR imaging in women at high-risk of breast cancer. Is something changing in early breast cancer detection?. [Review] [121 refs]." *European Radiology* 17;4;873-87.
Reason: Non-systematic review.

Saunders, C. M., et al. (2009) "A pilot study of trimodality breast imaging surveillance in young women at high risk of breast cancer in Western Australia." *Medical Journal of Australia* 191;6:330-33.
Reason: Included women with a personal history of breast cancer. Results for the sub-group of women with no personal history could not be extrapolated.

Schmutzler, R. K., et al.(2006) "Outcome of a structured surveillance programme in women with a familial predisposition for breast cancer." *European Journal of Cancer Prevention* 15;6:483-89.
Reason: Non-comparative study

Schrading, S., et al. (2008) "Mammographic, US, and MR imaging phenotypes of familial breast cancer." *Radiology* 246;1:58-70.
Reason: Describes imaging features of breast cancers detected in women with familial history.

Shah, P., et al. (2009) "Prospective study of breast MRI in BRCA1 and BRCA2 mutation carriers: effect of mutation status on cancer incidence." *Breast Cancer Research & Treatment* 118;3:539-46.

Reason: Non-comparative study

Shin, D. W. B. (2011) “Knowledge, attitudes, and practice on second primary cancer screening among cancer survivors: A qualitative study.” *Patient Education and Counseling* 85;1:74-78.
Reason: Population not relevant to PICO

Sim, L. S., et al. (2004) "Breast ultrasound in women with familial risk of breast cancer." *Annals of the Academy of Medicine, Singapore* 33;5:600-06.

Sung, J. S. M. (2011) Screening breast MR imaging in women with a history of lobular carcinoma in situ. *Radiology* 261;2: 414-420
Reason: Excludes relevant population

Sung, J. S., et al (2011) “Screening breast MR imaging in women with a history of lobular carcinoma in situ.” *Radiology* 261;2:414-420.
Reason: Population not relevant to PICO

Surgey E. (2011) "Dual MRI and mammographic screening for women at increased familial breast cancer risk: A tertiary centre experience." *European Journal of Surgical Oncology Conference*.var.pagings;1014.
Reason: Non-comparative study

Tardivon, A. (2010) "Surveillance of gene mutation carriers with mammography, ultrasound, and magnetic resonance imaging: Results of a multicentric prospective trial (REMAGUS interdisciplinary group)." *European Journal of Cancer*, Supplement Conference.var.pagings;224.
Reason: Non-comparative study

Taylor, L., et al. (2011) "Time for a re-evaluation of mammography in the young? Results of an audit of mammography in women younger than 40 in a resource restricted environment." *Breast Cancer Research & Treatment* 129;1:99-106.
Reason: Non-comparative study

Tilanus-Linthorst, M. M. A. (2007) "BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imaging screening trials." *Clinical Cancer Research* 13;24: 7357-62.
Reason: Non-comparative study

Trecate, G., et al. (2003) "Breast MRI screening in patients with increased familial and/or genetic risk for breast cancer: a preliminary experience." *Tumori* 89;2:125-31.
Reason: Non-comparative study

Trecate, G., et al. (2006) "MRI in the early detection of breast cancer in women with high genetic risk." *Tumori* 92;6: 517-23.
Reason: Non-comparative study

Vasen, H. F., et al. (2005) "Early detection of breast and ovarian cancer in families with BRCA mutations." *European Journal of Cancer* 41;4:549-54.
Reason: Non-comparative study

Warner, E., et al (2008) “Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer.” [Review] [35 refs]. *Annals of Internal Medicine* 148;9:671-679
Reason: More recent systematic review available (Robertson et al, 2011)

Warner, E., et al. (2011) "Improvement in DCIS detection rates by MRI over time in a high-risk breast screening study." *Breast Journal* 17;1:9-17.
Reason: Study of the impact of experience on the ability to detect DCIS in screening MRI.

Warner, E. and Ellen Warner. (2008) "The role of magnetic resonance imaging in screening women at high risk of breast cancer. [Review] [50 refs]." *Topics in Magnetic Resonance Imaging* 19;3:163-69.
Reason: Non-systematic narrative review.
Wunderlich, P., et al (2009) “Intensified Screening Program for Women with Hereditary Predisposition to Develop Breast Cancer - Our Study Results and Current Knowledge in the Literature.” *Geburtshilfe und Frauenheilkunde* 69;7:623-630.
Reason: Foreign Language

Yankaskas, B. C., et al. (2010) "Performance of first mammography examination in women younger than 40 years." *Journal of the National Cancer Institute* 102;10:692-701.
Reason: This was a study of women who received their first mammogram under the age of 40. Only 11% had a family history of breast cancer

Yau, T. K., et al (2008) “Surveillance mammography after breast conservation therapy in Hong Kong: Effectiveness and feasibility of risk-adapted approach.” *Breast* 17;2:132-137
Reason: No comparison

Yu, J., et al. (2008) "MRI screening in a clinic population with a family history of breast cancer." *Annals of Surgical Oncology* 15;2:452-61.
Reason: Retrospective review of MRI screening in women with a family history of breast cancer.

6.5 Appendix 1 (Evidence Tables CG14 and CG41)

Evidence Table: MRI surveillance (CG41, 2006)

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
Leach, M. O., Boggis, C. R., Dixon, A. K., et al 2005, "Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)", Lancet, vol. 365, no. 9473, pp. 1769-1778. UK Multi- centre study carried out between Aug 1997 and May 2004	Prospective cohort	++	A Comparison of contrast enhanced magnetic resonance imaging (CE MRI) with mammography for screening in women at high familial risk of breast cancer.	Total n=649 n = strong family history of breast cancer or high probability of *BRCA1*, *BRCA2* or *TP53* n=139 *BRCA1* mutation or first degree relative with mutation (known *BRCA1* n=82) n=86 *BRCA2* mutation or first degree relative with mutation	All women: 2% *BRCA1* 3% of increased risk *BRCA2* 5% of increased risk	Inclusion criteria: Known carriers of *BRCA1*, *BRCA2* *TP53* mutation; first degree relative of someone with *BRCA1*,*BRCA2* or *TP53* (the latter screened from age 25); strong family history of breast or ovarian cancer (annual risk of breast cancer of at least 0.9%); or family history consistent with classic Li- fraumeni syndrome Aged between 31-55 (mean age 40) No previous breast cancer or with any other cancer if their expected prognosis was <5 years.	Women had the opportunity to have at least two annual scans. 76% (1437 of 1881) of mammography and MRI examinations were performed on the same day. 4% (71 of 1881) were performed more than one month apart. Both MRI and mammography screenings were double reported and the results were blinded. BIRADS category 3 (indeterminate, probably benign) or above used as definition of a	mammography	Sensitivity: 95% CI All women: MRI 77% (60-90) mammography 40% (24-58) p=0.01 (MRI versus mammography) combined 94% (81-99) Women with *BRCA1* or first degree relative with *BRCA1* n=139 MRI 92% (64-100), mammography 23% (5-54) p=0.004 (MRI versus mammography) Combined 92% (64-100) Women with *BRCA2* or first degree relative with *BRCA2* n=86 MRI 58% (28-84)	PPV: 95% CI MRI 7.3% (4.9-10), mammography 10% (5.8-17) Combined 7% (6-8) NPV: MRI 99% (99-100) mammography 99% Combined 100% *BRCA1* group: PPV MRI 14% (7.2-23), mammography 9.1% (1.9-23) Combined 11% (8-14) NPV MRI 100%, mammography 97% (95-99) Combined 100% *BRCA2* PPV MRI 15% (10-19), mammography 32% (26-37), combined 18%	Medical Research Council, National Health Service	1881 screening tests performed 35 cancer s detected, 19 by MRI, 6 by mammography, 8 by both MRI and mammography, with two interval cases. *BRCA1* or first degree relative with *BRCA1* 13 cancers detected. 9 by MRI, 0 by mammography, 3 by both, 1

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
				(Known *BRCA2* n=38)		Exclusion criteria: women who underwent predictive genetic testing and had a negative result or those who developed cancer during the study.	positive test. The MRI score and the Mammography score were compared every year with the woman's true cancer status as ascertained by pathology or by the absence or presence of an interval cancer in the year after examination		mammography 50% (21-79) p=1.0 (MRI versus mammography) Combined 92% (62-100) Specificity: 95% CI All women: MRI 81%(80-83), mammography 93% (92-95) p=<0.0001(MRI versus mammography) Combined 77% (75-79) Women with *BRCA1* or first degree relative with *BRCA1* n=139 MRI 79% (75-83), mammography 92% (88-94) p=<0.0001 (MRI versus mammography) Combined 74% (69-78) Women with *BRCA2* or first degree relative with *BRCA2*	(13-23) NPV MRI 97% (95-99), mammography 97% (95-99) Combined 99% (99-100)		interval case *BRCA2* or first degree relative with *BRCA2* 12 cancers detected 5 by MRI, 4 by mammography, 2 by both, 1 interval cancer

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
									n=86 MRI 82% (77-87) mammography 94% (91-97), p=0.0001 (MRI versus mammography) Combined 78% (72-83)			
Kriege, M., Brekelmans, C. T., Boetes, et al. 2004, "Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition", New England Journal of Medicine, vol. 351, no. 5, pp. 427-437. Multi-centre study carried out in the Netherlands between Nov 1999 and Oct 2003	Prospecti ve cohort study	++	The value of regular surveillance in women at high risk, efficacy of MRI compared to mammography, quality of life effects during screening, cost- effectiveness of regular screening	Total n= 1909 n=358 mutation carriers (*BRCA1*, *BRCA2*, PTEN, *TP53*) n=1052 high risk group (30-49 % cumulative lifetime risk) n=499 moderate risk (15-29% cumulative lifetime risk)	1%	Inclusion criteria: Life time risk for breast cancer of 15% or more, Aged 25-70 (mean 40), or younger than 25 from families with very young age onset (<30 years), Exclusion criteria: Previous breast cancer or a personal history of breast cancer	Women screened every 6 months with clinical breast examination, and once a year with mammography and MRI independently. Both tests were carried out on the same day, or in the same time period, between day 5 and 15 of the menstrual cycle. BIRADS category 3 (probably benign) or above used as definition of a positive test. The results were blinded	mammography	Sensitivity for all cancers: mammography 40%, MRI 71.1% For invasive breast cancer: Sensitivity: mammography 33.3%, MRI 79.5 % Specificity: mammography 95.0%, MRI 89.8 %	PPV: mammography 8%, MRI 7.1% NPV: 100%	Dutch Health insurance Council	Median Follow-up 2.9 years (mean 2.7, range, 0.1 to 3.9 years) 50 cancer s detected in total (5 excluded from analysis). Cancers detected: In total. 32 by MRI, 22 by MRI only. 18 by mammogr aphy, 8 mammogr aphy only, 10 by both

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
							so the two examinations were not linked. Characteristics of cancers detected were compared with the characteristics of those in two different age-matched control groups					mammogr aphy and MRI
Warner, E., Plewes, D. B., Hill, K. et al. 2004, "Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography , and clinical breast examination", JAMA, vol. 292, no. 11, pp. 1317-1325 Single centre study carried out in Canada between Nov	Prospecti ve cohort study	++	Compare the sensitivity and specificity of four methods of breast cancer surveillance (mammograph y, MRI, ultrasound (not extracted) & clinical breast examination (CBE) (not extracted) .	Total n=236 With *BRCA1* or *BRCA2* mutations	5%	Inclusion criteria: *BRCA1* or *BRCA2*, between ages 25-65, (mean 46.6 years) Exclusion criteria: history of bilateral breast cancer, undergoing chemotherapy, known to have metastatic disease, women who weighed more than 91 kg	Between 1-3 annual screening examinations using 4 screening modalities (CBE,mammo graphy, ultrasound and MRI performed on the same day. Each imaging read and scored independently by different radiologist. Radiologists were blinded to results of CBE. BIRADS category 4 (suspicious	Mammography	Sensitivity: 95% CI MRI 77% (73-81) , Mammography 36% (32-41), Specificity: 95% CI MRI 95.4% (93-97), mammography 99.8% (99-100)	PPV: 95% CI MRI 46% (41-51) Mammography 89% (86-92) NPV: 95% CI MRI 99% (98-100) Mammography 97% (95-98)	Canadian Breast Cancer Research Alliance, The Terry Fox Foundati on, Internatio nal Breast MRI Consortiu m, Canadian national Breast Cancer Fund, Papoff Family	(Results broken down by year. Total for all years not given in original table, this has been calculated) Participan ts were followed up for 1 year from the date of last screening 22 cancers

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
1997 and March 2003.							abnormality, biopsy should be considered) or above used as definition of a positive test. All lesions with a score of 4 or 5 were biopsied					detected (16 invasive, 6 ductal carcinoma in situ). 17 by MRI 7 by MRI alone, 8 by mammography 2 by mammography alone. MRI detected 9 (75%) of 12 cancers missed by conventional surveillance (mammography & CBE) All 22 patients who had a cancer detected are currently alive and disease free

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
Kuhl, C. K., Schrading, S., Leutner, C. C., Morakkabati- Spitz, N., Wardelmann, E., Fimmers, R., Kuhn, W., & Schild, H. H. 2005, "Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer", *Journal of Clinical Oncology.*, vol. 23, no. 33, pp. 8469-8476. Ref ID: 224 single study centre study carried out at the University of Bonn Medical School, Germany between	Prospecti ve cohort	++	Comparison of sensitivity & specificity of mammography, breast ultrasound (not reported) and MRI imaging.	Total n= 529, previous history of breast cancer n=139, no previous history of breast cancer n=390 lifetime risk of 20% n=110, lifetime risk of 21-40% n= 241, mutation carriers n=43	All women: 3% Lifetime risk of 20%: 2% Lifetime risk of 21-40%: 3% Mutation carriers: 5%	Inclusion criteria: asymptomatic, meet criteria for high familial risk defined by consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid, corresponding to life time risk of breast cancer of at least 20% Exclusion criteria: current signs or symptoms of breast cancer, or had undergone bilateral mastectomy, or diagnosed with metastatic disease	Annual surveillance consisting of clinical breast examination (CBE), ultrasound, mammography and MRI performed within a time frame of 8 weeks. Each imaging study was read and scored by a different radiologist. Readers were informed of clinical findings of CBE and risk status of patient, but binded to results of imaging modalities. Diagnosis was coded using BI-RADS categories on a five point	Mammography	Sensitivity: All women: mammography 32.6% (30-35), MRI 90.7% (89-92), mammography + MRI 93.0% (92-94) Risk 20%: mammography 50.0% (45-55), MRI 100.0% (100), mammography + MRI 100.0% (100) Risk 21-40% mammography 25.0% (22-28) MRI 100.0% (100), mammography + MRI 100.0% (100) Mutation carriers: mammography 25.0% (18-32). MRI 100% (100), mammography + MRI 100%	PPV All women: mammography 23.7% (22-26), MRI 50.0% (47-53), mammography + MRI 42.1% (40-45) Risk 20%: mammography 21.4% (17-26), MRI 42.9% (32-43), mammography + MRI 30.0% (25-35) Risk 21-40% mammography 21.7% (19-25) MRI 55.6% (52-59), mammography + MRI 51.2% (55-62) Mutation carriers: mammography 28.6% (22-35). MRI 66.7% (60-74), mammography + MRI 47.1%	Förderverein für Radiologie an der Universität Bonn, German Cancer Aid	a total of 1452 annual surveillance rounds with a mean followup of 5.3 years (range, 2-7 years) Total of 43 cancers identified in 41 patients (34 invasive, 9 DCIS). 40 diagnosed by imaging. 14 by mammography, 39 by MRI, 40 by MRI & mammography

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
February 1996 and February 2002							scale. 4 or above was treated as a positive result and biopsied.		(100) Specificity: All women: mammography 96.8% (96-98), MRI 97.2% (96-98), mammography + MRI 96.1% (95-97) Risk 20%: mammography 96.5% (94-99), MRI 97.4% (94-98), mammography + MRI 95.5% (93-98) Risk 21-40% mammography 97.4% (96-99) MRI 97.7% (97-99), mammography + MRI 97.0% (97-99) Mutation carriers: mammography 96.9% (94-100). MRI 97.5% (95-100), mammography + MRI 94.4% (91-98)	(39-55) NPV not reported		

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
Lehman, C. D., Blume, J. D., Weatherall, P., et al. 2005, "Screening women at high risk for breast cancer with mammography and magnetic resonance imaging", *Cancer.*, vol. 103, no. 9, pp. 1898-1905. Multicentre study carried out by the International Breast MRI Consortium in the USA and Canada between July 1999 and Jan 2002	Prospecti ve study	+	Comparison of sensitivity, specificity, PPV and diagnostic yield of MRI and mammography	Total n=367	1%	Inclusion criteria: Asymptomatic high risk women age ≥ 25 years (mean 45) and lifetime risk of breast cancer > 25% based on family history or genetic besting. Women who had prior history of breast cancer within 5 years of entry date were eligible by having contralateral breast screened. Women who had breast cancer diagnosed > 5 years prior to study entry were eligible for bilateral screening provided they had a probability > 50% for breast cancer or were *BRCA1* or *BRCA2* Exclusion	Clinical breast examination (CBE), mammogram, MRI. CBE and mammogram performed within 90 days of MRI examination. MRI and mammography were interpreted without knowledge of the results of the other test. Separate MRI and mammogram readers were assigned for each institution Diagnosis was coded using the BI- ADS scoring system. All lesions given a score of 4 or 5 (positive for disease) were recommended for biopsy	mammography	Sensitivity 95% CI MRI 100% (100) Mammography 25% (21-29) Specificity 95% CI; MRI 95% (92-97) Mammography 99% (98-100)	PPV MRI 17.0% (CI 95% 14-21) mammography 25% (CI 95% 21-29) NPV MRI 100% (CI 95% 100) Mammography % (CI 95% 98-100)	National Cancer Institute, Office of National women's Health	One screening round performed No follow-up carried out. 27 biopsies performed of 38 that were recomme nded 4 cancers detected in total. 4 by MRI, 1 by mammogr aphy.

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
						criteria: pregnancy, pacemaker, magnetic aneurysm clip or other implanted magnetic device, severe claustrophobia, palpable lesions or mammographic abnormalities prior to assessment						
Pisano, E. D., Gatsonis, C., Hendrick, E., Yaffe, M., Baum, J. K., Acharyya, S., Conant, E. F., Fajardo, L. L., Bassett, L., D'Orsi, C., Jong, R., & Rebner, M. 2005, "Diagnostic performance of digital versus film mammography for breast- cancer screening", *New England Journal of Medicine*, vol.	Prospecti ve study	++	To assess the diagnostic accuracy between digital and film mammography	Total n=42,760 premenop ausal and perimnopa usal n=15803 heterogen eously or extremely dense breasts n=19897		Inclusion criteria: Asymptomatic Exclusion criteria: reported symptoms, pregnancy, breast implants, had undergone mammography within the preceeding 11 months, had a history of breast cancer treated with lumpectomy and radiation	A digital and film mammogram taken in random order. Digital and film examinations were independently interpreted by two radiologists. Readers rated mammograms using a seven-point malignancy scale suitable for ROC analysis and the BIRADS classification scale. Readers	Film mammogram	Sensitivity Means Digital mammography (DM) All women 0.70±0.03; <50 years 0.78±0.05 Premenopausal /perimenopausa l 0.72± 0.05 Heterogeneousl y dense or extremely dense breasts 0.70±0.04 Film	PPV Digital mammography All women 0.05±0.004 <50 years 0.03±0.005 Premenopaus al/perimenopa usal 0.04±0.005 Heterogeneou sly dense or extremely dense breasts 0.04±0.005 Film	National Cancer Institute	Follow-up carried out at one year Participan ts were classified as positive for cancer if pathologic ally verified within 455 after initial screening and negative if their study records showed

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
353, no. 17, pp. 1773-1783. Multicentre study carried out by the American college of Radiology Imaging Network during a two year period in the USA and Canada							also rated breast density according to the BIRADS scale scores of 0, 4 or 5 were recorded as positive		mammography All women ; 0.66±0.03 <50 years 0.51±0.07 Premenopausal /perimenopausa l 0.51±0.06 Heterogeneousl y dense or extremely dense breasts 0.55±0.04 Specificity Digital mammography All women 0.92±0.001 <50 years 0.90±0.003 Premenopausal /perimenopausa l0.90±0.002 Heterogeneousl y dense or extremely dense breasts 0.91±0.002	mammography All women 0.05±0.003 <50 years 0.02=0.004 Premenopaus al/perimenopa usal 0.03±0.004 Heterogeneou sly dense or extremely dense breasts 0.03±0.004 NPV not reported		negative findings after biopsy, if the followup mammogr am at 1 year was normal.

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
									Film mammography All women 0.92±0.001 <50 years 0.90±0.003 Premenopausal /perimenopausa l 0.90±0.002 Heterogeneousl y dense or extremely dense breasts 0.90±0.002			
Skaane, P. & Skjennald, A. 2004, "Screen-film mammography versus full-field digital mammography with soft-copy reading: randomized trial in a population-based screening program--the Oslo II Study", *Radiology* , vol. 232, no. 1, pp. 197-204.	RCT	+	Comparison of cancer detection rates, recall rates and PPV of screen-film mammography (SFM) with full-field digital mammography (FFDM) carried out between Nov 2000 and Dec 2001 by the Breast Cancer Screening Programme in Oslo.	Total n=25,263 aged 45-69 Total 45-49 age group n=10,619 (mean 47.4)	Not reported	Women aged 50-69 were part of the Norwegian Breast Cancer Screening Program. Women aged 45-49 were offered screening mammography only in Oslo county. All women were invited by letter to attend screening. Randomisation to either SFM or	Digital mammography SFM and FFDM images were interpreted independently by two of a team of eight radiologists.A five-point rating scale for probability of cancer was used for interpretation of both SFM and FFDM. A	Film mammography	N= 7,607 (71%) SFM Cancer detection rate 0.22% N=3,012 (29%) FFDM cancer detection rate 0.27% P=.686 Recall rate for SFM n=231 (3.0%) of 7,607 Recall rate for FFDM n=112 (3.7%) of 3,012	PPV SFM 7.4% FFDM 7.1% NPV not reported	Norwegia n Breast Cancer Screenin g Program me	No followup undertake n. SFM total of 17 cancers detected. 7 (41%) ductal carcinom as in situ, 10 (59%) invasive breast cancer. FFDM total of 8

Bibliographic reference	Study type	Evidence level	Aim of study	Number of patients	Prevalence	Patient characteristics	Type of test*	Reference standard	Sensitivity and specificity	Positive and negative predictive value	Source of funding	Additional comments
Ref ID: 231 Norway						FFDM was based on the last digit of the invitation number, with adjustments for age and area of residence From the 45-49 year age group 7,607 (71%) women allocated to SFM 3,164 (29%) allocated to FFDM	score of 2 or higher (probably benign) was automatically selected for a consensus meeting. The consensus meeting would decide which women should continue in the screening programme and which be recalled for diagnostic workup. A score of 4 (probable malignancy) or higher resulted in biopsy being undertaken Recall rate was defined as the percentage of patients requiring further imaging workup					cancers detected. 2 (25%) ductal carcinom as in situ, 6 (75%) invasive breast cancers Comparis ons between SFM and FFDM were available only during review of positive mammogr ams.

Effectiveness of breast screening in women with a family history of breast cancer and/or BRCA1/2 mutations (CG141: 2004)

Study	Design	Intervention(s)	Population	Results
Kerlikowske et al (1993)[1]	Cross-sectional	Mammography	31,814 US women aged ≥30	5 times as many breast cancers diagnosed in women aged ≥50 compared to aged <50. Women aged 50-59 had higher PPV compared to women aged 40-49 (P=0.004). Women with a family history had higher PPV compared to women without family history (40-49 years, P=0.01; 50-59 years, P=0.01). These groups should be targeted for screening.
Kerlikowske et al (1996)[2]	Cross-sectional	Mammography	28,271 US women aged ≥30	Sensitivity highest in women aged ≥50 who have fatty breast density (P<0.01), and lowest in women aged <50. Sensitivity particularly low when screening interval was 2 years, or in women with family history of breast cancer.
Sætersdal et al (1996)[3]	Follow-up	CBE, mammography and/or ultrasound	537 Norwegian women (mean age 43, range 20-76 years) with family history of breast cancer	8 breast carcinomas and 5 cases of atypical hyperplasia found, compared with 1.6 and 0.3 expected. Early diagnosis and treatment likely to be beneficial for this group of women.
Chart et al (1997)[4]	Follow-up	Mammography, CBE, BSE	1,044 Canadian women at increased risk of breast cancer	24 breast cancers diagnosed: 12 in high-risk group, 4 in moderate-risk group and 8 in group with slightly increased risk. 17 of 24 reported family history of breast cancer. Screening likely to be of use in this group.
Law (1997)[5]	Data review/ analysis	Mammography	Data on women taking part in UK NHS Breast Screening Programme (NHSBSP)	Risk of breast cancer induction very small compared to benefits of breast cancer detection for mammography. Benefits/risks not yet clear in women aged 40-47 and in women with family history of breast cancer. Caution advised in screening below age 30, or 40 if there is family history.

Study	Design	Intervention(s)	Population	Results
Kollias et al (1998)[6]	Follow-up	Annual CBE and biennial mammography	1,371 UK women aged <50 with family history of breast cancer	29 cancers (23 invasive and 6 in situ) detected; RR=5 when compared with age- matched UK women. Detection rates similar to those of women aged ≥50 in NHSBSP, but higher proportion of in situ cancers. Screening may be of benefit in this group.
Lalloo et al (1998)[7]	Data review/ analysis	Annual mammography	1,259 UK women aged <50 with family history of breast cancer	12 invasive cancers detected, giving ratio of 1.42 (95% CI, 0.73-2.48), compared to 8.45 expected cancers. Numbers of cancers detected greater than expected.
Boyd et al (1999)[8]	Data from nested case- control	Mammography	354 Canadian women with breast cancer; 354 matched controls aged 40-59.	Mammographic densities were compared. Women with at least 1 affected 1st-degree relative, RR=11.14 (95% CI, 1.54-80.39); at least 2 affected 1st or 2nd-degree relatives, RR=2.57 (95% CI, 0.23-28.22); any 1st or 2nd-degree relatives, RR=5.43 (95% CI, 1.85-15.88). Mammographic density may be strongly associated with breast cancer risk in this group.
Kerlikowske et al (2000)[9]	Cross-sectional	Mammography	389,533 US women aged 30-69 with and without 1st-degree family history of breast cancer	For both groups, sensitivity increased as women got older (P=0.001). PPV was higher in women with a family history than in women without (P=0.001).
Macmillan (2000)[10]	Data review/ analysis	Mammography, CBE, ultrasound	8,783 UK women aged <50 with significant family history of breast cancer	Cancer incidence was 11.3/1000/year; rate of cancer detection was 4.78/1000 at prevalent screening and 4.52 at incident screening. Interval cancers presented at rate of 2.45/1000. Rates similar to those of NHSBSP for women aged 50-64. Suggests screening of this group is effective with likely survival benefit.
Nixon et al (2000)[11]	Data from RCT	Mammography	29,179 Swedish women aged 40-74 with and without a family history of breast cancer	Higher proportion of high-risk mammographic patterns in women aged 40-49 with family history. Interval cancers higher in women with family history; and shorter mean sojourn time (1.89 years compared to 2.70) in older women with family history. Annual screening of benefit to women in this group aged 40-49.

Study	Design	Intervention(s)	Population	Results
Tilanus-Linthorst et al (2000)[12]	Follow-up	CBE, mammography. MRI in subgroup of women	294 Dutch women aged 22-75 at moderate (15-25%) breast cancer risk and 384 women aged 20-74 at high (>25%) risk	26 breast cancers detected, significantly more often found in early stage than the 24 cancers detected in symptomatic women with a family history referred during study period (P=0.018). MRI detected 3 cancers occult at mammography. Earlier screening may be of benefit.
Brekelmans et al (2001)[13]	Follow-up	Monthly BSE, annual mammography, 6-monthly CBE	1,198 Dutch women: 449 moderate and 621 high-risk women, 128 with BRCA1/2 mutations	35 breast cancers detected after median follow-up of 3 years. Detection rates were 3.3 (95% CI, 1.1-8.6) for moderate-risk; 8.4 (95% CI, 5.4-13.2) for high-risk; and 33 (95% CI, 17-63) for BRCA1/2 per 1,000 person-years. Ratio of observed vs expected cancers in age-matched average risk population was 2.7, 7.0 and 23.7, respectively.
Goffin et al (2001)[14]	Data review/ analysis	Mammography	161 Ashkenazi Jewish women diagnosed with invasive breast cancer aged <65.	Breast cancers ≤2cm in size observed in BRCA1/2 mutation carriers significantly less likely to be detectable than similar cancers in noncarriers (P<0.001). Suggests that mammography is insensitive in detecting breast cancer in BRCA1/2 mutation carriers.
Gui et al (2001)[15]	Data review/ analysis	Annual mammography, CBE	1,500 UK women at standard risk of breast cancer (lifetime risk <1:6) and 1,078 women at moderate/high risk (lifetime risk ≥1:6).	31 cancers detected, 12 in standard risk group and 19 in moderate/high risk group. Incidence ratio of 2.8 (95% CI, 1.7-4.2) in moderate/high risk group was significantly higher than incidence in normal population. Incidence ratio in standard risk group was similar to general population (1.1; 95% CI, 0.6-1.8). 26/31 (84%) cancers were palpable, 14 (54%) of which not detected by mammography.
Law et al (2001)[16]	Data review/ analysis	Mammography	Data on women taking part in UK NHS Breast Screening Programme (NHSBSP)	Breast cancers detected exceeded those induced by large margin in women aged >50. Margin reduced in younger women but stayed positive to age of 40, similarly in younger women with family history of breast cancer. Caution advised in screening women aged<35.
Myles et al (2001)[17]	Data review/ analysis	Mammography	2,998 women aged 19-71 with moderate family history of breast cancer	50 breast cancers detected; observed rate of 4.46/1000 person-years compared to expected rate of 3.75/1000 person-years. Screening test sensitivity estimated as 83%, programme sensitivity as 70%.
Møller et al (2002)[18]	Data review/ analysis	Annual mammography and CBE	249 women attending high-risk breast cancer clinics in Norway, Scotland, England and Holland diagnosed with breast cancer	20% of women had carcinoma in situ, 54% infiltrating cancer without spread and 26% with spread. 36 had BRCA1 mutations and 8 had BRCA2 mutations. BRCA1 mutation associated with infiltrating cancer, high grade and lack of oestrogen (P<0.05 for each), with 5-year survival of 63% vs 91% for noncarriers (P=0.01). Current screening protocols appear satisfactory.
Scheuer et al (2002)[19]	Follow-up	Monthly BSE, CBE 2-4 times/year, annual mammography (also genetic counselling and testing)	251 US BRCA1/2 mutation carriers aged 24-79	Mean follow-up 24.8 months. Genetic counselling and testing led to increased BSE/CBE, mammography and risk-reducing operations. This resulted in diagnosis of early-stage tumours. More frequent screening recommended in this group.
Kuhl et al (2000)[20]	Follow-up	MRI, mammography and ultrasound	192 asymptomatic and 6 symptomatic German women suspected/proved to carry BRCA mutation	15 breast cancers detected: 9/192 asymptomatic women and all 6 symptomatic women. 4/9 cancers in asymptomatic women detected with combined mammography/ultrasound; all 9 cancers detected by MRI. Sensitivity of mammography 33%; ultrasound 33%; combined mammography/ultrasound 44%; MRI 100%. MRI more accurate in this high-risk group.

Study	Design	Intervention(s)	Population	Results
Tilanus-Linthorst et al (2000)[21]	Follow-up	MRI, normal surveillance (mammography, CBE, ultrasound and FNA)	109 Dutch women, mean age 42, with >25% risk of breast cancer due to family history	MRI detected 3 breast cancers occult at mammography vs 2 expected cancers. MRI was false-positive in 6 women; no false-negative results. MRI successful in this group, but cost may be prohibitive.
O'Driscoll et al (2001)[22]	Pilot follow-up	Ultrasound, mammography	149 UK women, mean age 42, at moderate risk of breast cancer due to family history	All but one of mammograms was normal; 1 fibroadenoma detected by both mammography and ultrasound. 1 biopsy carried out on mammographic/ultrasound criteria and 9 biopsies on ultrasound criteria alone. Biopsies found 7 fibroadenomas, 2 areas of fibrocystic change, and 1 carcinoma not detected by mammography. Screening with mammography and ultrasound beneficial in this group.
Stoutjesdijk et al (2001)[23]	Data review/ analysis	MRI, mammography	179 Dutch women aged 21-71 with a family history of breast cancer	13 cancers detected; all detected by MRI, 7 not detected by mammography. For whole cohort, area under each curve (AUC) for mammography was 0.74 (95% CI, 0.68-0.79) and for MRI was 0.99 (95% CI, 0.98-1.0). Subset of 75 women who had both MRI/mammography, AUC for mammography was 0.70 (95% CI, 0.60-0.80) and for MRI was 0.98 (95% CI, 0.95-1.0). MRI more accurate than mammography.
Warner et al (2001)[24]	Follow-up	Mammography, ultrasound, MRI, CBE	196 Canadian women aged 26-59 with BRCA1/2 mutations or strong family histories of breast/ovarian cancer	6 invasive and 1 non-invasive cancers detected; prevalence 6.2% in mutation carriers. MRI detected all 6 invasive cancers; 3 detected by ultrasound, 2 by mammography and 2 by CBE. MRI was superior to mammography and ultrasound in this high-risk group.
Hou et al (2002)[25]	Follow-up	Mammography, ultrasound, CBE	935 Taiwanese women aged >35 with family history of breast cancer	21 cancers detected; 16 invasive and 5 non-invasive. 19 were detected by ultrasound, 11 by mammography and 7 by CBE. Sensitivity of ultrasound was 90.4%, mammography 52.4%, CBE 33.3%, or combined mammography/CBE 66.7%. Ultrasound more accurate than mammography and CBE in this high-risk group.

7 Risk Reduction and Treatment Strategies

7.1 Risk Factors

7.2 Risks Associated with Family History

No evidence reported

7.3 Menstrual and Reproductive Factors

7.3.1 Evidence statement

Older age at 1st live birth, or at 1st birth, is associated with significant increases in breast cancer risk. (III)

Increased parity has been found to be associated with a decrease in breast cancer risk;

38% decrease in risk in women who reported 5 or more live births

32% decrease in risk in women who reported 3 or more births compared to women who reported 1 birth (III)

Earlier menarche is associated with an increase in risk of breast cancer. (III)

For women with a family history, the relative risk of menstrual and reproductive factors is consistent with the population. (III)

7.3.2 Summary of menstrual/reproductive factors and breast cancer risk evidence

The above meta-analysis evidence regarding the effect of menstrual and reproductive factors on breast cancer risk is of varying quality, covers different time periods, and relates to specific populations of women, namely from the Italian and Japanese populations.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

Age at menarche
Both studies observed an increased breast cancer risk associated with younger age at onset of menstruation. Significant increases of 32% and 19% in women aged 12-14 years and less than 12 years at menarche, respectively, compared to women aged 15 year or over at menarche were found in the earlier study (Negri et al 1988). Conversely, in the second study (Nagata et al 1995), onset of menstruation at age 16 or over was found to be significantly associated with a 32% decrease in breast cancer risk, relative to women aged less than 14 years at menarche.

Age at 1st (live) birth
Older age at 1st live birth (Negri et al) or at 1st birth (Nagata et al 1995) was associated with significant increases in breast cancer risk in both studies. In the first of the studies, women aged between 22-24 years, 25-27 years and 28 years or over had increases in risk of 22%, 40% and 75%, respectively, relative to women aged less than 22 years (Negri et al 1988). In the second study, women aged between 25-29 years, 30-34 years and 35 years or more had odds rations of 1.32, 1.71 and 2.26, relative to women aged under 24 years and younger years (Nagata et al 1995).

Parity
In both studies increased parity was found to be associated with a decrease in breast cancer risk, with significant decreases in risk of 38% in women who reported 5 or more live births (Negri et al 1988), and 32% in women who reported 3 or more births (Nagata et al 1995), compared to women who reported one birth.

Menopausal status

In the first of the studies (Negri et al 1988), women who experienced an earlier menopause (aged between 45-49 and less than 45 years) had a 23% and a 27% decrease, respectively, in breast cancer risk, relative to women who were aged 50 years or over at menopause. In the second study (Nagata et al 1995), no increased breast cancer risk was observed in women aged 50 or more at menopause compared to women aged under 50 years. However, premenopausal women were found to have a 2-fold increase in breast cancer risk relative to women aged under 50 years at menopause.

Women with a family history

The Collaborative reanalysis found that the relationships between risk factors for women with a family history were similar to those for women without a family history.

7.3.3 Comment

Women who reach menarche (the first menstrual period) at a relatively early age (12 or younger) and those who reach menopause at a relatively late age (55 or older) are more likely than other women to develop breast cancer. Nulliparity and late age at first birth both increase lifetime incidence of breast cancer. These relationships are believed to be mediated through estrogen produced within the woman's body. During the reproductive years, a woman's body produces high levels of estrogen. Women who start to menstruate at an early age and/or reach menopause at a late age are exposed to high levels of estrogen for more years than are women who have a late menarche or early menopause. Another aspect of reproductive history that is associated with breast cancer risk is age at first pregnancy. Women who have their first full-term pregnancy at a relatively early age have a lower risk of breast cancer than those who never have children or those who have their first child relatively late in life. Pregnancy may lead to lasting changes in the sensitivity of breast tissue to cancer-causing agents, as well as in the maturation of breast tissue. In addition, several hormonal changes occur after a full-term pregnancy and may persist for years.

7.3.4 Studies

Two meta-analyses and a collaborative group re-analysis were identified from the literature which evaluated the association between menstrual/reproductive factors and breast cancer risk in the female population in general. The Collaborative group also looked at issues relating to women with first degree relatives with breast cancer.

Collaborative Group on Hormonal Factors in Breast Cancer (2001)

The Collaborative group looked at the relevance of breast cancer in first degree relatives on a range of other risk factors for breast cancer. The relationships between risk factors for women with a family history were similar to those for women without a family history. They argued that reproductive factors that reduce the risk ration for breast cancer, such as high parity, early childbearing and early menopause, should lead to a greater reduction in the absolute incidence of breast cancer in women with a family history of the disease than in women without such a history, just because the relevant risk ratios are similar in both groups.

Nagata et al (1995)

Results of 7 published and 1 unpublished epidemiological studies identified between 1966 and 1995 which evaluated the effect of menstrual and reproductive factors on breast cancer incidence among Japanese women were combined in this meta-analysis. Synthesis of results found a significantly lower odds ratio (OR) for women with onset of menstruation after age 16 (OR=0.68; 95% CI, 0.59-0.77), relative to women with aged less than 14 at menarche. In terms of breast cancer risk and age at 1st birth, significantly higher ORs were observed for women in any age group for 1st birth after age

25, and for nulliparous women, compared to women with 1st birth before age 25. Women aged 25-29 years had an OR of 1.32 (95% CI, 1.14-1.53), aged 30-34, an OR of 1.71 (95% CI, 1.41-2.09) aged 35 years or more, an OR of 2.26 (95% CI, 1.85-2.77), and nulliparous women, an OR of 1.56 (95% CI, 1.27-1.91). A significant protective effect of higher parity (3 or more children) on breast cancer risk was noted (OR=0.68; 95% CI, 0.54-0.86), relative to women who had 1 child. Also menopausal status influenced breast cancer risk, with premenopausal women at significantly higher risk (OR=2.21; 95% CI, 1.53-3.20) compared to women with menopause before age 50; an increased OR was not noted, however, for women with menopause after age 50. Findings suggest that early age at menarche, late age at 1st birth and premenopausal status were significantly associated with increased breast cancer risk among a population of Japanese women.

Negri et al (1988)

In this meta-analysis of 3 Italian case-control studies published between 1986 and 1987 (a systematic quality assessment of included papers was not performed), the impact of menstrual and reproductive factors on breast cancer risk was assessed in 4,072 women with, and 4,099 women without, breast cancer. Combined results showed that women with younger ages at onset of menstruation (aged 12-14 years and less than 12 years) were at significantly increased risk of developing breast cancer (RR=1.32; 95% CI, 1.15-1.52 and RR=1.19; 95% CI, 1.00-1.42, respectively) relative to women who were aged 15 years or over at menarche. In terms of menopausal status, there was a significant trend towards decreasing breast cancer risk with earlier menopause, with women aged 45-49 years and less than 45 years at menopause at lower risk of breast cancer (RR=0.77; 95% CI, 0.67-0.90 and RR=0.73; 95% CI, 0.61-0.88, respectively), relative to women aged 50 years or more at menopause. High parity (5 live births or more) was associated with a significantly decreased breast cancer risk (RR=0.62; 95% CI, 0.50-0.76). Women whose age at their 1st live birth was between 22-24 years, 25-27 years and 28 years or more had a 22% (95% CI, 1.06-1.43), 40% (1.20-1.63) and 75% (1.50-2.04) increased risk of breast cancer, respectively, relative to women aged less than 22 years at 1st live birth. Results also indicated a 2-fold increase in breast cancer risk in women with a history of breast cancer in 1st degree relatives compared to women with no family history. The authors conclude that menstrual and reproductive factors have a strong influence on breast cancer risk.

7.4 Reproductive and Fertility Issues

There is little evidence regarding history of induced abortion as a potential modifying factor for the development of breast cancer in the general female population, and no evidence relating to women with a family history of breast cancer.

7.4.1 Comment

The guideline development group thought that the limited studies available are inconclusive

7.4.2 Studies

One meta-analysis has been identified from the literature which evaluates the association between induced abortion and breast cancer risk in the female population in general. No studies have been identified which evaluate a relationship between induced abortion and breast cancer risk in women with a family history of breast cancer.

Brind et al (1996)
Twenty-eight observational studies describing 23 independent studies which published data between 1966 and 1996 on the effect of history of induced abortion on breast cancer risk were combined in a meta-analysis (note: included studies do not appear to have undergone systematic quality assessment). Breast cancer risk was significantly increased with any history of induced abortion (reported by 21 of the studies), with an overall odds ratio (OR) of 1.3 (95% CI, 1.2-1.4). When parity was taken into account, breast cancer risk was observed to be significantly increased in nulliparous women (OR=1.3; 95% CI, 1.0-1.6); in parous women who underwent induced abortion before their 1st-term pregnancy (OR=1.5; 95% CI, 1.2-1.8); and in women who underwent induced abortion after their 1st-term pregnancy (OR=1.3; 95% CI, 1.1-1.5). The authors conclude that induced abortion increases a woman's risk of breast cancer regardless of parity or timing of abortion relative to 1st-term pregnancy. Furthermore, the authors state that the consistently positive associations found amongst included studies in terms of induced abortion and breast cancer incidence rule out the possibility that the association results from bias or any other confounding variable.

7.5 Sub-fertility and induced ovulation

7.5.1 Comment

Studies of sub-fertility and induced ovulation in relation to breast cancer risk show inconsistent results.

7.5.2 Studies

One systematic review looked at the issue of sub-fertility and induced ovulation (by use of fertility drugs). One study looked at incidence of cancer following fertility treatment in a UK clinic.

Meta-analyses, systematic reviews and re-analyses

Klip et al (2000)
This systematic review looked at the potential long term effects of fertility drugs, as well as the indications for fertility drug use on the risk of cancers of the ovary, breast and endometrium. As the reason for fertility drug use was of concern (i.e. might it confound any association between fertility drug use and cancer risk) they only included studies that specifically examined the cause of

infertility. They examined data from cohort studies and case control studies. Different studies looked at different causes of sub-fertility and cancer risk and others looked at the use of fertility drugs and cancer risk (including breast cancer) whilst some studies looked only at breast cancer risk. Data from seven cohort studies that presented standardised incidence rates for breast, ovary and endometrium cancer, did not show that the risk of breast cancer was significantly different from that in the general population. The authors also argued that studies of sub-fertility in relation to breast cancer risk show inconsistent results. There are methodological difficulties with many of the studies and they argued that even some of the larger studies had inadequate power to reliably assess breast cancer risk in relation to sub-fertility diagnosis. They found only a few studies which assessed breast cancer risk in relation to fertility drug use. These studies had inconsistent results and were based on short follow-up. Overall they concluded that the association between fertility drug use and cancer risk has been examined in a few studies with inconsistent results.

Doyle et al (2002)

This study aimed to investigate the incidence of cancer in a cohort of women attending a large infertility clinic in the UK. Women (UK residents, over the age of 20 at time of treatment, received at least one cycle of infertility treatment) were identified between January 1975 and December 1989, followed up and cancer incidence rates calculated. The study cohort comprised 5556 women, 75% of whom had received ovarian stimulation drug treatment at the clinic. On average the group who received ovarian stimulation were slightly older and had a higher proportion of nulliparous women after the last treatment cycle than the group who did not receive ovarian drug stimulation treatment. A total of 118 cancers were incident in the cohort from the beginning of 1990 until the end of 1997. including 55 breast, 4 uterine and 6 ovarian. There was no significant difference between stimulated and unstimulated groups ($p=0.89$, 0.07, 0.53 for breast, uterus and ovary respectively). Compared with the general population the numbers of cancer of the breast and uterus were higher than expected in both stimulated and unstimulated group but not significantly so (all $p>0.38$). The authors concluded therefore that overall the incidence of breast, uterine and ovarian cancers was no greater than expected on national rates over the period of follow-up, and that they found o evidence for a link between ovarian stimulation treatment and increased cancer incidence.

7.6 Hormonal Contraceptives

7.6.1 Evidence statements

- Use of oral contraceptives slightly increases the risk of breast cancer. (III)
- This increase in risk appears to be confined to current and recent use (within 5-10 years, relative risk 1.24 for current users). (III)
- In women with a positive family history, the relative risk is consistent with findings in the general population. (III)
- One study has shown an increased risk for BRCA1 mutation carriers (odds ratio 1.20, relative risk under 40 = 1.40). (III)
- There is no evidence regarding the progesterone only contraceptives and risk associated with family history.

7.6.2 Summary of oral contraceptive use and breast cancer risk evidence

The above evidence regarding the use of oral contraceptives and their impact on breast cancer risk is of varying quality, covers different time periods, and relates to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in Appendix 14. Of the meta-analyses/re-analysis, four (Romieu et al 1990, Delgado-Rodriguez et al 1991, Hawley et al 1995, Collaborative Group 1996) combine evidence from approximately the same time periods, with some form of quality assessment of included studies undertaken in two of the syntheses. Of the remaining two meta-analyses (Rushton et al 1992, Schlesselman 1995), both combine evidence published after 1980, with no quality assessment of included studies in either synthesis.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

Ever-use of oral contraceptives

Findings of 2 meta-analyses and the 2 recent case-control studies suggest that ever-use of OCs in all women is not associated with an increased risk of breast cancer (Romieu et al 1990, Hawley et al 1995, van Hoften et al 2000, Marchbanks et al 2002). The re-analysis found, however, that ever-use of OCs in all women was associated with a statistically significant 7% increase in breast cancer risk (Collaborative Group 1996). A further meta-analysis similarly found a 7% increase in risk of breast cancer when case-control studies where combined, but no association when cohort studies were combined (Delgado-Rodriguez et al 1991).

In 3 meta-analyses and one case-control study, no association between ever-use of OCs in postmenopausal women and increased breast cancer risk was observed (Romieu et al 1990, Delgado-Rodriguez et al 1991, Rushton et al 1992, van Hoften et al 2000).

Findings relating to ever-use of OCs in premenopausal women, however, were inconsistent, with no association with increased risk of breast cancer observed in one of the case-control studies (van Hoften et al 2000), but a 14% and 16% increased risk observed in 2 meta-analyses (Delgado-Rodriguez et al 1991, Rushton et al 1992, respectively).

Current use of oral contraceptives

Two studies which assessed the impact of current use of OCs on risk of breast cancer in all women produced different findings, with a statistically significant 24% increase in breast cancer risk observed in the re-analysis (Collaborative Group 1996), but no increase observed in one of the case-control studies (Marchbanks et al 2002).

Duration of oral contraceptives

Increasing duration of OC use in all women was not found to be associated with an increased risk of breast cancer in 2 meta-analyses (Romieu et al 1990, Hawley et al 1995) and the 2 case-control studies (van Hoften et al 2000, Marchbanks et al 2002). In a further meta-analysis, however, increasing duration of OC use in all women was found to be associated with increased risk, with a 27% increase observed for more than 8 years of OC use (Rushton et al 1992).

Findings relating to increasing duration of OC use and risk of breast cancer in premenopausal and postmenopausal women were also inconsistent between studies. A 46% increased risk of breast cancer after 10 years of OC use in premenopausal women was observed in one meta-analysis (Romieu et al 1990), whereas duration of OC use of more than 10 years in premenopausal women was not found to be associated with increased risk in a case-control study (van Hoften et al 2000). Similarly, increasing duration of OC use in postmenopausal women was not found to be associated with increased risk in one meta-analysis (Schlesselman 1995), although duration of OC use of more than 10 years was associated with a statistically significant doubling in breast cancer risk in a case-control study (van Hoften et al 2000).

Cessation of oral contraceptive use

In the re-analysis which assessed breast cancer risk in all women after stopping OC use, a 16% increased risk was observed between 1-4 years after stopping OC use, and a 7% increase between 5-9 years after stopping use (Collaborative Group 1996). In the same study, no increased risk of breast cancer in all women was observed 10 or more years after they stopped OC use. In a case-control study, however, no increase in risk of breast cancer was observed in all women relating to time since they stopped OC use (Marchbanks et al 2002).

Oral contraceptive use before 1st full-term pregnancy

Statistically significant increases in risk of breast cancer in women who used OCs before their 1st full-term pregnancy was observed in 3 meta-analyses (Romieu et al 1990, Delgado-Rodriguez et al 1991, Hawley et al 1995). In one of the meta-analyses (Romieu et al 1990), a 72% increased risk for 4 or more years' OC use was found in this subgroup of women.

Oral contraceptive use in women with a family history of breast cancer

There was consistent evidence that the effects of OC use on breast cancer risk was similar in women with and without a family history (Romieu et al 1990, Delgado-Rodriguez et al 1991, Collaborative Group 1996, Marchbanks et al 2002).

Oral contraceptive use in women with a mutation in the BRCA1 or BRCA2 gene

There is evidence from one case-control study that ever use of OCs was associated with a 20% increase in breast cancer risk in women who were BRCA1 mutation carriers, although BRCA2 mutation carriers were not found to be at increased risk (Narod et al 2002).

7.6.3 Comment

Numerous scientific studies have investigated the relationship between the use of oral contraceptives (birth control pills) and the risk of breast cancer. In considering any increase in breast cancer risk, one has to recognize the addition of exogenous oestrogen but it may be that at least part of the effect is due to the fact that the oral contraceptive pill does prevent women from becoming pregnant, thereby reducing the breast cancer protection of an early pregnancy.

7.6.4 Studies

Five meta-analyses, one collaborative re-analysis and 3 recent case-control studies which evaluate the impact of oral contraceptive (OC) use on breast cancer risk have been identified from the literature.

Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (1996)
This re-analysis combined the findings of 54 published and unpublished case-control and cohort studies, reported to represent about 90% of the epidemiological evidence on breast cancer risk and OC use (included studies did not undergo quality assessment). The relative risk of breast cancer in women who had ever used OCs compared to women who had never used them was statistically significant (RR=1.07 (SD 0.02), 2p=0.00005). In terms of duration of OC use, there was a weak indication of a trend of increasing risk with increasing duration (P=0.05). For each age group at 1st OC use between less than 20 years to 35 years and over, relative risks were slightly greater than 1.0, with the largest increase in women who started use as teenagers. Similarly, relative risks were slightly above 1.0 in each 5-year period of time since 1st OC use, with a trend of decreasing risk with increasing time since 1st use (P=0.002). There was also evidence of an increased risk of breast cancer being diagnosed in current users (RR=1.24 (SD 0.04), 2p<0.00001), in recent users (RR=1.16 (SD 0.04), 2p=0.00001), and 5-9 years after stopping use (RR=1.07 (SD 0.03), 2p=0.009). For women who stopped use 10 or more years previously, the relative risk of breast cancer did not differ significantly from 1.0, and there was a strong trend of decreasing risk with time since last use (P<0.00001). There was no significant difference in the association between time since last use of OCs and breast cancer risk between women with and without a family history of breast cancer. The authors conclude that there is a small increase in breast cancer risk in women using OCs and in the 10 years after they stop, although this increased risk does not persist beyond 10 or more years.

Schlesselman (1995)
Seventy-nine epidemiological studies published between 1980 and 1994 were combined in this meta-analysis to evaluate the net effect of duration of OC use and risk of breast, cervical, endometrial, ovarian and liver cancer (included studies did not undergo quality assessment). Pooled findings for 25 studies relating to breast cancer risk and OC use in older women (>45 years to <60 years) suggest a non-significant trend (P=0.35) of slightly increasing risk with increasing duration of OC use, with relative risks of 1.062, 1.068 and 1.072 for 4, 8 and 12 years of OC use, respectively. These findings indicate no adverse effect of OC use on breast cancer risk in this age group of women.

Hawley et al (1993)
A synthesis of the findings of 38 case-control studies carried out between 1966-1990 was performed, with individual studies assigned a quality rating score. Analyses found no statistically significant association between breast cancer risk and ever-use of OCs for all studies pooled (RR=1.08; 95% CI, 0.55-1.61), nor when 'higher quality' studies were combined (RR=1.07; 95% CI, 0.78-1.36). Long-term duration (up to 14 years) of OC use also did not increase breast cancer risk

(P=0.386 for all studies combined, and 0.189 for 'higher quality' studies combined). A significant association was observed, however, between risk and OC use before 1st full-term pregnancy (P<0.001 for all studies combined, and 0.011 for 'higher quality' studies combined). The data suggest that there is no increased breast cancer risk in women who have ever used OCs, or who have used them for long durations, although OC use before a 1st full-term pregnancy appears to increase a woman's risk. The authors state, however, that the findings may be confounded by inclusion of lower quality studies in the synthesis.

Rushton et al (1992)

This meta-analysis combined the findings of 21 case-control and 6 cohort studies published between 1980 and 1989 (included studies did not undergo quality assessment). Breast cancer risk increased significantly by 16% in women aged less than 45 years (RR=1.16; 95% CI, 1.07-1.25), although not in women aged 45 years or more. Risk was greatest in women in the 30-34 years age group (RR=1.25; 95% CI, 1.04-1.50). No significant association was observed between OC use and breast cancer risk in parous women, although risk almost reached significance in nulliparous women (RR=1.21; 95% CI, 0.99-1.47). Findings also suggested a steady increase in breast cancer risk with duration of OC use, with a RR of 1.04 (95% CI, 0.94-1.16) for durations of less than 2 years to 1.27 (95% CI, 1.12-1.44) for more than 8 years of OC use. The authors conclude that risk of breast cancer from OC use may be increased by about 20% in younger, nulliparous women and in long-use duration subgroups. They note, however, that there was substantial heterogeneity between study findings.

Delgado-Rodriguez et al (1991)

A synthesis of 26 case-control and 6 cohort studies published between 1966 and 1990 was carried out in this meta-analysis. Ever-use of OCs was significantly associated with breast cancer risk in case-control studies (RR=1.07; 95% CI, 1.03-1.12), but not in cohort studies. An increased risk with ever-use was also observed in premenopausal women when all studies were pooled (RR=1.14; 95% CI, 1.05-1.24), although not in postmenopausal women. Additionally, OC use increased breast cancer risk in women with cancer diagnosed before age 45 (RR=1.15; 95% CI, 1.08-1.23), and in women who used OC before their 1st full-term pregnancy (RR=1.17; 95% CI, 1.06-1.30). No significant association between breast cancer risk and OC use was observed in women with a family history of breast cancer. In conclusion, these findings suggest an increased risk of premenopausal breast cancer in early OC users.

Romieu et al (1990)

The results of 27 case-control and 5 cohort studies published between 1966 and 1989 were pooled according to study type in this meta-analysis (included studies did not undergo quality assessment). For the case-control studies, there was no association between an increased breast cancer risk and ever-use of OC (RR=1.06; 95% CI, 0.98-1.14), duration of 10 or more years' use of OC (RR=1.14; 95% CI, 0.90-1.42), nor when analyses were restricted to studies published after 1980, when lower dose OCs were introduced (RR=1.22; 95% CI, 0.91-1.63). Ever-use of OCs in women with a family history of breast cancer was also not associated with increased breast cancer risk. There was, however, a statistically significant 46% increase in risk for 10 years of OC use when data were limited to premenopausal women (P=0.001). Furthermore, 4 or more years of OC use before 1st full-term pregnancy in women aged less than 46 years was associated with a significantly increased breast cancer risk (RR=1.72; 95% CI, 1.36-2.19). Pooled data for the cohort studies showed no adverse effect of breast cancer risk for ever-use and duration of OC use. The authors conclude that there was no increase in breast cancer risk for women, including those with a family history of breast cancer, who ever used OCs, even after long duration of use. There was, however, an increased risk

of premenopausal breast cancer in women with long duration of OC use, especially in women who used OCs before their 1st full-term pregnancy.

Other Studies

Marchbanks et al (2002)
Women aged 35-64 years took part in a US case-control study, with OC use in 4,575 women (cases) who developed invasive breast cancer compared to OC use in 4,682 women who had not developed the disease. Similar numbers of cases and controls had used some type of OC (77% vs 79%, respectively), although there were significant differences between the two arms on a number of variables, including the number of term pregnancies and the presence or absence of a family history of breast cancer. There was little evidence that OCs increase breast cancer risk in any of the categories of OC usage. For current OC users, the odds ratio was 1.0 (95% CI, 0.8-1.3) and for previous users was 0.9 (95% CI, 0.8-1.0). Breast cancer risk did not increase with longer durations of use, with higher doses of estrogen, or among women who had begun using OCs at a young age. Former use was associated with a small but significant reduction in RR among the older women. There was a non-significant RR of 1.5 among the older women who were currently using low dose estrogen, compared with older women who had never used OCs. No association between ever-use and current use of OCs and family history of breast cancer was observed. The authors conclude that current or former OC use is not associated with increased breast cancer risk, nor is starting OC use at a young age.

Narod et al (2002)
Breast cancer risk associated with OC use in women with a mutation in the BRCA1 or BRCA2 gene was evaluated in this matched case-control study carried out at 52 centres in 11 countries worldwide. Cases (n=1,311) and controls (n=1,311) were aged 46-47 years, and were mainly US (45.8%) or Canadian (22.8%) residents. Most cases and controls were white (about 60%) or Jewish (about 30%), with almost 75% of women in each group carrying the BRCA1 mutation. After adjusting for parity and ethnicity, the odds ratio (OR) indicated an increased breast cancer risk for ever users of OCs who were BRCA1 mutation carriers relative to never users (OR=1.20; 95% CI, 1.02-1.40), although BRCA2 mutation carriers were not at increased risk (OR=0.94; 95% CI, 0.72-1.24). Analyses were subsequently confined to BRCA1 mutation carriers only. Compared to never users of OCs, results showed that for those who used OCs for 5 or more years, the adjusted OR was 1.33 (95% CI, 1.11-1.60). Breast cancer risk was also increased in women who ever used OCs before the age of 30 (OR=1.29; 95% CI, 1.09-1.52), in women who had ever used OCs who were diagnosed with breast cancer before the age of 40 (OR=1.38; 95% CI, 1.11-1.72), and in women who first used OCs before 1975 (OR=1.42; 95% CI, 1.17-1.75). The authors conclude that OC use is associated with increased breast cancer risk in BRCA1 mutation carriers, but not in BRCA2 mutation carriers, although it is acknowledged that data were limited in this subset of women.

Grabrick et al (2000)
This paper reports on material from a historical cohort of 426 families of breast cancer probands, diagnosed between 1944 and 1952, with follow-up data on families collected by telephone between 1991 and 1996. A total of 394 sisters and daughters of the probands, 3002 granddaughters and nieces and 2754 women who married into the families made up the participants. Limitations of the data meant that the relationship between oral contraceptive use and risk could be more robustly investigated into use of earlier (pre 1975) preparations of the oral contraceptive pill. Their findings suggested that in women with a strong family history of breast cancer, breast cancer risk may be raised by use of oral contraceptives. Their analysis suggests that after accounting for age and birth cohort, ever use of oral contraceptives was associated with a significantly increased risk of breast

cancer among sisters and daughters of the probands (RR, 3.3; 95% confidence interval (CI), 1.6-6.7). An increase in risk was not found amongst granddaughters and nieces of the probands (RR, 1.2; 95% CI, 0.8-2.0). They argued that these findings were essentially unchanged after adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education. Their results showed the most evident increase in risk amongst those who had used pre 1975 formulations of the oral contraceptive pill and they had insufficient cases of breast cancer to provide a robust analysis of post 1975 preparations.

Van Hoften et al (2000)

In a Dutch case-control study carried out between 1982 and 1984, OC use in 309 pre- and postmenopausal women who developed breast cancer (cases) was compared to that of 610 pre- and postmenopausal women (controls) who had not developed the disease. Women aged <55 years and >55 years were defined as premenopausal and postmenopausal, respectively, as data on menopausal status was not available. Although women who had ever used OCs had a slightly increased risk of breast cancer, especially those aged over 55 years, this association was not statistically significant, either for the total group of women or for the 2 subgroups of age. A small, non-significant increased breast cancer risk for between 1-10 years' duration of OC use was observed, although there was a significant doubling in risk in women aged over 55 years who had used OCs for more than 10 years (odds ratio=2.05; 95% CI, 1.07-3.95). The data suggest, therefore, that OC use for over 10 years is associated with a twofold increased risk of breast cancer in women aged over 55 years, but not in younger women.

7.7 Breast Feeding

7.7.1 Evidence statement

- Breastfeeding confers a protective effect on breast cancer risk. (III)
- The protective effect of breast feeding is in addition to the protective effect of pregnancy alone. (III)
- The reduction in breast cancer risk is related to total duration of breast feeding. (III)
- The Collaborative Group found that each twelve months of breastfeeding confers a reduction of about 4%. (III)
- The relative risk reduction is similar in women with a family history. (III)

7.7.2 Summary of breastfeeding and breast cancer risk evidence

Results of one systematic review, 1 meta-analysis and 1 collaborative re-analysis conclusively found a significant protective effect of breastfeeding on breast cancer risk. For the systematic review, the evidence was suggestive of a slight decrease in risk limited to premenopausal women, especially women from non-Western countries with long durations of breastfeeding. The meta-analysis found a significant reduction of 16% in breast cancer risk associated with ever breastfeeding compared to never breastfeeding, which was more marked in women who were non-menopausal at the time of breast cancer diagnosis. A significant trend towards decreasing risk with increasing duration of breastfeeding was also observed, with a 28% reduction in breast cancer risk in women who breastfed for at least 12 months. In the collaborative re-analysis, similarly, breast cancer risk was significantly reduced by 4.3% for each year of breastfeeding, in addition to a reduction in risk associated with each birth. For women with a family history of breast cancer, similar risk reductions were observed.

7.7.3 Comment

If breast-feeding does protect against breast cancer, it may do so by delaying the resumption of ovulation (with its accompanying high estrogen levels) after pregnancy. The benefits of breast-feeding for the infant are well established, and all authorities agree that breast-feeding is the preferred method of infant feeding unless it is contraindicated for a specific medical reason.

7.7.4 Studies

One systematic review, 1 meta-analysis and 1 collaborative re-analysis have been identified from the literature which evaluates the association between breastfeeding and breast cancer risk in the female population in general. No studies have been identified which evaluate a relationship between breastfeeding and breast cancer risk in women with a family history of breast cancer, although reference to this subgroup of women is made in one of the above-identified studies.

Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (2002a)
Eighty percent of the world-wide epidemiological evidence, consisting of 47 case-control and cohort studies from 30 countries was combined in this collaborative re-analysis of 50,302 women with invasive breast cancer and 96,973 women without the disease. Comparison of cases and controls found that cases had fewer births than controls, were more likely to be nulliparous, were less likely to have breastfed and had shorter lifetime duration of breastfeeding. In terms of effect of breastfeeding on breast cancer risk, after stratifying for parity, lifetime duration of breastfeeding, age factors and menopausal status, the RR of breast cancer was significantly reduced by 4.3% for each year of breastfeeding (CI, 2.9-5.8; P<0.0001). This decrease was in addition to a reduction in RR of breast cancer of 7% observed for each birth (P<0.0001). Adjustment for factors such as whether women were from developed or developing countries, or whether women had a family history of breast cancer did not alter the size of these associations. Public health implications of the lack of, or short duration of, breastfeeding and the high incidence of breast cancer in developed countries are discussed.

Lipworth et al (2000)
In this systematic review, 28 epidemiological studies published between 1966 and 1998 were assessed (note: included studies do not appear to have undergone systematic quality assessment) to evaluate whether a history of breastfeeding decreases breast cancer risk. In terms of ever breastfeeding and breast cancer risk, evidence of an inverse association was limited and inconclusive, with findings either suggestive of no association, or a definite but small protective effect. In studies which found a protective effect, RRs for parous women who had ever breast fed ranged from 0.54 to just less than 1.0, compared to women who had never breast fed. Evidence for an association between breast cancer risk and number of children breast fed was inconsistent, with studies either showing significant reductions in risk or no trend of decreasing risk with increasing number of children breast fed. In terms of duration of breastfeeding, reductions in ORs for premenopausal women who breast fed for at least 12 months were observed in some studies, although other studies found no reduction in risk. Overall, there appeared to be evidence of a protective effect on risk among women in non-Western countries with long durations of breastfeeding. In most studies, any protective effect of breastfeeding appeared to be strongest, or confined to, premenopausal women. The authors conclude that breastfeeding confers a relatively weak protective effect on breast cancer risk, limited to premenopausal women, although they note that potential confounding factors make comparison of study findings difficult.

Bernier et al (2000)
Twenty-three case-control studies published between 1980 and 1998 which evaluated the relation between breastfeeding and breast cancer were combined in a meta-analysis. Using a random effect model, the combined OR for ever versus never breastfeeding was 0.84 (95% CI, 0.78-0.91), suggesting a slight but significant protective effect. For ever versus never breastfeeding mothers, a significant decrease in breast cancer risk for women who were non-menopausal at the time of breast cancer diagnosis was also observed (OR=0.81; 95% CI, 0.72-0.91). For women who breastfed for at least 12 months, a significant decrease in combined OR was observed, relative to women who had never breastfed (OR=0.72; 95% CI, 0.65-0.80). Across categories of duration, a trend towards decreasing risk with increasing duration of breastfeeding was observed (P<0.0005). Findings are suggestive of a slight but significant reduction in breast cancer risk in women who had ever breastfed. This decrease appeared to be related to duration of breastfeeding, and was noted in women who were not menopausal at the time of breast cancer diagnosis.

7.8 Hormone Replacement Therapy (HRT)

7.8.1 Evidence statement

- The totality of the evidence suggests that HRT is associated with an increase in breast cancer risk. (III)
- The risk associated with HRT is small for short duration use (up to 2 years) but is in the region of a two fold risk for women taking combined HRT for 10 years or more. (III)
- The benefits of early menopause on the relative risk of breast cancer are unlikely to be completely removed by taking HRT until about 50 years of age. (IV)
- The Million Women Study found that the relative risk of breast cancer in current users increased with increasing total duration of use of HRT. (III)
- The Collaborative Group found that risk appears to be confined to current users and women who have used HRT in the last 5 years. (III)
- The Million Women Study suggests that there is little or no overall increase in the relative risk of breast cancer in past users of HRT. (III)
- The Collaborative Group found that risk of HRT use disappears 5 years after stopping. (III)
- The Collaborative Group has shown that there is 2.3% increase in relative risk for every year used. (III)
- In women with a positive family history, the relative risk is consistent with findings in the general population. (III)
- The Million Women Study found that the associated risk was substantially greater for oestrogen-progestagen than for other types of HRT. (III)

7.8.2 Summary of HRT and breast cancer risk evidence

The above evidence regarding the use of HRT and its impact on breast cancer risk is of varying quality, relating to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in Appendix 13. The 4 meta-analyses (Dupont et al 1991; Steinberg et al 1991; Sillero-Arenas et al 1992; Colditz et al 1993) combine evidence from approximately the same time periods and databases, with some form of quality assessment of included studies undertaken in 3 of the syntheses. The re-analysis (Collaborative Group 1997) includes more recent studies, although quality assessment of included studies does not appear to have been systematically undertaken. Included studies in the qualitative review (Bush et al 2001), which has the most comprehensive coverage of all the syntheses, have also not undergone quality assessment.

The Million Women Study presented results from over a million women in the UK, of whom 50% were ever users of HRT. The main analyses were concerned with

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings of these meta-analyses/reviews.

Ever-use of HRT

Ever-use of HRT in postmenopausal women was associated with a statistically significant increase in relative risk of breast cancer of 1.43 in the Million Women Study and 1.06 and 1.14 in two of the other studies (Sillero-Arenas et al 1992; Collaborative Group 1997, respectively). However, in a third study (Colditz et al 1993), ever-use of HRT in postmenopausal women was not associated with an increase in breast cancer risk.

Duration of HRT use

The Million Women Study found that for current users of each type of HRT, breast cancer increased with total duration of use. Three studies found that breast cancer risk in postmenopausal women increased in relation to increasing duration of HRT use, by 30% after 15 years (Steinberg et al 1991), 63% after 12 years (Sillero-Arenas et al 1992) and 35% after 5 or more years (Collaborative Group 1997). A further study (Colditz et al 1993) found that breast cancer risk increased by 20% after more than 10 years of HRT use, and by 30% after more than 15 years of use, although some studies included premenopausal women. The 2 remaining identified studies (Dupont et al 1991; Bush et al 2001) both found inconsistencies in study results and were thus unable to confirm an association between duration of HRT use and breast cancer risk.

Cessation of HRT use

The Million Women Study found that the increased risk of breast cancer associated with HRT use begins to decline when HRT is stopped and reaches the same level as women who have never taken HRT after about 5 years. One study (Collaborative Group 1997) found that the increased risk of breast cancer associated with HRT use reduces after HRT is stopped and has disappeared after about 5 years' cessation of use.

HRT use and breast cancer mortality

The Million Women Study found that the relative risk of death from breast cancer was raised in women who were current users of HRT (RR=1.22), but not in past users (RR=1.05) compared with never users of HRT. One study (Bush et al 2001) found a significant association between HRT use and a reduction in death from breast cancer, with risk estimates of less than 1.0.

HRT use in women with a family history of breast cancer

The Million Women Study examined some of their results in a way to see what if any impact some factors, including family history, had. Family history did not have an impact on the relative risks examined (only BMI had a modifying impact on the relative risks examined). Other identified studies which assessed breast cancer risk of HRT use in relation to women with a family history of breast cancer (Steinberg et al 1991; Colditz et al 1993; Collaborative Group 1997), findings were inconsistent. In one study (Collaborative Group 1997), patterns of increased breast cancer risk associated with ever-use, current/recent use and long-term use of HRT were found for women with a family history of breast cancer which matched the study's findings for postmenopausal women in general; and in a second study (Steinberg et al 1991), ever-use of ERT was associated with increased breast cancer risk in all women with a family history of breast cancer compared to women with no history (RR=3.4 compared to RR=1.5). However, in the third study (Colditz et al 1993), no significant

association was found between breast cancer risk and HRT use in women with a family history of breast cancer.

7.8.3 Comment

Factors that influence the amount of estrogen produced by a woman's body over her lifetime (such as the ages at the onset of menstruation and at menopause) are known to influence breast cancer risk. Possible effects on breast cancer risk are only one of the many factors that need to be considered by a woman and her physician when making decisions about ERT/HRT.

7.8.4 Studies

Meta-analyses, systematic reviews and re-analyses

Bush et al (2001)
A systematic review was conducted to assess whether there was evidence to support an association between use of ERT or HRT and risk of breast cancer (note: included studies do not appear to have undergone systematic quality assessment). Forty-five studies were identified which assessed the association between ERT and breast cancer risk; 20 which assessed the association between HRT and breast cancer risk; 5 which assessed the risk of HRT and death from breast cancer; and 6 which assessed the risk of HRT and breast cancer survival (overall total of 55 studies). Data on risk estimates for breast cancer in ever-users of ERT and HRT compared to never-users showed an overall lack of consistency and only modest increases or decreases in risk of breast cancer. A similar lack of consistency was shown in findings from studies which evaluated breast cancer risk by duration of hormone use. However, in studies which assessed the risk of HRT and death from breast cancer, there was consistently a lower risk of death from breast cancer in hormone users compared to non-users. The authors conclude that the evidence does not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more estrogen only.

Collaborative Group on Hormonal Factors in Breast Cancer (1997)
Epidemiological data from 51 studies in 21 countries was combined to evaluate the relationship between breast cancer risk and use of hormone replacement therapy (HRT), involving data on 52 705 women with breast cancer and 108 411 women without breast cancer (note: included studies do not appear to have undergone systematic quality assessment). Main analyses were based on 53 865 postmenopausal women of whom 17 830 (33%) had used HRT at some time. The main findings were that for current/recent users of HRT the relative risk of breast cancer increased by a factor of 1.023 (95% CI; 1.011-1.036; 2p=0.0002) for each year of use; the relative risk for women who had used HRT for 5 years or more was 1.35 (95% CI, 1.21-1.49; 2p=0.00001) . However, for past users (5 or more years after cessation of HRT use) there was no significant increase in relative risk, either overall or in relation to duration of use. Of the factors examined which may have affected these results (including family history of breast cancer), only weight and body-mass index had a significant effect among current/recent users who had a duration of HRT usage of 5 years or more. The authors conclude that breast cancer risk is increased in women using HRT and increases with longer duration of use; however, this increased risk is reduced after HRT use ceases and has largely disappeared after about 5 years.

Colditz et al (1993)
Data from 31 published reports (25 case-control and 6 follow-up studies; references not provided) of the effect of oestrogen use on breast cancer risk was combined in a meta-analysis (note: included

studies do not appear to have undergone systematic quality assessment). Overall, results indicated that ever-use of hormone replacement therapy is not associated with an increased risk of breast cancer (RR 1.02; 95% CI, 0.93-1.12); however, current use was found to be associated with increased risk (RR 1.40; 95% CI, 1.20-1.63). No significant trend was observed between years of oestrogen therapy and risk of breast cancer when data from 17 of the studies was combined, although women with 10 or more years of oestrogen usage had a relative risk of 1.23 (95% CI, 1.08-1.40). Data combined from 4 studies indicated that ever-use of oestrogen therapy plus progestin was not associated with a reduced risk with an overall relative risk of 1.13 (95% CI, 0.78-1.64). There was no evidence to support a differential effect of oestrogen therapy among women with a family history of breast cancer compared to those without, nor among women with a prior history of benign breast disease. The authors conclude that although their results excluded a large effect of oestrogen therapy on breast cancer risk, they were unable to rule out some risk associated with current or long-term use.

Sillero-Arenas et al (1992)

The effect of HRT after menopause on breast cancer risk was evaluated in a meta-analysis of 37 studies (23 case-control, 13 cohort and one clinical trial). Results found that overall, ever-use of HRT had a small but statistically significant effect on risk of breast cancer (RR 1.06; 95% CI, 1.00-1.12). Those women who had experienced a natural menopause seemed to be at increased risk (RR 1.13; 95% CI, 1.04-1.22). A significant weighted relative risk was observed in current HRT users (RR 1.23; 95% CI, 1.12-1.35), especially in those who had a natural menopause (RR 1.63; 95% CI 1.26-2.10). The authors conclude that HRT may increase the risk of breast cancer, especially in women with natural menopause.

Steinberg et al (1991)

In this meta-analysis, 16 case-control studies were identified which evaluated the effect of oestrogen replacement therapy (ERT) on the risk of breast cancer. Study findings were combined to quantify the proportional increase in breast cancer risk for each year of ERT use. Risk of breast cancer did not appear to increase for women who experienced any type of menopause until at least 5 years of oestrogen use, with a significant mean proportional increase in risk of 0.015 (95% CI, 0.004-0.021) per year of use. Findings showed a 30% increase in the risk of breast cancer after 15 years of oestrogen use (relative risk (RR) 1.3; 95% confidence interval (CI), 1.2-1.6). This increase was largely due to results of studies that included premenopausal women or women using estradiol (with or without progestin). Findings from 5 of the studies, 2 of which included premenopausal women, showed that in women with a family history of breast cancer, those who had ever used ERT had a significantly higher breast cancer risk (RR 3.4; 95% CI, 2.0-6.0) than those who did not (RR 1.5; 95% CI, 1.2-1.7).

Dupont et al (1991)

This study was conducted to evaluate the relationship between ERT and breast cancer; 28 studies were identified (18 case-control, 10 cohort studies) from the literature. The overall relative risk of breast cancer associated with ERT from all studies was 1.07; however, the authors note that relative risks varied widely from this overall estimate and were significantly different from each other ($P<0.00005$). The authors examined the effects of type, duration and dosage of treatment and make the following conclusions. There is some evidence to suggest that breast cancer risk may increase slightly with duration of treatment, and some studies suggest that a daily dosage of 1.25mg or more of conjugated estrogens may also increase breast cancer risk (RR of 2.0 or less in all studies). There is consistent evidence from multiple studies that a daily dosage of 0.625 mg or less of conjugated estrogens for several years does not appreciably increase the risk of breast cancer (RR 1.08; 95% CI,

0.96-1.2). ERT consisting of 0.625 mg/d of conjugated estrogens is not contraindicated because of breast cancer risk in women with a history of benign breast disease.

Other Studies

Million Women Study (2003)

The Million Women Study was a prospective cohort study. It was set up to investigate the relationships between various patterns of use of HRT and breast cancer incidence and mortality. It recruited 1,084,110 women through 66 centres who provide screening through the NHS Breast Screening Programme, in the period May 1996-March 2001. Data collection was via questionnaires issued to women with their invitation to screening letter. Main analyses were presented for postmenopausal women, with a defined time since menopause (828,923 women). The findings showed that HRT causes a duration-dependent increase in the risk of breast cancer. The associated increased risk in breast cancer begins to decline when HRT use is stopped and by 5 years since cessation, the relative risk reaches the same level as women who have never taken HRT. The relative risk of breast cancer incidence for ever users of HRT compared with never users was 1.43 (1.36-1.50, p<0.0001). Amongst those who had ever used HRT, those who were current users had a relative risk of breast cancer incidence of 1.66 (1.58-1.75, p<0.0001) and past users had a relative risk of 1.01 (0.94-1.09, p<0.0001). (Further details including relative risks associated with different durations of HRT use can be found in Appendix 13).

Ursin et al (2002)

This US case-control study was conducted to determine whether any particular subgroup of women is at particularly high risk of breast cancer if they use postmenopausal combined oestrogen and progestin replacement therapy (EPRT). (The study also aimed to determine whether tumour characteristics in women who develop cancer while using ERT or EPRT are different from those in women not using these therapies.) Data were presented for 1 897 postmenopausal women and 1 637 controls with an age range of 55-72 years, who had not undergone simple hysterectomy. No association between EPRT use and women with a family history of breast cancer was found (first degree relative vs none; P=0.57). No association was also found between EPRT use and other subgroups of women in terms of body mass index, alcohol intake, parity, and history of benign breast disease. The authors conclude that they found no evidence to suggest that particular subgroups of women, including women with a family history of breast cancer, are at higher risk of developing breast cancer if they use EPRT.

Sellers et al (1997)

A study using questionnaire and registry data was conducted to determine whether HRT was associated with increased risks for breast cancer and total mortality in women with a family history of breast cancer. Data were obtained from a random sample of 41 837 postmenopausal US women (age range 55-69 years) who enrolled in an observational study of risk factors for cancer with a follow-up period of 8 years. A family history of breast cancer was reported by 12.2% of the cohort of women at risk. Frequency of reported use of HRT did not differ by family history, with 38.3% of women without a family history and 37.7% with a family history (P>0.2); also duration of use was similar (P>0.2). Among women with a family history of breast cancer, those who were current users of HRT (for at least 5 years' duration) developed breast cancer at an age-adjusted annual rate of 61 cases per 10 000 person-years (95% CI, 28-94 cases). This rate was not statistically significantly higher than the rate in women who had never used HRT (46 cases per 10 000 person years (CI, 36-55 cases)). Among women with a family history, those who used HRT had a significantly lower risk for total mortality compared to women who had never used HRT (RR 0.67; CI, 0.51-0.89). The authors

conclude that in women with a family history of breast cancer, HRT use is not associated with a significantly increased breast cancer incidence but is associated with a significantly reduced total mortality rate.

HRT and effect on breast cancer risk in women with a family history of breast cancer

The Million Women Study looked at the relative risks of incident invasive breast cancer in relation to recency and type of HRT use and examined them separately by age, family history of breast cancer, BMI and ever use of oral contraceptives. The only factor that seemed to modify the relative risk estimates materially was BMI (with relative risks being larger among thinner women, i.e. those who had a BMI$\leq$25kg/m^2).

Two other studies were identified which assessed the role of HRT in breast cancer risk in women with a family history of breast cancer. These studies were reported as being included in the Collaborative Group Reanalysis (1997) (see above).

Oestrogen and oestrogen-progesterone replacement therapy

Million Women Study (2003)
The Million Women Study presented findings that showed that different HRT regimens were associated with different relative risks of breast cancer incidence. Preparations used by current users of HRT were as follows: 41% were taking preparations containing oestrogen only, 50% were taking combinations of oestrogen-progestagen, 6% reported taking tibolone, 1% said they were using other preparations and unknown in 2% of participants. As well as increased relative risks for all current use for oestrogen only, tibolone and combination preparations, the relative risks were significantly different between the different types. They found that the relative risk associated with oestrogen-progestagen combinations was substantially higher (RR=2.00, 1.88-2.12, p<0.0001) than found with oestrogen only preparations (RR=1.30, 1.21-1.40, p<0.0001) and tibolone (RR=1.45, 1.25-1.68, p<0.0001).

Schairer et al (2000)
This recent study was a follow-up of participants in the Breast Cancer Demonstration Project, using data from 1980-1995. It was population based not confined to those with a family history. After exclusions, 46,355 subjects were available for analysis. It was confined to women who were menopausal before the start of follow-up period or who became menopausal during the course of the study (those who did not have a menstrual period for at least 3 months due to natural menopause or bilateral oophorectomy). The mean duration of follow-up was 10.2 years with a median of 12.3 years with a maximum follow up of 16 years and minimum of less than 1 year. The average age at start of follow-up was 58 years. Relative risks were given, after adjustment for attained age, age at menopause, education, BMI and mammographic surveillance. Adjustment for race, period of follow-up, age at first live birth, family history of breast cancer, history of benign breast disease and clinical breast examination did not alter estimates.

They report increases in risk associated with use of oestrogen only and oestrogen-progesterone. These increases were largely restricted to recent use (defined as current use and past use occurring within previous 4 years). The relative risks were 1.2 (95% CI, 1.0-1.4) for oestrogen only and 1.4 (95% CI, 1.1-1.8) for oestrogen-progesterone. The relative risk of breast cancer increased by 0.01 (95% CI, 0.002-0.03) for each year of oestrogen only use (P=0.01 for trend) and 0.08 (01 (95% CI, 0.02-0.16) for oestrogen-progesterone only use (P=0.01 for trend).

Associations with duration of oestrogen only use among recent users varied according to BMI (P=0.002 for score test), with increases in risk evident only in women with a BMI of 24.4 kg/m² or less. In this group, the relative risks increased by 0.03 (95% CI, 0.01-0.06) for each year of oestrogen only use.

They concluded that their results suggest that the combined oestrogen-progesterone regimen is associated with greater increases in breast cancer risk than oestrogen alone. Oestrogen alone was associated with increased risk in lean but not heavy (24.4 kg/m²) women.

7.9 Alcohol Consumption

7.9.1 Evidence statement

- Risk of breast cancer increases with alcohol consumption. (III)
- The Collaborative Group reported an increase of 7.1% in relative risk for each additional 10g per day intake of alcohol. (III)
- There is no good evidence that the relative risk associated with increasing alcohol consumption is different for women with a family history compared to women as a whole. (III)

7.9.2 Summary of alcohol consumption and breast cancer risk evidence

Results of 4 meta-analyses identified from the literature, which evaluate the impact of alcohol consumption on breast cancer risk in women, consistently show statistically significant increases in relative risks. Associations vary slightly between studies in terms of specific intake of alcohol and increase in breast cancer risk, with definitions of an alcoholic drink in relation to equivalent gram weight showing slight differences between studies. One study (Longnecker et al, 1988) observed significant increases in risk with an alcohol intake of 24 g (defined as about 2 drinks) per day, although only weak or modest associations at lower levels of alcohol consumption. A subsequent study by Longnecker (1994), however, found significantly increased relative risks of breast cancer associated with an intake of 1, 2 or 3 drinks per day (1 drink defined as 13 g of alcohol), showing strong evidence of a dose-response relationship. The third identified meta-analysis (Smith-Warner et al, 1998) found significantly increased breast cancer risks in women who drank 30-60 g (defined as about 2-5 drinks) per day, although no increased risks were observed in women who drank 60 g or more per day compared with non-drinkers. Other breast cancer risk factors, including family history of breast cancer, did not influence these results. The fourth and most recent meta-analysis (Ellison et al, 2001) found a significant linear increase in breast cancer risk with increasing intake of alcohol of 6, 12 and 24 g (defined as about one-half, 1 and 2 drinks, respectively) per day.

Results of a systematic review (Steinberg et al, 1991) found inconsistencies in results across studies, with the authors unable to support a causal association between alcohol intake and breast cancer risk.

Results of the collaborative reanalysis of worldwide data (Collaborative Group, 2002) found that the lifetime risk of breast cancer is estimated to increase by about 0.7 per 100 women for each extra unit of alcohol consumed daily, although this increase should be considered in the context of the beneficial effects of a moderate intake of alcohol. Smoking has little or no independent effect on breast cancer risk.

A cohort study (Vachon et al, 2001) which evaluated the association between alcohol consumption and breast cancer risk in women with a family history of breast cancer compared to those who married in to these families found significantly increased risks in 1st-degree relatives of breast cancer patients who drank daily compared to non-drinkers, but non-significant increases for 2nd-degree relatives. For women who married in to these families and reported daily intake of alcohol, no significantly increased breast cancer risks were observed. The authors, however, advise caution in interpreting these findings due to methodological limitations.

7.9.3 Comment

Women who drink moderate amounts of alcohol have been found to have a slightly higher risk of breast cancer than do those who abstain. It is uncertain, however, whether this association reflects a cause-and-effect relationship. The weaker an association is, the more difficult it is to tell whether that association is due to a true cause-and-effect relationship or to something else. It is extremely difficult to determine whether any effect reflects a true cause-and-effect relationship or is due to other factors—such as difficulties in measurement or differences between the lifestyles of drinkers and abstainers. The use of alcohol may vary among women who differ with regard to other factors that are known to influence breast cancer risk—such as age, obesity, and reproductive history.

Studies

Five meta-analyses/systematic reviews which evaluate the impact of alcohol consumption on breast cancer risk for women in general have been identified from the literature. One cohort study which assesses the effect of alcohol consumption on breast cancer risk in women with a family history of breast cancer has been identified.

Meta-analyses, systematic reviews and re-analyses

Collaborative Group on Hormonal Factors in Breast Cancer (2002b)
This study reanalysed 80% of worldwide data on the relationship between breast cancer and consumption of alcohol and/or tobacco, involving 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. The relative risk of breast cancer increased significantly with increasing intake of alcohol, increasing by 7.1% for each additional 10 g per day of alcohol ($P<0.00001$) in both ever-smokers and never-smokers. Adjustments for 11 potential confounding factors (including family history of breast cancer, use of hormonal preparations and menopausal status) did not alter the magnitude of this increase in relative risk. However, the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. Analysis of data for 22,255 cases and 40,832 controls who reported no alcohol intake found that breast cancer risk in ever smokers did not differ significantly from that of never smokers (RR=1.03, SE 0.023, NS). The authors note that among women who drank alcohol, the findings for an association between smoking and breast cancer were difficult to extricate from the effects of alcohol itself. They conclude that smoking has little or no independent effect on breast cancer risk, and the increase in breast cancer risk attributed to alcohol needs to be interpreted in the context of the beneficial effects of a moderate intake.

Ellison et al (2001)
This meta-analysis combined the findings of 42 cohort and case-control studies (the authors note that the quality of included studies varied widely, although details of quality assessment are not reported) on breast cancer incidence, and 2 studies on breast cancer mortality, in order to assess breast cancer risk and breast cancer mortality according to alcohol intake. In comparison to non-drinkers, women who consumed 6 g (about one-half drink) per day had a 4.9% increased breast cancer risk (95% CI, 1.03-1.07); those who drank 12 g (about 1 drink) and 24 g (about 2 drinks) per day had 10% (95% CI, 1.06-1.14) and 21% (95% CI, 1.13-1.30) increased risks, respectively. Results of the 2 studies which evaluated breast cancer mortality and alcohol consumption gave a risk estimate of slightly below 1.0 for up to 6 g per day. In conclusion, the authors suggest a modest relation of alcohol consumption to breast cancer risk.

Smith-Warner et al (1998)

The results of 6 prospective studies (included studies do not appear to have been systematically quality assessed) with a total sample of 322,647 women, including 4,335 women with invasive breast cancer, were combined to assess breast cancer risk by type and intake of alcohol, and the impact of potential risk modifiers (including family history of breast cancer). Alcohol consumption was positively associated with risk of invasive breast cancer, with an intake of 30-60 g (about 2-5 drinks) per day giving a RR of 1.41 (95% CI, 1.18-1.69) compared to non-drinkers. However, the association was not statistically significant for women who consumed 60 g or more per day (RR=1.31; 95% CI, 0.86-1.98) compared to non-drinkers. A significant linear increase in risk was also observed for alcohol intakes of less than 60 g per day (RR=1.09; 95% CI, 1.04-1.13) for an increment of 10 g (about 0.75-1 drink) per day. There were no statistically significant interactions between breast cancer risk and alcohol intake when other breast cancer risk factors (for example, menopausal status, family history of breast cancer, HRT use and body mass index) were taken into account. The authors conclude that alcohol intake is associated with a linear increase in invasive breast cancer risk, and that this association is not modified by other factors.

Longnecker (1994)

A meta-analysis and qualitative review was carried out to evaluate the association between alcohol intake and risk of breast cancer from the results of 10 cohort and 28 case-control studies. Synthesis of risk estimates found significantly increased breast cancer risks associated with an intake of 1, 2 or 3 drinks per day, with relative risks of 1.11 (95% CI 1.07-1.16), 1.24 (95% CI, 1.15-1.34) and 1.38 (95% CI, 1.23-1.55), respectively. There was no evidence of variation in size of association by study design (cohort compared to case-control). A qualitative review of studies found no evidence of effect modification on these results, apart from limited data on an association with estrogen replacement therapy. The authors conclude that there is strong evidence of a dose-response relation between alcohol consumption and breast cancer risk.

Steinberg et al (1991)

The association between alcohol consumption and breast cancer risk in women was assessed by systematic review of 6 cohort and 20 case-control studies. Study findings were inconsistent across both types of study designs. Only one of the 3 cohort studies which assessed overall breast cancer risk in drinkers compared to non-drinkers observed a significant association with a relative risk among drinkers of 1.5 (95% CI, 1.1-2.2). However, 5 of the cohort studies found breast cancer risk to be significantly increased in women with 'high' levels of alcohol intake, with the highest risk estimate of 3.18 (95% CI, 1.14-8.85) in women with an intake of more than 6 drinks per day. Of the 11 case-control studies which compared breast cancer risk in drinkers versus non-drinkers, 5 found significant positive associations (RRs varied from 1.2-2.5). A significant dose-response gradient with increasing alcohol intake was also observed in 8 case-control studies. In 4 studies where no significant association was found between alcohol and breast cancer risk, a significant increase in risk was observed in women who drank more than a specified amount daily. There was some evidence from 2 studies of a decrease in risk associated with increased alcohol consumption. In conclusion, the authors found insufficient evidence to support a causal relationship between alcohol intake and breast cancer risk.

Longnecker et al (1988)

In this meta-analysis of 12 case-control and 4 cohort studies, breast cancer risk in women by intake and ever-consumption of alcohol was evaluated. For both the case-control and cohort studies a statistically significant dose-response relation between alcohol consumption and breast cancer risk was observed (P=0.01 and <0.05, respectively). Risk estimates associated with an alcohol intake of

24 g of alcohol (about 2 drinks) per day relative to non-drinkers were 1.4 (95% CI, 1.0-1.8) for case-control studies, and 1.7 (95% CI, 1.4-2.2) for cohort studies. At lower levels of alcohol consumption, there were weak to modest associations for both study designs. A synthesis of 6 case-control studies found an overall risk estimate for ever-consumption of alcohol compared with never-use of 1.1 (95% CI, 1.0-1.2). The authors conclude that their findings were strongly supportive of an association between alcohol intake and breast cancer risk.

Other Studies

Vachon et al (2001)

This cohort study investigated the association between alcohol intake and breast cancer risk in 5,042 women from 426 families with a history of breast cancer compared to 3,990 women who married in to these families. Data were included from 2,974 surrogates (usually 1st-degree relatives) where relatives were deceased or unable to provide data. Ever-use of alcohol in all study participants compared to non-drinkers was associated with a 22% increased risk (95% CI, 0.99-1.50). Among 1st-degree relatives of women with breast cancer, daily drinkers had a significantly increased risk compared with non-drinkers (RR=2.45; 95% CI, 1.20-5.02). This increase was less evident among 2nd-degree relatives (RR=1.27; 95% CI, 0.73-2.22). In comparison, there was no significantly increased breast cancer risk in those women who married-in and reported daily alcohol intake. Similar findings were observed when analyses where restricted to families at particularly high risk of breast cancer (i.e. families that had 3 or more breast and/or ovarian cancers). The authors conclude that alcohol-associated breast cancer risks may be modified by genetic susceptibility. They acknowledge, however, that their findings should be interpreted cautiously due to factors such as recall bias, potentially poor data quality and lack of generalisability.

7.10 Smoking

7.10.1 Evidence statement

- There is no good evidence for an association between smoking and breast cancer. (IV)
- In the Collaborative reanalysis, for women who reported they did not drink, compared to women who never smoked the relative risk of breast cancer was close to 1 in current or past smokers. (III)
- A recent large meta analysis concluded that cigarette smoking increases breast cancer risk, with a higher risk in premenopausal women and in those who started smoking at an earlier age. (III)

7.10.2 Summary of smoking and breast cancer risk evidence

Results from a systematic review and a meta-analysis which assessed the association between smoking and breast cancer risk reached different conclusions, with the systematic review (Palmer et al) finding either no, or very small positive, associations and the meta-analysis (Khuder et al) finding significant increases in risk in ever, former and current smokers, with particularly high risks observed for premenopausal women and those who initiated smoking at an earlier age. The Collaborative group concluded that smoking has little or no independent effect on breast cancer risk.

Two North American observational studies both found that smoking significantly increased breast cancer risk. In the cohort study (Terry et al), ever smoking (although not former smoking) increased risk; also smoking of very long duration and high intensity was associated with particularly high risk, with, for example, an 83% increase in breast cancer risk in women who smoked 20 or more cigarettes per day over 40 years or more, relative to never-smokers. In the case-control study (Band et al), results suggested increases in risk in premenopausal women who smoked before a 1st pregnancy (but only when smoking was initiated within 5 years of onset of menarche) and in nulliparous premenopausal women. Postmenopausal women, however, were not at increased breast cancer risk, with some subsets of women showing a reduction in risk associated with smoking. A third North American observational study found a significant 2.4-fold increase in breast cancer risk of smoking in sisters and daughters from families at high risk of breast and/or ovarian cancer.

7.10.3 Comment

There is some evidence that cigarette smoking may be associated with a small increase in breast cancer risk. However, because the results of scientific studies have not been consistent, this relationship is currently regarded as merely speculative

7.10.4 Studies

One meta-analysis and, one systematic review and one re-analysis have been identified from the literature which evaluate the association between smoking and breast cancer risk in the female population in general. Two recent observational studies (1 cohort and 1 case-control) have been identified which evaluate the relationship between smoking and breast cancer risk in a similar population. A further recent cohort study has been identified which assesses the association between smoking and breast cancer risk in families at high-risk of breast and/or ovarian cancer.

Meta-analyses, systematic reviews and reanalyses

Khuder et al (2001)
The relationship between smoking and breast cancer was evaluated in this meta-analysis of 31 case-control and 9 cohort studies published between 1984 and 2001 (note: included studies do not appear to have been quality assessed). Breast cancer risk was significantly increased in women who ever smoked (RR=1.10; 95% CI, 1.02-1.18), in current smokers (RR=1.11; 95% CI, 1.01-1.22), and in former smokers (RR=1.10; 95% CI, 1.00-1.21). Although risk was significantly raised in postmenopausal women, premenopausal women who were ever smokers or former smokers were at higher risk (RR=1.21; 95% CI, 1.08-1.36 and RR=1.30; 95% CI, 1.19-1.51, respectively). A significant dose-response trend was observed (P<0.01) for breast cancer risk according to the number of cigarettes smoked per day, with a RR of 1.03 (95% CI, 1.01-1.06) in women who smoked 1-10 cigarettes per day, increasing to 1.30 (95% CI, 1.05-1.61) in women who smoked 40 or more cigarettes per day. A significant dose-response trend was also observed (P<0.01) for breast cancer risk and duration of smoking, with a combined RR of 1.03 (95% CI, 1.02-1.04) associated with smoking for 1-19 years, increasing to 1.12 (95% CI, 1.07-1.17) with 30 or more years of smoking. Initiation of smoking at a younger age (mean 14 years) was associated with a significant increase in risk (RR=1.14; 95% CI, 1.06-1.23). The authors conclude that cigarette smoking increases breast cancer risk, with a higher risk in premenopausal women and in those who started smoking at an earlier age.

Palmer et al (1993)
Fourteen case-control and 5 cohort studies published up to 1992 were reviewed to evaluate a causal relationship between cigarette smoking and breast cancer risk (included studies did not undergo quality assessment). Review of the evidence found that cigarette smoking did not appear to reduce breast cancer risk, and there was also little evidence to suggest that smoking increases risk. Most studies found either no association or very small positive associations for ever smoking, current smoking or heavy smoking. There was inconsistent evidence about whether women who initiate smoking in their early teens are at increased breast cancer risk. Adjusting for risk factors such as parity, family history of breast cancer and body mass index did not influence risk estimates. The authors discuss the possibility of bias and confounding amongst studies.

Collaborative Group on Hormonal Factors in Breast Cancer (2002)
This study reanalysed 80% of worldwide data on the relationship between breast cancer and consumption of alcohol and/or tobacco, involving 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. The relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. Analysis of data for 22,255 cases and 40,832 controls who reported no alcohol intake found that breast cancer risk in ever smokers did not differ significantly from that of never smokers (RR=1.03, SE 0.023, NS). The authors note that among women who drank alcohol, the findings for an association between smoking and breast cancer were difficult to extricate from the effects of alcohol itself. They conclude that smoking has little or no independent effect on breast cancer risk, and the increase in breast cancer risk attributed to alcohol needs to be interpreted in the context of the beneficial effects of a moderate intake.

<u>Other Studies</u>

Terry et al (2002)
Breast cancer risk and the effect of ever, former and never cigarette smoking was evaluated in a prospective cohort study of 89,807 women recruited between 1980 and 1985 in Canada. A

significant increase in breast cancer risk was observed for women who had ever smoked, with an age-adjusted RR of 1.15 (95% CI, 1.05-1.27), compared to women who had never smoked. Women who were former smokers, however, were not at increased risk (RR=1.00; 95% CI, 0.91-1.10), compared to never-smokers. In terms of duration of smoking, women who had smoked for 40 years or longer had about a 60% increased breast cancer risk compared to never-smokers (RR=1.61; 95% CI, 1.19-2.19). Intensity of smoking also increased risk, with women who smoked 30-39 and 40 or more cigarettes a day having RRs of 1.21 (95% CI, 1.04-1.42) and 1.37 (95% CI, 1.15-1.62), respectively. Women with at least 40 pack-years of cigarette consumption over 40 years or more were at particularly high risk (RR=1.83; 95% CI, 1.29-2.61). In terms of breast cancer risk and age at initiation of smoking, and years since stopping smoking, there were no clear associations. Adjusting for multiple variables, including family history of breast cancer, did not affect any of the associations found across smoking measures. Overall findings suggest that smoking of very long duration and high intensity is associated with increased breast cancer risk.

Band et al (2002)

In a Canadian case-control study, 318 premenopausal and 700 postmenopausal women listed on the British Columbia cancer registry were compared to 340 premenopausal and 685 postmenopausal population-based controls in terms of effect of cigarette smoking on breast cancer risk. Study findings showed that the effect of smoking on breast cancer risk differed between pre- and postmenopausal women. In premenopausal women, risk was raised in women who smoked before a 1st pregnancy, but only when smoking was initiated within 5 years of onset of menarche (OR=1.69; 95% CI, 1.13-2.51). In nulliparous premenopausal women, risk was also significantly increased in women who smoked 20 or more cigarettes per day (OR=7.08; 95% CI, 1.63-30.8) and for 20 or more pack-years (OR=7.48; 95% CI, 1.59-35.2). Findings for postmenopausal women, however, showed no associations between smoking and breast cancer risk, except a reduced risk observed in women who started to smoke after a 1st full-term pregnancy (OR=0.64; 95% CI, 0.42-0.98) and whose body mass index increased since early adulthood (OR=0.49; 95% CI, 0.27-0.89).

Couch et al (2001)

The association between cigarette smoking and breast cancer risk in 132 high-risk US families (defined as families with 3 or more members affected with breast and/or ovarian cancer) was evaluated in a historical cohort study involving 1,891 women who had ever smoked and 2,246 women who had never smoked. Among sisters and daughters of breast cancer patients, those who ever smoked had a 2.4-fold increase in breast cancer risk (95% CI, 1.2-5.1) compared to never-smokers. No association was observed in nieces, granddaughters or women who married in to the families. When analyses were restricted to 35 families at highest-risk (defined as having 5 or more members with breast and/or ovarian cancer), sisters and daughters who had ever smoked were at 5.8-fold increased breast cancer risk (95% CI, 1.4-23.9), compared with never smokers. Again, no increased risk was observed in nieces and granddaughters. The authors conclude that smoking may significantly increase breast cancer risk in sisters and daughters from families at high risk of breast and/or ovarian cancer.

7.11 Weight and Physical Activity

7.11.1 Evidence statement

- No specific evidence was found between the relationship between diet and exercise and familial breast cancer risk.
- Moderate physical exercise is associated with a decrease risk in breast cancer in the general population. (III)
- A high BMI is associated with a significant increase in post menopausal breast cancer risk in the general population. (III)

7.11.2 Comment

In scientific studies, obesity has been consistently associated with an increased risk of breast cancer among postmenopausal women. As is the case with reproductive risk factors, this relationship may be mediated by oestrogen production. Fat cells produce some and obese postmenopausal women, therefore, tend to have higher blood oestrogen levels than non-obese women do. Obesity does not seem to be a risk factor for breast cancer in premenopausal women. In these younger women, the ovaries are the main producers of oestrogen. The much smaller amount of oestrogen produced by the fat cells doesn't appear to have any significant impact on breast cancer risk. Scientific studies have consistently shown that the risk of breast cancer is lower among physically active premenopausal women than among sedentary women. The effect of physical activity on breast cancer risk may be due at least in part to effects of exercise on the female hormones. Although the effects of obesity and physical inactivity on breast cancer risk are not as strong as the effects of previous breast disease or family history of breast cancer, they are important risk factors because they are modifiable. Exercise and weight control currently represent the most effective lifestyle changes that a woman can make to reduce her risk of breast cancer. Lack of physical activity is an established risk factor for premenopausal breast cancer and represents part of a complete approach to weight management. In addition, women who stay active can also reduce their risk of other diseases, such as coronary heart disease and colon cancer, and they can increase their quality of life.

7.11.3 Studies

An IARC report (2002b) reported findings from many cohort and case –control studies, which looked at reproductive and lifestyle factors. These were for general populations rather than those with a family history. A systematic review by Harvie et al (2003) looked at the effect of central obesity on breast cancer risk.

Weight

Premenopausal women:

A recent IARC report reported that for premenopausal women, in populations with a high incidence of breast cancer, those with high BMIs (over 28kg/m²) were found to have a slightly reduced breast cancer risk. It also reported that despite this reduced breast cancer incidence risk, the breast cancer mortality rate is not lower among heavier premenopausal women (IARC 2002b: 237).

Harvie et al (2003) found that waist measurement or waist to hip ration had little, if any effect, on risk of breast cancer. However they did find that using adjusted data (adjusted for BMI) showed a relative reduction (42%) in women with the smallest waist to hip ratio and that there was a relationship between central obesity and increased risk.

Postmenopausal women:

A recent IARC report reported that more than 100 studies over nearly 30 years in populations in many countries have established that increased body weight increases breast cancer risk among postmenopausal women. It went on to say that almost all of these studies have shown that this association is largely independent of a wide variety of reproductive and lifestyle risk factors, also that recent studies have indicated that it is independent of the effect of physical activity. The association between being overweight and breast cancer appears to increase in a stepwise fashion with advancing age after the menopause (IARC 2002b: 237).
Harvie et al (2003) found that women with the smallest waists (quintile) had a lower relative risk of breast cancer than those in the highest waist measurement quintile (39%, using unadjusted but pooled data) and similar findings for waist to hip measurement (34%, using unadjusted but pooled data). This relationship was attenuated when adjustment for BMI was made.

Physical activity

Most of the more than 30 epidemiological studies, conducted in Asia, Europe and North America, demonstrated lower breast cancer risk among the most physically active women. In 8 of the 14 cohort studies and in 14 of the 19 case-control studies, lower breast cancer risk was seen among women who were most active. The decrease in risk of breast cancer was, on average, about 20-40%. (IARC 2002b: 238)

7.12 Evidence Tables

Table 7.1: Menstrual/reproductive factors

Author(s) Study	Research question(s)	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Negri et al (1988) Risk factors for breast cancer: pooled results from three Italian case- control studies	To assess the role of menstrual/reproductive factors and breast cancer risk	Meta-analysis Databases not searched Not stated Multiple logistic regression	Not stated	3 case-control studies conducted in Italy Not applicable Not applicable	**Numbers:** cases: 4,072; controls: 4,099 **Age (years) at menarche:** ≥15: 15% cases; 17.6% controls. 12-14: 67.9% cases; 64.3% controls. <12: 17.1% cases; 18.1% controls **Age (years) at menopause:** ≥50: 33.8% cases; 28.5% controls. 45-49: 18.4% cases; 19.6% controls. <45: 11.3% cases; 13.2% controls. Premenopause: 36.5% cases; 38.7% controls **Parity:** 0: 20.2% cases; 18.2% controls. 1: 20.9% cases; 19.2% controls. 2: 31.4% cases; 30.7% controls. 3-4:	Breast cancer risk according to: menstrual and reproductive factors; family history; body weight (results not reported in this extraction table)

Results

Breast cancer risk and age at menarche: Risk of breast cancer in women who were aged 12-14 years and <12 years at menarche was significantly increased (RR=1.32; 95% CI, 1.15-1.52 and RR=1.19; 95% CI, 1.00-1.42, respectively), relative to women who were aged 15 years or over at menarche.

Breast cancer risk and menopausal status: There was a statistically significant trend towards decreasing breast cancer risk with earlier menopause; RR=0.77 (95% CI, 0.67-0.90) and 0.73 (95% CI, 0.61-0.88) in women who experienced menopause aged 45-49 years and less than 45 years, respectively, relative to women who were aged 50 years or over at menopause.

Breast cancer risk according to parity: Women who reported 5 live births or more had a significantly decreased risk of breast cancer, with a RR of 0.62 (95% CI, 0.50-0.76).

Breast cancer risk and age at 1st live birth: There was a strong direct relation between age at 1st live birth and breast cancer risk, with a RR of 1.75 (95% CI, 1.50-2.04) in women aged 28 years or more at 1st live birth, relative to women aged less than 22 years.

Breast cancer risk and history of breast cancer in 1st-degree relatives: Women with a family history of breast cancer had a 2-fold increase in breast cancer risk compared to women with no family history (RR=2.06; 95% CI, 1.69-2.51).

Authors' conclusions: These findings confirm the influence of menstrual and reproductive factors and family history on breast cancer risk.

Further information: Comprehensive search for studies not carried out. Included studies did not undergo quality assessment.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants:**	**Outcome(s)**
Nagata et al (1995) Effects of menstrual and reproductive factors on the risk of breast cancer: meta-analysis of the case-control studies in Japan	To evaluate the effect of menstrual and reproductive factors on breast cancer incidence among Japanese women	Meta-analysis MEDLINE January 1966-March 1995 Weighted least-squares linear regression model; Greenland's method	**Included:** epidemiological studies of breast cancer among Japanese women with reference to menstrual/ reproductive factors **Excluded:** studies based on Japanese A-bomb survivors	7 published and 1 unpublished case-control studies Not applicable Not applicable	Number of case-controls provided for individual studies only. Further details on participants' characteristics not reported	Breast cancer risk in Japanese women according to menstrual and reproductive factors (age at menarche, age at 1st birth, parity and age at menopause)

Results

Combined Odds Ratio (OR) Estimates of Menstrual and Reproductive Factors for Breast Cancer among Japanese Women

Variable	OR	95% CI[a)]
Age at menarche		
-13	**1.00**	
14-15	**0.96**	**(0.83-1.12)**
16+	**0.68**	**(0.59-0.77)**
Age at first birth		
-24	**1.00**	
25-29	**1.32**	**(1.14-1.53)**
30-34	**1.71**	**(1.41-2.09)**
35+	**2.26**	**(1.85-2.77)**
Nulliparous	**1.56**	**(1.27-1.91)**
Parity		
1	**1.00**	
2	**0.95**	**(0.75-1.20)**

Breast cancer risk and age at menarche: The combined OR was significantly lower for women with onset of menstruation after age 16 compared to those before age 14.

Breast cancer risk and age at 1st birth: A significantly higher OR was observed for women in any age group for 1st birth after age 25 compared to women with 1st birth before age 25. Nulliparous women were also at elevated risk compared to women with 1st birth before age 25.

Breast cancer risk and parity: A significant protective effect of high parity (3+ children) was noted, even after adjusting for age at 1st birth and other menstrual factors.

Breast cancer risk and menopausal status: Premenopausal women had a significantly higher risk compared to women with menopause before age 50, although an increased OR was not noted for women with menopause after age 50.

Authors' conclusions: The findings confirm that late age at 1st birth, early age at menarche and premenopausal status were significantly associated with breast cancer risk among Japanese women. Parity was also one of the independent risk factors of breast cancer.

Further information: Details of search strategy not reported. The authors state that variation between study results was minimal.

3+	**0.68**	**(0.54-0.86)**	
Age at menopause			
-49	**1.00**		
50+	**0.98**	**(0.74-1.31)**	
Premenopausal	**2.21**	**(1.53-3.20)**	

Table 7.2: Hormone replacement therapy

	Databases searched **Coverage**	**Included studies** **Quality assessment**	**Heterogeneity**	**Menopausal status**	**Outcome(s)**	**Main results**
Steinberg et al (1991) **Systematic review/meta- analysis**	MEDLINE, CANCERLIT, Current Contents, EXCERPTA MEDICA 1966-1989	***16 published case-control studies.*** Quality scores (devised by authors) assigned on scale of 0-100	Studies reported as homogeneous, except when dose-response slopes from all studies were combined.	Pre- and postmenopausal. Analyses by combined and separate menopausal groups.	Mean proportional increase in breast cancer (BC) risk for each year of ERT use. Subgroup analysis (including women with family history of BC).	Increase per year of ERT use for both pre- and postmenopausal groups (0.062 and 0.011). Risk (all women) did not increase until at least 5 yrs of ERT use, with 30% increase after 15 yrs. Ever- use: all women with family history was sig. higher (RR=3.4) compared to women with no history (RR=1.5).
Dupont et al (1991) **Systematic review/some meta- analysis**	MEDLINE 1972-1990	28 published case-control/cohort studies. Quality assessment by checklist devised by authors	Statistical adjustment for heterogeneity of studies not undertaken.	9/28 studies included small proportions of premenopausal women (figures not supplied)	BC risk by type, duration and dosage of ERT. BC risk of ERT in women with history of benign breast disease.	Use of ERT and BC risk: RR=1.07, but significant difference between studies (P<0.00005). Results overall are inconsistent.

	Databases searched Coverage	Included studies Quality assessment	Heterogeneity	Menopausal status	Outcome(s)	Main results
Sillero-Arenas et al (1992) **Systematic review/meta- analysis**	MEDLINE 1971-1990 Search strategy not reported. Non-English language studies included	36 published case-control/cohort studies and 1 clinical trial. Quality assessment of studies undertaken using published guidelines.	Statistical adjustment for heterogeneity undertaken.	Postmenopausal	BC risk by ever-use, duration, time since last use and type/dose of HRT	Ever-use of HRT: small sig. increase in BC risk (RR=1.06), esp. women with natural menopause (RR=1.13). Current/recent use increases risk, esp. in women with natural menopause. Risk also sig. increases by 63% in long-term users (>12 yrs).
Colditz et al (1993) **Systematic review/meta-analysis**	MEDLINE ? to 1991. Search strategy not reported	31 published case-control/cohort studies. No quality assessment of studies reported.	Random effects method used to adjust for variance between study findings.	Not stated, although subgroup analysis by menopausal status undertaken.	BC risk by ever-use, current/recent use, duration, and dose/type of HRT. Subgroup analysis (including women with family history of BC and menopausal status).	Ever-use (all and postmenopausal women): no sig. increase in risk (RR=1.02 and 1.03). Current/recent use (all women): sig. increase in risk (RR=1.40). Duration: sig. increase in risk with long-term use (>10 years: +20%; >15 years: +30%). No significant association of HRT dose/type, or in women with family history of BC.
Collaborative Group (1997) **Re-analysis**	Studies identified by collaboration members. Coverage reported as 90% of epidemiological evidence, including unpublished studies.	51 case-control/cohort studies. No systematic quality assessment of studies reported.	Statistical adjustment for heterogeneity of studies undertaken.	Postmenopausal	BC risk by ever-use, duration and time since last use of HRT. Subgroup analysis (including women with family history of BC)	Ever-use: sig. increase in RR of 1.14. Current/recent use: risk increases by factor of 1.023 for each yr of use. Past users: no sig. increase in risk. Similar patterns in women with family history of BC.

	Databases searched Coverage	Included studies Quality assessment	Heterogeneity	Menopausal status	Outcome(s)	Main results
Bush et al (2001) **Systematic review only**	MEDLINE, Dialogweb 1975-2000	55 published case-control/cohort studies	Not applicable	Menopausal status not taken into account	BC risk and mortality/survival from BC of HRT use	Inconsistent results for BC risk and HRT use. Consistent evidence that HRT reduces death from BC.

Million Women Study

Author (s) Study Objective	Research Question	Review type Databases used Time period covered Data analysis	Study Inclusion/ Exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants: Total sample number Age	Outcome (s)
Million Women Study Collaborators Million Women Study To investigate the effects of specific types of	Breast cancer and hormone replacement therapy in the million women study	Cohort Study Main analyses of risk of breast cancer in relation to HRT were restricted to postmenopausal women with a defined time since menopause National Health Service Breast Screening Programme (NHSBSP) included		Average period for analyses of cancer incidence – 2.6 years Average period for analyses of mortality – 4.1 years	1,084,110 women recruited 550,172 (50%) were ever-users of HRT 828,923 postmenopausal women included in main analyses Average age 55.9 years	
Results						

- Current use of HRT is associated with an increased risk of incident and fatal breast cancer.
- There is greater risk associated with oestrogen-progestagen than other types of preparation.

Relative risks: breast cancer risk

Ever users HRT compared to never users 1.43 (1.36-1.50, p<0.0001) Amongst ever users
current users 1.66 (1.58-1.75, p<0.0001)
past users 1.01 (0.94-1.09, p=0.8)

- Relative risk of breast cancer in current users at baseline increased with increasing total duration of use of HRT.

Relative risk of incident invasive breast cancer in relation to recency and type of HRT used

	Cases/population	Relative risk (95% FCI)*
All never users	2894/392 757	1.00 (0.96-1.04)
All past users	1044/150 179	1.01 (0.95-1.08)
Current users of:		
Oestrogen only	991/115 383	1.30 (1.22-1.38)
Oestrogen-progestagen	1934/142 870	2.00 (1.91-2.09)
Tibolone	184/18 186	1.45 (1.25-1.67)
Other/unknown types	93/9548	1.44 (1.17-1.76)

Relative risk of fatal breast cancer in relation to use of HRT at baseline

HRT use at baseline	Deaths/populatio	Relative risk (95% FCI)*
Never users	238/392 757	1.00 (0.88-1.14)
Current users	191/285 987	1.22 (1.05-1.41)
Past users	88/150 179	1.05 (0.85-1.29)

Relative risk of incident invasive breast cancer in relation to recency, total duration of use and type of HRT used at baseline

Total duration of use of HRT by type of HRT used at	Cases/population	Relative risk (95% FCI)*
Never users of HRT	2894/392 757	1.00 (0.96-1.04)
Past users of HRT		
<1 year	311/47 606	0.94 (0.84-1.05)
1-4 years	384/55 823	1.01 (0.92-1.12)
5-9 years	230/29 614	1.14 (1.00-1.30)
≥10 years	80/11 654	1.05 (0.84-1.30)
Current users of oestrogen-only HRT		
<1 year	25/4452	0.81 (0.55-1.20)
1-4 years	251/29 582	1.25 (1.10-1.41)
5-9 years	416/47 310	1.32 (1.20-1.46)
≥10 years	277/31 862	1.37 (1.22-1.54)
Current users of oestrogen-progestagen combinations		
<1 year	97/9771	1.45 (1.19-1.78)
1-4 years	582/49 240	1.74 (1.60-1.89)
5-9 years	850/56 912	2.17 (2.03-2.33)
≥10 years	362/23 673	2.31 (2.08-2.56)
Current users of other/unknown HRT types		
<1 year	19/1728	1.63 (1.04-2.56)
1-4 years	83/8794	1.34 (1.08-1.66)
5-9 years	102/10 342	1.42 (1.17-1.72)
≥10 years	59/4739	1.93 (1.50-2.50)

Author (s)	Research question	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Dupont et al (1991)[2]	To evaluate the relationship between estrogen replacement therapy (ERT) and breast cancer risk in terms of the effect of type, duration of use and dosage of treatment.	Systematic review/meta-analysis MEDLINE 1972 to approx. 1990 Adjusted relative risks; Woolf's method; chi-squared statistics; Monte Carlo simulation study	**Included:** studies published in peer-reviewed journals **Excluded:** studies with fewer than 5 patients; unpublished studies; studies which included substantial numbers of premenopausal women.	18 case-control and 10 cohort studies ERT ≤6 months-≥20 years	Total numbers of case/controls not reported; numbers recruited into individual studies not reported. No information on characteristics of combined sample reported.	Risk of breast cancer by type, duration of use and dosage of ERT.
Results						

Use of ERT and breast cancer risk: The overall combined RR was 1.07. RRs from separate studies varied widely from this estimate and were significantly different from each other (P<0.00005). Confidence intervals for 7 of the 28 studies do not include the combined RR estimate.

Type of ERT and breast cancer risk: The authors did not combine data on this outcome due to heterogeneity of study results, but reported individual study results only. For one study of women who had taken exogenous estrogens, an overall RR for breast cancer risk was 1.1 (95% CI, 1.0-1.3); however, women who took estradiol preparations had a 20% increase in breast cancer risk that increased significantly with lengthening duration of treatments (P=0.001). Risk of breast cancer among women in the same study who took conjugated estrogens was not significantly increased (P=0.70). In another study, an increased breast cancer risk was associated with estradiol and diethylstilbestrol use, although not with ethinyl estradiol. The authors report 2 studies which evaluated the effect of estrogen plus progestins on breast cancer risk; one study found a fourfold elevation in breast cancer risk in women taking this therapy for 6-9 years; however, this risk was not significantly different from 1.0. Another study reported that adding progestins to menopausal estrogens decreased breast cancer risk.

Duration of ERT and breast cancer risk: Again, the authors did not combine data on this outcome due to heterogeneity of study results, reporting individual study results only. Overall, they report that several studies found a modest, but consistent and statistically significant trend of increasing risk with increasing duration of treatment; however, other studies have failed to find any evidence of a positive duration-risk relationship.

Dosage of ERT and breast cancer risk: Combined data show overall RR estimate for daily conjugated ERT dosage of $\leq$0.625mg as 1.08 (95% CI, 0.99-1.2); results of the studies are consistent and provide strong evidence that low-dosage conjugated estrogen therapy does not appreciably increase breast cancer risk. Combined RR for women who took $\geq$1.25mg/d was also low; however, the RRs from different studies differ significantly from each other (P<0.00005), although none of the estimated RRs are greater than 2.0.

Authors' conclusions: Although the evidence on ERT and breast cancer risk is not consistent, it is likely that duration, dosage and type of estrogen affect breast cancer risk. There is some evidence to suggest that breast cancer risk may increase slightly with duration of treatment. Also some studies suggest that a daily dosage of 1.25mg or more of conjugated estrogens may increase risk, although this risk is probably not more than doubled. There is, however, consistent evidence that a daily dosage of 0.625mg or less of conjugated estrogens for several years does not increase the risk of breast cancer.

Further information: Literature search of MEDLINE database only. Some included studies had a small proportion of premenopausal women in their case and/or control groups.

Author (s)	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Steinberg et al (1991)[1]	To investigate the impact of duration of estrogen replacement therapy (ERT) on breast cancer risk	Meta-analysis ***MEDLINE, CANCERLIT, Current Contents, EXCERPTA MEDICA*** 1966-Sept 1989 Dose-response curves/slopes; regression analysis; relative/attributable risks	**Included:** studies on effect of ERT on breast cancer risk in women who experienced natural menopause or who underwent premenopausal hysterectomy, with or without bilateral oophorectomy **Excluded:** studies that did not distinguish between noncontraceptive/contraceptive estrogen use; included subjects with a previous history of breast cancer; were unpublished reports	16 case-control studies Non-contraceptive, menopausal estrogen Reported as 'at least 10 years' in most studies (recommended length of exposure to ERT at time of studies was 8-10 years post-menopause)	Total sample for all studies not provided. Numbers/ages/age ranges of cases/controls provided for each study separately. Further information on characteristics of participants not reported.	Duration of ERT use and risk of breast cancer Ever-use of ERT and risk of breast cancer among: women with a family history of breast cancer; women who had benign breast disease; women who were nulliparous or parous; women who experienced 1st full-term pregnancy at less than 20 years, 20-30 years, or more than 30 years.
Results						
Duration of ERT and breast cancer risk: For women who experienced any type of menopause, breast cancer risk did not appear to increase until after at least 5 years of estrogen use, with a significant mean proportional increase in risk of 0.015 (95% CI, 0.004-0.021) per year of use. A 30% increase in breast cancer risk was observed after 15 years of estrogen use (RR 1.3; 95% CI, 1.2-1.6). However, this increase in risk was largely due to results of studies that included premenopausal women or women using estradiol (with or without progestin), studies for which the estimated RR was 2.2 (95% CI, 1.4-3.4). The mean proportional increase in risk per year for the studies which included premenopausal women was about 5 times greater than the increase for the data from studies which did not include premenopausal women. **ERT and breast cancer risk in women with a family history of breast cancer:** In women with a family history of breast cancer who had ever used ERT, a significantly higher risk was						

observed (RR=3.4; 95% CI, 2.0-6.0)
compared to women with no family history (RR=1.5; 95% CI, 1.2-1.7).

Effect of Estrogen Replacement Therapy on Relative Risk of Breast Cancer in Women, Stratified by Family History

Type of Stratification	Strata	No. of values*	Mean Relative Risk (95% Confidence Interval)	*P* for Equality of Means
Family history of breast cancer	Yes	7	3.4 (2.0-6.0)	0.003
	No	7	1.5 (1.2-1.7)	

* Some studies used two durations of estrogen use, which we assumed to include different women.

ERT and breast cancer risk in other subgroups: The effects of ERT use were similar among parous and nulliparous women and among women with or without benign breast disease. RR of breast cancer increased with increasing age at 1st full-term pregnancy more for women who took ERT than for women who did not (P<0.01); however, individual CIs for each age at 1st full-term pregnancy included 1.00. RR of breast cancer did not increase with ever-use of ERT in any of the menopause categories (RRs were 1.0 for all categories).

Influence of quality scoring on findings: Studies which scored highly in terms of quality showed a significantly increased risk of breast cancer with increasing duration of ERT use, but the results of moderate and low-scoring studies showed approximately 0% increase.

Further information: The authors note that there was heterogeneity where dose-response slopes from all 16 studies were combined. They suggest that this was due to the differences

The Effect of Estrogen Replacement Therapy on the Risk of Breast Cancer in Women, Pooled Data From 16 Case-Control Studies, 1976 Through 1989

Menopause Type	**No. of Studies Include**	**Model and Risk Assumptions***	Mean Proportional Increase in Risk for Each Year of Estrogen Use†
Studies with premenopausal women	5	Dose-response slopes combined, assumes equal risk	0.062 (0.043-0.081)
	4‡	Dose-response slopes combined, assumes equal risk	0.055 (0.025-0.086)
	4‡	Relative risks combined, assumes equal risk	0.055 (0.039-0.072)
Studies with no premenopausal women	11	Dose-response slopes combined, assumes equal risk	0.011 (0.003-0.018)
	10‡	Dose-response slopes combined, assumes equal risk	0.015 (0.007-0.022)
	11	Relative risks combined, assumes equal risk	0.008 (- 0.002-0.019)

Author (s)	Research question(s)	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Intervention Follow-up period	Characteristics of participants	Outcome(s)
Sillero-Arenas et al (1992)[5]	To evaluate whether there is an association between menopausal hormone replacement therapy (HRT) and breast cancer.	Meta-analysis MEDLINE Jan 1971-June 1990 Multivariate adjusted relative risk (RR) estimates, pooled and weighted according to precision of estimate; Woolf's chi-squared (assessment of heterogeneity of studies); weighted least-squares regression model; subgroup analysis (case-control or cohort; type of menopause)	**Included:** studies which presented original data; assessed HRT as exposure; analysed breast cancer as effect; were based on morbidity data; were English, French, Spanish, Italian, German or Portuguese languages; where RRs could be derived. **Excluded:** unpublished studies. Also no attempt made to obtain missing data or clarify methodologies.	Total: 37: 23 case-control studies; 13 cohort studies; 1 clinical trial HRT <12 months->12 years	Total sample number for all studies not provided. Numbers of cases/controls provided for each study separately. Further information on characteristics of participants not reported.	Risk of breast cancer by ever-use, duration, time since last use and type of HRT.

Results

Ever-Use of Hormone Replacement Therapy and Risk of Breast Cancer				
	N	RR (95% CI)	Association (Xassoc)	Heterogeneity (X^2w)

Ever-use of HRT and breast cancer risk: Overall weighted RR for all study designs was 1.06 (95% CI, 1.00-1.12), indicating that ever-use of HRT has a small but statistically significant effect on risk of

Overall				
All designs		27	1.06 (1.00-1.12)	2.02*
87.93† Case-control		19	1.01 (0.95-1.08)	0.30
45.61† Cohort		8	1.16 (1.05-1.28)	
2.94‡	37.75†			
Natural menopause				
All designs		20	1.13 (1.04-1.22)	3.00‡
59.99† Case-control		12	1.04 (0.95-1.14)	0.84
20.04* Cohort		8	1.44 (1.23-1.69)	4.48†
28.06†				
Surgical menopause				
All designs		21	1.04 (0.93-1.16)	0.70
15.90				
Case-control		15	1.01 (0.89-1.14)	0.16
13.24				
Cohort		6	1.17 (0.90-1.52)	1.20

RR = relative risk; CI = confidence interval.
There were no statistically significant differences between weighted RRs from case-control and cohort designs after applying Schlesselman's X^2
*P<.05.
†P<.01.
‡P<.001.

breast cancer. RR was higher overall in cohort studies, giving a 16% increase in risk of breast cancer (RR=1.16 [95% CI, 1.05-1.28]). When results were stratified by type of menopause, higher RR estimates were found for natural menopause (RR=1.13 [95% CI, 1.04-1.22]), especially when cohort studies were combined (RR=1.44 [95% CI, 1.23-1.69]). Heterogeneity was highly significant in all these RR estimates. No significant RRs were found for surgical menopause.

Ever-use of HRT and breast cancer risk by duration of use: Dose-response association not found when studies were pooled. However, there was an association between ever-use of HRT in women with natural menopause; long-term users (longer than 12 years) showed a significant 63% increase in breast cancer risk (RR=1.63 [95% CI, 1.26-2.12]). Same relationship seen in women with surgical menopause, although with no linear trend.

Breast cancer risk by time since HRT first used/last used: No trends shown, except for a decreasing but nonsignificant trend when analysing time since last use in women who underwent surgical menopause. Current HRT in women with natural menopause increased breast cancer risk (RR=1.63 [95% CI, 1.26-2.10]), with heterogeneity of RRs highly significant (P<0.001). However, neither RR nor heterogeneity was significant in current users who experienced surgical menopause.

Ever-use of HRT and breast cancer risk by type/dose of hormone: Overall weighted RR obtained from 3 studies which reported data on combination of estrogen plus progestin was 0.99 (95% CI, 0.72-1.36). In 8 studies which provided results on risk of breast cancer in users of conjugated estrogens, an 8% increase in risk of breast cancer was observed (RR=1.08 [95% CI, 1.00-1.16]). Results on estrogen dose were combined where the dose was
0.625mg or less. Combined results on ever-use (4 studies) gave a non-significant RR of 1.05 (95% CI 0.88-1.26).

Authors' conclusions: Current and recent use of HRT in menopausal women increases breast cancer risk, with a stronger effect in women with natural menopause and those who received conjugated estrogens. Breast cancer risk is also increased in long-term HRT users, including women who underwent bilateral oophorectomy. Estrogen doses of 0.625mg/day or less appear safe.

Further information: Details of search strategy not provided.

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Colditz et al (1993)[3]	1. To evaluate the role of current compared with past use of hormone replacement therapy (HRT) and breast cancer risk 2. To examine the relation of estrogen plus progestin compared with estrogen therapy alone and breast cancer risk 3. To examine the relation between duration of HRT and breast cancer risk	Meta-analysis MEDLINE To July 1991 DerSimonian and Laird random effects model; fixed effects model; estimate of variance; weighted linear regression	**Excluded:** studies which did not report number of cases or size of comparison group. Inclusion/exclusion criteria not further specified.	31 case-control and cohort studies HRT; estrogen plus <1 year->20 years	Total numbers of case/controls not reported; numbers recruited into individual studies not reported. No information on characteristics of combined sample reported	Risk of breast cancer by ever- use, current/recent use, duration and dosage of HRT. Risk of breast cancer by subgroup (including family history of breast cancer and menopausal status) of HRT.

Results

Meta-analysis of hormone replacement therapy and breast cancer: Summary of results

	Inverse-variance weighted average		DerSimonian and Laird random effects model 1	
	Relative risk meta	95% Confidence interval	Relative risk meta	95% Confidence interval
Ever users				
All studies	1.04	0.99-1.10	1.02	0.93-1.12
Case-control	1.02	0.96-1.08	1.00	0.91-1.10
Population	1.01	0.91-1.13	1.01	0.89-1.11
Hospital	1.02	0.92-1.13	0.93	0.77-1.14
Nested	1.00	0.90-1.12	0.99	0.81-1.21
Other	1.12	0.87-1.46	1.20	0.78-1.85
Follow-up	1.12	1.01-1.24	1.12	0.87-1.45
Duration of use				
≥ 10 yr	1.23	1.08-1.40	1.23	1.08-1.40
≥ 15 yr	1.29	1.04-1.60	1.29	1.04-1.60
≥ 20 yr	1.51	0.98-2.34	1.51	0.98-2.34
Time since first use				
≥ 10 yr	1.13	1.01-1.25	1.17	0.99-1.39
≥ 15 yr	1.05	0.91-1.22	1.09	0.91-1.32
≥ 20 yr	1.05	0.83-1.33	1.16	0.71-1.89
Dose				
1-49 mg mo	1.05	0.85-1.29	1.05	0.85-1.29
> 49 mg mo	1.02	0.82-1.25	1.11	0.75-1.65
< 1.25 mg	0.99	0.76-1.30	1.05	0.75-1.47
> 1.24 mg	1.05	0.82-1.34	0.94	0.57-1.57
Preparation				
Conjugated estrogens	1.05	0.97-1.14	1.05	0.97-1.14
Estrogen-progestogen	1.23	0.95-1.60	1.13	0.78-1.64
Diethylstilbestrol	1.20	0.88-1.64	1.28	0.77-2.14

Ever-use of HRT and breast cancer risk: There was no association between ever-use of HRT and increased risk of breast cancer (RR=1.02, 95% CI 0.93-1.12). This finding was unchanged in separate analyses of the 25 case-control and 6 cohort studies.

Current/recent use of HRT and breast cancer risk: ***Combining data from 3 studies, the overall RR is significantly elevated among current users compared with never-users, suggesting a 40% increased risk of breast cancer (RR=1.40, 95% CI 1.20-1.63).***

Duration of HRT and breast cancer risk: ***Combining data from 17 studies, no relation between years of HRT and risk of breast cancer was observed (RR for each year of hormone use was 1.000 in zero- intercept model and 1.010 in varying Y intercepts model). Results unchanged when case-control and cohort studies examined separately. Long-term HRT use: there was a statistically significant 20% (based on 9 studies) to 30% (based on 5 studies) increase in risk with ≥10 and ≥15 years of HRT use, respectively. The RR for ≥20 years of HRT use (based on 2 studies) suggested a 50% nonsignificant increase.***

Time since 1st use of HRT and breast cancer risk: No consistent association ≥10, ≥15 or ≥20 years after 1st use observed (although number of studies providing data was small).

Dosage/type of HRT and breast cancer risk: No association between different doses of HRT and risk of breast cancer observed: RR for women using <1.25mg/day was 1.05 (95% CI, 0.75-1.47) and RR for women using ≥1.25mg/day was 0.94 (95% CI, 0.57-1.57). 9 studies which assessed risk among conjugated estrogen users showed a similar lack of excess risk (RR=1.05, 95% CI, 0.97-1.14). Combined data from 4 studies indicated that ever-use of combination therapy with estrogen and progestin was associated with a RR of 1.13 (95% CI, 0.78-1.64) compared to never-users, similar to results for estrogen alone.

Subgroup analysis - family history of breast cancer: Combined data from 10 studies indicated no difference in RR of breast cancer for ever-use of HRT between women with and without a family history (RR=1.07 [95% CI, 0.73-1.56] vs RR=1.11 [95% CI, 0.94-1.31] respectively).

Subgroup analysis – type of menopause: Combined results (9 studies) of HRT use after natural menopause show little increase in risk (RR=1.19, 95% CI 0.97-1.45). Similar results shown in combined data (7 studies) of HRT use in women with menopause from bilateral oophorectomy (RR=1.18, 95% CI, 0.98-1.42). **Menopausal status:** RR for ever-use of HRT in studies restricted to postmenopausal women was 1.03 (95% CI, 0.94-1.14), and among studies that controlled statistically for menopausal status was 1.06 (95% CI, 0.86-1.30).

Authors' conclusions: Women who have used HRT in the past are not at increased risk of breast cancer, although current use may be associated with increased breast cancer incidence. Long-term use may lead to slight increases in breast cancer risk. Family history of breast cancer does not appear to modify the relation between HRT and breast cancer risk.

Further information: Literature search of MEDLINE database only, with no search strategy reported. No reported quality assessment of papers. References of included studies not supplied (available from authors on request).

Colditz et al (1993)[3]

Author (s)	Research question(s)	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Collaborative Group on Hormonal Factors in Breast Cancer (1997)[4]	To assess the relationship between breast cancer risk and use of hormone replacement therapy (HRT)	Collaborative re- analysis Not reported Not reported Mantel-Haenszel stratification technique; relative risks (RRs)	**Included:** studies which included at least 100 women with invasive breast cancer; which had collected data on use of HRT/reproductive and menopausal factors. **Excluded data (from main analyses):** data relating to premenopausal, perimenopausal women and postmenopausal women with an unknown age at menopause.	51 North American/ European epidemiological studies (prospective; case-control with population controls; case-control with hospital controls) HRT <1 year-≥20 years	**Sample number:** Main analyses on relation between breast cancer risk and use of HRT included 53 865 postmenopausal women (17 949 cases and 35 916 controls). **Median year of birth:** 1925 **Median year of diagnosis (cases):** 1985 **Median age at diagnosis (cases):** 60 years **Ever-use of HRT:** Cases: 30%; controls: 34% **Median age at 1st use:** 48 years **Median age at last use:** 53 years **Mean parity:** 3.1	Risk of breast cancer and ever- use, duration and time since last use of HRT. Risk of breast cancer of HRT by subgroup analysis (including family history of breast cancer).
Results						

Ever-use of HRT and breast cancer risk: For all studies combined there was a significant increase in the RR of breast cancer associated with ever-use of HRT (RR=1.14 [SE 0.03], 2p=0.00001). There was no significant variation in results between the 3 types of study design or between individual studies.

Ever-use of HRT and breast cancer risk by duration of use: Median duration of use in ever-users of HRT was 2 years. Total duration of use was <1 year in 26%, ≥5 years in 34%, and ≥10 years in 15%. RR of breast cancer was significantly associated with increasing duration of HRT use (chi-squared for trend across all categories of duration [1 df] 8.7; P=0.003).

Duration of HRT use and time since last use: For women whose last HRT use was <5 years before diagnosis, there was strong evidence of a trend of increasing RR of breast cancer with increasing duration of use: the risk increased by a factor of 1.023 (SE 0.060) for each year of use (2p=0.0002). However, for women who stopped HRT use ≥5 years before diagnosis, there was no significant overall increase in RR of breast cancer (1.07 [SE 0.05]).

Subgroup analysis: similar patterns of risk were observed for most subgroups (eg family history of breast cancer, ethnic group, education). However, weight and body-mass index showed a significant association among current or recent users who had a duration of use of HRT of 5 years or longer (chi-squared for heterogeneity [1 df] 12.8, P=0.0004 for weight categories; 10.2, P=0.001 for body-mass index categories).

Authors' conclusions: For current or recent users of HRT the RR of breast cancer increases in relation to increasing duration of use; however, for past users (use of HRT stopped 5 or more years ago) there is no significant increase in RR of breast cancer, either overall or in relation to duration of use.

Further information: Databases not used to search for studies; studies identified by consultation with collaboration members only. Systematic quality assessment of studies not undertaken; consistency checks only made.

Author (s)	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants	Outcome(s)
Bush et al (2001)[6]	1. What is the risk of being diagnosed with breast cancer among postmenopausal women who ever received any form of estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) compared with never-users? 2. What is the risk of death from disease among patients with breast cancer who have used ERT/HRT compared with never-users?	Systematic review MEDLINE, Dialogweb 1975-2000 Qualitative review	**Included:** studies which evaluated ERT/HRT and breast cancer risk and mortality rates; which contained original data; which were published in peer-reviewed journals **Excluded:** if there were multiple publications from one study population, risk estimate from most recent publication only was used.	55 case-control/cohort studies ERT or HRT **Follow up range:** 6 months-20 years	Total sample number for all studies not provided. Numbers of cases/controls provided for each study separately. Further information on characteristics of participants not reported.	Breast cancer incidence Mortality from breast cancer Breast cancer survival
Results						

ERT and breast cancer risk (45 studies): Studies show lack of consistency in findings and only small increases/decreases in risk of breast cancer for estrogen users: 20% of studies reported risk estimates <0.9; 33% reported risk estimates >1.1; and 47% reported risk estimates between 0.9-1.1. None reported risk estimates >2.0.

HRT and breast cancer risk (20 studies): Studies show lack of consistency in findings. Only 4 studies reported statistically significant findings: 2 showed a significantly higher risk of breast cancer with HRT use, and 2 found a significantly protective effect of HRT on breast cancer risk. One small study of HRT use found no increase in breast cancer among women taking combined therapy for up to 22 years.

HRT and breast cancer risk/death from breast cancer (5 studies): Studies show lack of consistency regarding risk of breast cancer with hormone therapy. However, consistency regarding hormone use and mortality rates from breast cancer: risk estimates for death from breast cancer in hormone users compared with nonusers are <1.0 in all 5 studies, with several showing statistical significance.

HRT and breast cancer risk/breast cancer survival (6 studies): Studies show lack of consistency regarding risk of breast cancer with hormone therapy. However, consistency regarding hormone use and breast cancer survival: risk estimates for breast cancer survival in hormone users vs nonusers are <1.0; 2 estimates are statistically significant.

Breast cancer risk by duration of hormone use (8 studies): Lack of consistency in results: women using hormone therapy for the longest durations (>5 years->20 years) compared with nonusers had: 1. a significantly elevated risk of breast cancer in 3 studies (in one for ERT, one for any hormone therapy, and one for HRT); 2. a non-significantly elevated risk of breast cancer in 5 studies (3 for any hormone therapy, one for HRT, and one for ERT);
and 3. no increase in risk in 2 studies for any hormone therapy.

Authors' conclusions: Evidence relating to the association between estrogen and breast cancer is inconsistent, and the distribution of risk estimates is what would be expected if there were no association (ie most of the estimates of risk are about 1.0, and the range of estimates is limited). The authors conclude that the evidence does not support an association between ERT or HRT use and breast cancer. However, there is consistent evidence that suggests that estrogen users are less likely to die from breast cancer than nonusers.

Further information: Included studies were not assessed for quality and reliability. The authors report that there may be a possibility of confounding in some studies, eg oophorectomy status, menopausal status, ethnicity, socio-economic factors.

Author (s)	Study Design	Objectives	Setting and location	Number of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Survey methods	Main outcome measures

Sellers et al (1997)[7]	The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer Follow-up survey (part of the Iowa Women's Health Study)	To determine whether HRT is associated with increased risks for breast cancer and total mortality in women with a family history of breast cancer	Iowa, US	35 919	**Included:** all women between 55-69 year who had valid Iowa driver's licence in 1985. **Excluded:** women who were premenopausal; had had total or partial mastectomy; had history of any cancer other than skin cancer; had unknown family history of breast cancer.	**Age at menarche (%):** <12 yrs: 15.4; 12-13 yrs: 56.2; >13 yrs: 27.4 **Age at menopause (%):** <45 yrs: 23.4; 45-49 yrs: 25.4; >49 yrs: 47.9 **Type of menopause (%):** natural: 64.9; hysterectomy: 30.9; other: 1.8 **Age at 1st live birth (%):** <30 yrs: 84.7; ≥30yrs: 5.7; nulliparous: 8.6 **Waist-to-hip ratio (%):** <0.78: 24.9; 0.78-0.82: 24.9; 0.83-0.89: 24.9; >0.89: 24.9 **Body mass index (%):** <23.46 kg/m^2: 25.0; 23.46-26.11 kg/m^2: 25.0; 26.12-29.68 kg/m^2: 24.9; >29.68 kg/m^2: 25.0 **Education (%):** less than high school: 19.0; high school graduate: 41.7; some post-high school: 26.6; college graduate or more: 12.4 **Alcohol use (%):** 0 g/d: 56.3; <5 g/d: 25.0; ≥5 g/d: 18.7	Data collection: 4 mailed questionnaires; State Health Registry of Iowa; National Death Index **Sampling:** random sample of approx. 94% of female Iowa residents in required age group. 41837 women returned 1st questionnaire (42.7% response rate). Only minor demographic differences seen at baseline between respondents and non-respondents. **Analysis:** Age-adjusted RRs; proportional hazards regression for multivariate- adjusted RRs	Risk of postmenopausal breast cancer Cause-specific mortality Total mortality
Results								

Risk factors and incidence of breast cancer: After 8 years follow-up, there were 1085 cases of postmenopausal breast cancer. Early age at menarche, late age at 1st birth, high waist-to-hip ratio, high body mass index, education, and alcohol intake were associated with increased risk of breast cancer; high body mass index at age 18 years was associated with decreased risk (subsequent analyses adjusted for these factors).

HRT and incidence of breast cancer by family history: A family history of breast cancer in mothers or sisters was reported by 12.2% of women. Approx. 38% reported having ever used HRT. Frequency of reported use did not differ by family history: 38.3% of women without a family history vs 37.7% with a family history (P>0.2). Duration of HRT use was similar (P>0.2).

Association of Use of Hormone Replacement Therapy with Risk for Postmenopausal Breast Cancer by Family History of Breast Cancer

Use of Hormone Replacement Therapy	No Family History of Breast Cancer			Family History of Breast Cancer		
	Cases	Age-Adjusted Incidence Rate per 10 000 Person-Years (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*	Cases	Age-Adjusted Incidence Rate per 10 000 Person-Years (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
	n			*n*		
Never	528	36 (32-39)	1.00 (reference)	97	46 (36-55)	1.00 (reference)
Former (duration ≤ 5 years)	202	37 (31-42)	1.01 (0.85-1.20)	45	54 (38-70)	1.19 (0.81-1.73)
Former (duration > 5 years)	27	29 (17-40)	0.80 (0.53-1.19)	8	51 (14-87)	1.17 (0.55-2.47)
Current (duration ≤ 5 years)	41	46 (31-61)	1.31 (0.94-1.83)	7	70 (17-122)	1.37 (0.59-3.18)
Current (duration > 5 years)	67	41 (31-51)	1.13 (0.86-1.50)	13	61 (28-94)	1.35 (0.72-2.53)

* Adjusted for age, age at menarche, age at menopause, type of menopause, age at first live birth, waist-to-hip ratio, body mass index, body mass index at 18 years of age, education level, and alcohol use.

Rate of breast cancer among women without a family history of breast cancer who were currently receiving HRT and had been for at least 5 years was 41 cases per 10 000 person-years, a rate not significantly greater than the 36 per
10 000 person-years in women who had never received HRT. Multivariate adjustment for other risk factors did not change these results. Rate of breast cancer among women with a family history of breast cancer who were current long-term users of HRT were 61 per 10 000 person-years compared with 46 per 10 000 person-years in women who had never received HRT. RRs were higher in women who currently received HRT than in those who formerly received HRT, but none of the RRs were statistically significant. Results of a formal test for association between family history and HRT use were not statistically significant (P>0.2).

HRT and total mortality: A total of 2035 deaths were documented during the study. Among women with no family history of breast cancer, age-adjusted mortality rates ranged from 70 per 10 000 person-years for women who had never received HRT to 51 per 10 000 person-years for women who were currently receiving HRT and had been for at least 5 years. This apparent protective effect of HRT was also evident in women with a family history of breast cancer. Multivariate-adjusted RRs for death were 0.84 (95% CI, 0.67-1.06) in women without a family history of breast cancer and 0.55 (95% CI, 0.28-1.07) in women with a family history.

HRT and cause-specific mortality in women with a family history of breast cancer: Use of HRT among women with a family history of breast cancer was associated with decreased rates of death from coronary heart disease, stroke, all cancers combined and all other causes of death combined. Although not statistically significant, results suggested that women with a family history of breast cancer who used HRT had an increased rate of death from breast cancer (RR 1.9 [95% CI, 0.6-5.7]).

Authors' conclusions: Study data suggests that HRT use in women with a family history of breast cancer is not associated with a significantly increased incidence of breast cancer but is associated with a significantly reduced total mortality rate.

(Sellers et al (1997))[7]

Table 7.3: Hormonal contraceptives

OC use and risk of breast cancer: summary of study findings

Study	Databases searched Coverage	Included studies Quality assessment	Heterogeneity	Age ranges/ menopausal status	Outcome(s)	Main results
Romieu et al (1990) Meta-analysis	MEDLINE 1966-1989	27 case-control and 5 cohort studies No quality assessment	Random effects model used to adjust for between study variance	Various age ranges according to individual studies. Some analyses by pre/postmenopausal status.	Breast cancer (BC) risk by OC ever-use, duration of use, time since 1st use, duration of use before 1st full-term pregnancy. BC risk by OC use in women with a family history (FH) of BC.	No increase in risk with ever-use or long duration of use. 46% increase in risk of premenopausal BC with long duration of OC use (P=0.001), esp. in women using OCs before 1st full-term pregnancy (RR=1.72; 95% CI, 1.36-2.19). No increased risk in women with a FH of BC.
Delgado-Rodriguez et al (1991) Meta-analysis	MEDLINE 1966-1990	26 case-control and 6 cohort studies Quality assessment of studies using published guidelines	Woolf's chi-squared used to test for heterogeneity among studies	Various age ranges according to individual studies. Some analyses by pre/postmenopausal status.	BC risk by OC ever-use, duration of use, ever-use according to age at diagnosis, use before age 25, use before 1st full-term pregnancy. OC use according to parity and FH of BC	Increased risk with ever-use for premenopausal women (RR=1.14; 95% CI, 1.05-1.24). Also increased risk in women who used OCs before 1st full-term pregnancy (RR=1.17, 95% CI, 1.06-1.30). No increased risk in women with FH of BC.
Rushton et al (1992) Meta-analysis	Databases not specified 1980-1989	21 case-control and 6 cohort studies No quality assessment	Substantial heterogeneity of studies discussed	Analyses by 8 categories of age from <25-55 yrs, and by <45 and ≥45 yrs.	BC risk by OC use, age at diagnosis, parity and total duration of use	BC risk increased by 16% in women <45 , greatest in 30-34 age group. No increase in older women. Steady increase in risk with duration of OC use: 27% increase for >8 yrs' use.

Hawley et al (1995 Meta-analysis	MEDLINE 1966-1990	38 case-control studies. Quality assessment and quality scored, all studies included. Analysis by higher/ lower scoring	Test for homogeneity of RR estimates carried out	Various age ranges according to individual studies	BC risk by OC ever-use, duration of use, use before 1st full-term pregnancy	Ever-use: no statistically significant increase in BC risk (RR=1.08; 95% CI, 0.55-1.61). Also no association with long-term use (P=0.386). OC use before 1st full-term pregnancy significantly associated with increased BC risk (P<0.001).

Study	Databases searched Coverage	Included studies Quality assessment	Heterogeneity	Age ranges/ menopausal status	Outcome(s)	Main results
Schlesselman (1995) Meta-analysis	MEDLINE 1980-1994	79 epidemiological studies, 25 of which relating to BC risk.	Heterogeneity between studies not discussed	Women aged ≥45 yrs and less than 60 yrs	Risk of BC by duration/recency of OC use (also risk of cervical, endometrial, ovarian and liver cancer)	Duration of OC use: no statistically significant association with increased BC risk in this age group of women
Collaborative Group on Hormonal Factors in Breast Cancer (1996) Re-analysis	Databases not specified Included studies date between 1976-1992	54 case-control and cohort studies No systematic quality assessment	Heterogeneity assessed using chi-squared tests	Various ages according to individual studies	BC risk by OC ever-use, duration of use, age at 1st use, time since 1st/last use. Subgroup analysis including women with FH of BC.	Statistically significant increase in risk in current users (RR=1.24 [SD 0.04], 2p<0.00001) and in 10 yrs after use stops. No significant increase in risk 10 or more yrs after stopping, or in women with FH of BC.
Van Hoften et al (2000) **Case-control study**	Not applicable	Not applicable	Not applicable	Women aged ≤55 yrs and >55 yrs	BC risk by OC ever-use and duration of use	No statistically significant increase in risk with ever-use of OCs for combined/separate groups. No increase in risk for duration of use of 1-10 yrs, but doubling of risk in women >55 yrs for >10 yrs use (OR=2.05; 95% CI, 1.07-3.95). No increase in younger age group.

Marchbanks et al (2002) Case-control study	Not applicable	Not applicable	Not applicable	Women aged 35-64 yrs	BC risk by OC current/former use, duration of use, age at 1st use, time since last use, type/dose. Subgroup analysis, including women with FH of BC.	No statistically significant increases in risk for ever-use, current/former use, duration of use, age at 1st use, interval since last use, estrogen dose. No association between OC use and BC risk in women with FH of BC.
Narod et al (2002) Case-control study	Not applicable	Not applicable	Not applicable	Women aged 46-47 BRCA1 or BRCA2 mutation carriers only	BC risk by OC ever use, duration of use, use before age 30, age at BC diagnosis, year of 1st use.	BC risk increased in BRCA1 mutation carriers (OR=1.20; 95% CI, 1.02-1.40), but not in BRCA2 mutation carriers. BRCA1 mutation carriers only: 29% increased BC risk in women with ever use <30 years; 38% increased risk with ever use where BC diagnosed at <40 years; 42% increased risk with 1st use before 1975.

Author(s) Study	Research question(s)	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants: Total sample number	Outcome(s)
Romieu et al[1] (1990) Oral contraceptives and breast cancer: review and meta-analysis	To evaluate the relation between use of oral contraceptives (OCs) and the incidence of breast cancer	Meta-analysis MEDLINE 1966-1989 Der-Simonian and Laird random effects method; weighted least-squares regression model.	All epidemiological studies evaluating the association between OC use and breast cancer, published in English and French.	27 case-control studies; 5 cohort studies Oral contraceptives <1 year-≥15 years	Total sample number for all studies not provided. Numbers of cases/controls provided for each study separately. Age range reported for each study separately Ethnicity not reported	Breast cancer risk by ever-use, duration of use, time since first use of OC, and duration of OC use before 1st full-term pregnancy. Breast cancer risk of OC use in women with a family history of breast cancer.
Results						

Case-control studies (x27)

Ever-use: There was no association between breast risk and OC use when findings from 24 of the studies were pooled, although a significant association found with the remaining 3 studies. Relative risk (RR) estimates ranged from 0.7-2.0. Overall RR for all studies was 1.06 (95% CI, 0.98-1.14).

Duration of use: RR of breast cancer for ≥10 years of OC use was 1.14 (95% CI, 0.90-1.42). Post-1980 studies (change in OC composition): RR increased to 1.22 (95% CI, 0.91-1.63) for ≥10 years of use. No trend observed in breast cancer risk with increasing duration of OC use. However, when data were limited to premenopausal women, there was a statistically significant 46% increase in risk for 10 years of OC use (P=0.001). Pooled data available on ≥4 years of OC use before 1st full-term pregnancy in women aged <46 years (8 studies), showed an RR for breast cancer of 1.72 (95% CI, 1.36-2.19). Similar estimates shown in post-1980 studies (change in OC composition).

Family history of breast cancer and OC use (4 studies): Ever-use: no association observed compared with women with a family history who had not used OCs (RR=1.14 vs RR=1.44, respectively).

Cohort studies (x5)

Ever-use: Pooled RR for any use of OC did not show an adverse effect on breast cancer risk (RR=1.06; 95% CI, 0.92-1.22).

Duration of use: No increase in risk observed in studies with long duration of OC use.

Authors' conclusions: There is no increase in breast cancer risk for women who ever used OCs, even after long duration of use (results consistent across study designs). However, there was an increased risk of premenopausal breast cancer in women with long duration of OC use, especially in women who used OCs before their 1st full-term pregnancy. OC use did not increase breast cancer risk in women with a family history of breast cancer.

Further information: MEDLINE only searched, with no search strategy provided. Included studies were not quality-assessed.

Author(s) Study	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-	Characteristics of participants: Total sample number	Outcome(s)
Delgado-Rodriguez[2] et al (1991) Oral contraceptives and breast cancer. A meta- analysis	To evaluate the relationship between oral contraceptive (OC) use and breast cancer risk.	Meta-analysis MEDLINE Jan 1966-June 1990 Miettinen's method; Greenland; Woolf's X^2; weighted least-squares regression model; Rosenthal's method	**Included:** Primary data presented; OC assessed as exposure; outcome was breast cancer (any type of malign histological tumour); based on morbidity data; English, French, Spanish, Italian, German or Portuguese languages; RRs could be derived. **Excluded:** Unpublished studies	26 case-control studies; 6 cohort studies Oral contraceptives <12 months->96 months	Total sample size or sample sizes for individual studies not provided. Age range: <37-≥56 years Details of ethnicity not provided.	Breast cancer risk and: ever-use and duration of use of OC; ever-use according to age at diagnosis; OC use before age 25; OC use before 1st full-term pregnancy; OC use according to parity and family history of breast cancer.
Results						

Ever-use of OC: RR for all study designs was statistically significant at 1.06 (95% CI, 1.02-1.10). By type of design, ever-use was significant in case-control studies (RR=1.07; 95% CI, 1.03-1.12), but not in cohort studies (RR=1.03; 95% CI, 0.95-1.12). In studies with data on premenopausal women, RR observed was higher (RR=1.14; 95% CI, 1.05-1.24) than for all studies pooled, whereas there were no statistically significant RRs for data on postmenopausal women.

Duration of use of OC: Long-term (>96 months) use was associated with an increase in breast cancer risk in premenopausal women, but there was significant heterogeneity between studies. Studies on postmenopausal women showed a nonsignificant association between long-term OC and breast cancer risk (RR=1.22; 95% CI, 0.55-2.71).

Ever-use of OC and age at diagnosis: OC use increased breast cancer risk in women with cancer diagnosed before age 45 (usually premenopausal), with RR=1.15 (95% CI, 1.08-1.23). The RR in OC users (all durations combined) before age 25 was 1.26 (95% CI, 1.10-1.44).

OC use before 1st full-term pregnancy: Women who used OC before their 1st full-term pregnancy showed a significant 17% increase of premenopausal breast cancer (RR=1.17; 95% CI, 1.06-1.30).

OC use and parity: No significant association was found.

OC use in women with a family history of breast cancer: No significant association was found (the authors do not provide data on this variable).

Authors' conclusions: There is an increased risk of premenopausal breast cancer in early OC users. There is no evidence that family history of breast cancer is associated with OC use and breast cancer.

Further information: Only MEDLINE database searched for publications, with no search strategy provided.

Author(s) Study	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-	Characteristics of participants: Total sample number	Outcome(s)
Rushton et al[3] (1992) Oral contraceptive use and breast cancer risk: a meta-analysis of variations with age at diagnosis, parity and total duration of oral contraceptive use	To evaluate the relationship between risk of breast cancer and oral contraceptive (OC) use	Meta-analysis Databases searched not reported 1980-1989 Meta-regression (Greenland); normal least- squares model	**Included:** published studies	21 case-control studies; 6 cohort studies Oral contraceptives Follow-up periods reported for individual studies	Total sample number for all studies not provided. Numbers of cases/controls provided for each study separately. Age ranges not reported Limited data on ethnicity reported for individual studies only	Breast cancer risk by OC use; variations by age at diagnosis, parity and total duration of use

Results

OC use and age at diagnosis: Breast cancer risk increased significantly by 16% in women <45 years (RR=1.16; 95% CI, 1.07-1.25); there was a small non-significant increase in risk for women ≥45 years (RR=1.03; 95% CI, 0.94-1.13). Risk was greatest in the 30-34 years age group, the RR being 1.25 (95% CI, 1.04-1.50).

OC use and parity: There was no significant association between OC use and breast cancer risk in parous women (RR=1.03; 95% CI, 0.95-1.13), although risk almost reached significance in nulliparous women (RR=1.21;
95% CI, 0.99-1.47).

Duration of OC use: There was a steady increase in RR from 1.04 (95% CI, 0.94-1.16) for durations of <2 years to 1.27 (95% CI, 1.12-1.44) for >8 years of OC use.

Authors' conclusions: Risk of breast cancer from OC use may be increased by about 20% in younger, nulliparous women and in long use duration subgroups. The authors note that a substantial proportion of heterogeneity between studies remained unexplained.

Further information: Details of databases searched and search strategies used not reported. Quality assessment of included studies not carried out.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of** **participants: Total sample number** **Age** **(mean/SD/range)**	**Outcome(s)**
Hawley et al[4] (1993) Do oral contraceptive agents affect the risk of breast cancer? A meta- analysis of the case- control reports	To assess the association between oral contraceptive use and the development of breast cancer	Meta-analysis MEDLINE 1966-1990 Woolf's method for pooling RRs; weighted least-squares regression; Spearman's rank correlation coefficient	**Included:** published and unpublished case-control studies; English language **Excluded:** case series, anecdotes, nonexperimental studies, cohort studies, interim case-control studies with data included in later report	38 case-control studies Oral contraceptives Follow-up periods reported studies	Total sample number for all studies not provided. Numbers of subjects ranged from 51-4,714 cases and from 95-13,072 controls. Age range reported for each study separately Ethnicity not reported	Risk of breast cancer and ever-use of OC; duration of OC use; and OC use before 1st full-term pregnancy
Results						

Ever-use of OCs: There was no statistically significant association with risk of breast cancer, with a RR of 1.08 (95% CI, 0.55-1.61) for all studies pooled (n=37). Also no association observed when 'higher quality' studies
(n=11) were combined (RR=1.07; 95% CI, 0.78-1.36).

Duration of OC use (up to 14 years): There was no statistically significant association with risk of breast cancer: r_S (Spearman's) =+0.036 (P=0.386) for all studies (n=34); r_S =-0.153 (P=0.189) for 'higher quality' studies
(n=9).

OC use before 1st full-term pregnancy: A significant association was observed with breast cancer risk: r_S=+0.434 (P<0.001) for all studies (N=28) and +0.497 (P=0.011) for 'higher quality' studies (n=9).

Authors' conclusions: The data suggest that women who have ever used OCs, or who have used them for long durations, have no increased risk for breast cancer. There is however an association between OC use before a 1st
full-term pregnancy and an increased breast cancer risk. The authors state, however, that the data were confounded by low quality studies and should be treated with caution.

Further information: All eligible studies were quality-assessed and given a score (maximum of 33), with all studies included in the analysis, regardless of quality score. Studies which scored >14 were considered to be of higher quality. The authors note that there was statistical homogeneity between studies for all categories analysed, although they discuss the potential for bias due to poor study design.

Author(s) Study	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants: Total sample number Age (mean/SD/range)	Outcome(s)
Schlesselman[5] (1995) Net effect of oral contraceptive use on the risk of cancer in women in the United States	To estimate the net effect of oral contraceptive (OC) use on risk of cancer in women aged 20-54 in the United States	Meta-analysis MEDLINE 1980-August 1994 Weighted regression of log relative risk; standard life-table methods	**Included:** published epidemiological studies; English language	All studies: 79; breast cancer studies: 25 Oral contraceptives Breast cancer studies only: of OC users who developed breast cancer, 2,900+ cases had >4 years' use, and 1,200+ had >8 years' use)	**Breast cancer studies only:** 19,800+ women who developed breast cancer before age 60; cases: 8,000+ women All included women were aged ≥45-<60 years Ethnicity not reported	Risk of cancer (breast, cervical, endometrial, ovarian and liver) and effect of OC use, taking into account all-cause mortality, cancer incidence and duration and recency of OC use. (Only results for risk of breast cancer are reported here.)
Results						
Duration of OC use and breast cancer risk: There was a nonsignificant trend of slightly increasing breast cancer risk with increasing duration of OC use (P=0.35, one-sided). RRs are 1.062, 1.068 and 1.072 for 4, 8 and 12 years of OC use, respectively. **Authors' conclusions:** The findings indicate no adverse effect of OC use on breast cancer risk in women aged ≥45 to <60 years. **Further information:** There was no quality assessment of included studies.						

Author(s) Study	Research question(s)	Review type Databases used Time period covered Data analysis	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants: Total sample number Age (mean/SD/range) Ethnicity	Outcome(s)
Collaborative Group on Hormonal Factors in Breast Cancer[6] (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies	To evaluate the relationship between breast cancer risk and use of hormonal contraceptives	Collaborative re-analysis Specific databases searched not reported Studies listed by dates 1976-1992 Mantel-Haenszel stratification technique; chi-squared tests	**Included:** epidemiological studies including at least 100 women with invasive breast cancer; that obtained information on use of hormonal contraceptives and on reproductive history; published and unpublished studies **Excluded from analysis:** 22 cases and 125 controls who were aged ≤15 years or ≥90 years; 350 cases and 1,096 controls with unknown use of oral contraceptives (OCs)	54 case-control (with hospital and population controls) and cohort studies Hormonal contraceptives <1 year-≥15 years	Cases: 53,297 women with breast cancer; controls: 100,239 women without breast cancer Median age at diagnosis of breast cancer: 49 years (median year of diagnosis was 1984). At time of diagnosis, 9% of women with breast cancer were <35 years; 25% were 35-44 years, 33% were 45-54 and 33% were 55 and older. Ethnicity not reported (further details of included women reported elsewhere)	Breast cancer risk and ever-use of combined OCs, duration of OC use, age at 1st OC use, time since first OC use, and time since last OC use Subgroup analysis of breast cancer risk and use of OC, including women with a family history of breast cancer
Results						

Ever-use of combined OCs: RR of breast cancer in women who had ever used OCs compared with women who had never used them was slightly above 1.0, and the excess was statistically significant (RR=1.07 [SD 0.02],
2p=0.00005). There was some heterogeneity in results between individual studies and between types of study design.

Duration of OC use: A quarter of ever-users used OCs for <1 year, with median total duration of use 3 years. The RR was slightly above 1.0 for each of the 5 broad categories of use (<1 year, 1-4 years, 5-9 years, 10-14 years and ≥15 years). There was no significant heterogeneity of RR of breast cancer between categories of duration of use, but there was a weak indication of a trend of increasing risk with increasing duration (P=0.05).

Age at 1st OC use: Median age at starting use of OCs was 26 years. The RR was slightly greater than 1.0 for each of the 5 age groups (≤20, 20-24, 25-29, 30-34, and ≥35 years) and was largest for women who started use as teenagers. There was some heterogeneity in RRs between the 5 categories of age at 1st OC use (P=0.01), but no significant trend with increasing age at 1st use.

Time since 1st OC use: Median years since 1st use of OCs was 16 years. The RRs were slightly above 1.0 in each 5-year period of time since 1st use. There was evidence of heterogeneity of risk between the 5 categories
(P=0.01) and of a trend of decreasing risk with increasing time since 1st use (P=0.002).

Time since last OC use: There was evidence of an increased risk of breast cancer being diagnosed in current users (RR=1.24 [SD 0.04], 2p<0.00001) and in women who stopped use 1-4 years previously (RR=1.16 [SD 0.04],
2p=0.00001), with some evidence of an increased risk 5-9 years after stopping (RR=1.07 [SD 0.03], 2p=0.009). For women who stopped use ≥10 years ago, the RR did not differ significantly from 1.0. There was substantial heterogeneity in RRs between the 5 categories of time since last use (P<0.00001) and a strong trend of decreasing risk with time since last use (P<0.00001).

Women with a family history of breast cancer: RRs according to time since last use of OCs for women with and without a family history of breast cancer were similar and not statistically significant.

Authors' conclusions: In women taking combined OCs and in the 10 years after they stop, there is a small increase in breast cancer risk, although this increased risk does not persist and there is no evidence of an increased breast cancer risk ≥10 years after stopping OC use.

Further information: No detail regarding databases searched, with no search strategy provided. Included studies did not undergo systematic quality assessment.

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis

Van Hoften et al[7] (2000)	Long-term oral contraceptive use increases breast cancer risk in women over 55 years of age: the DOM cohort [DOM3 cohort] Nested case-control study	**Cases (C1):** Oral contraceptive (OC) use in pre- and postmenopausal women who have developed breast cancer **Controls (C2):** OC use in pre- and postmenopausal women who have not developed breast cancer	Utrecht, The Netherlands	**C1**: 309 **C2**: 610	**Included:** All women born between 1932-1941 living in Utrecht and vicinity invited for breast screening programme between Jan 1982-April 1984. **Excluded:** women with history of breast cancer; who had used drugs for menopausal complaints; who had undergone oophorectomy, hysterectomy, or medical/x-ray treatment of ovaries.	**Mean age (years): C1**: 45.4; **C2**: 45.5 **Ever married (%): C1**: 90.3; **C2**: 95.1 **No. of children (%):** None: **C1**: 14.9; **C2**: 12.6 1-2: **C1**: 48.2; **C2**: 45.2 ≥3: **C1**: 36.9; **C2**: 42.1 **Mean age at 1st delivery (%):** 16-22: **C1**: 14.8; **C2**: 17.4 23-26: **C1**: 45.2; **C2**: 43.0 27-30: **C1**: 28.9; **C2**: 28.7 >30: **C1**: 11.0; **C2**: 10.9 **Premenopausal (%): C1**: 92.9; **C2**: 85.9 **Postmenopausal (%): C1**: 7.1; **C2**: 14.1 **Maternal history of breast cancer (%): C1**: 10.7; **C2**: 3.8	Nov 1982-May 1996	Breast cancer incidence by ever-use of OCs and duration of OC use Logistic regression; odds ratios
Results								

Breast cancer risk according to participant characteristics: Women who were never married, smoked, had <3 children, had an early menarche, were still premenopausal, or reported a history of maternal breast cancer had an increased risk of breast cancer. For year of birth, age at time of questionnaire, education, alcohol consumption, body mass index and age at 1st delivery, no association was observed.

Ever-use of OCs: A total of 192 C1 women (62.1%) and 352 C2 women (57.7%) had ever used OCs. Although women who had ever used OCs had a slightly increased risk of breast cancer, especially those >55 years, this association was not statistically significant, either for total group of women or for the 2 subgroups of age.

Duration of OC use: The mean duration of OC use for C1 women was 7.5 years and 7.2 years for C2 women. A small, nonsignificant increased breast cancer risk for a duration of use between 1-10 years was observed, with no essential difference between age groups. There was, however, a significant doubling in breast cancer risk in women >55 years who had used OCs for >10 years' duration (OR=2.05; 95% CI, 1.07-3.95). No continuous trend of increasing RR observed with duration of OC use for the total group of women (P=0.41), for women aged ≤55 years (P=0.79), or for women >55 years (P=0.18) at the time of breast cancer diagnosis.

Odds Ratios and 95% Confidence Intervals of Breast Cancer in Relation to Various Measures or Oral Contraceptive Use

OC [1] use	Number of case/controls	All women OR[3] (95% CI)	OR[4] (95% CI)	Number of cases/controls	<55 OR (95% CI)	OR[4] (95% CI)	Number of case controls	>55 OR (95% CI)	OR[4] (95% CI)
OC use at any time									
Never	117/258	1.00	1.00	80/258	1.00	1.00	37/258	1.00	1.00
Ever	192/352	1.19 (0.90-1.58)	1.31 (0.96-1.79)	128/352	1.10 (0.79-1.53)	1.24 (0.86-1.78)	64/352	1.35 (0.87-2.11)	1.45 (0.89-2.37)
Total duration of OC use (years)									
0	117/258	1.00	1.00	80/258	1.00	1.00	37/258	1.00	1.00
1-10	141/265	1.16 (0.86-1.57)	1.27 (0.92-1.77)	99/265	1.11 (0.78-1.57)	1.25 (0.85-1.82)	42/265	1.21 (0.74-1.96)	1.26 (0.74-2.14)
>10	51/87	1.29 (0.86-1.95)	1.43 (0.92-2.22)	29/87	1.08 (0.66-1.78)	1.22 (0.72-2.07)	22/87	1.77 (0.97-3.23)	2.05 (1.07-3.95)

[1]Oral contraceptive – [2]Age in years at the time of the diagnosis of breast cancer – [3]Odds ratio adjusted for age at the time of the questionnaire – [4]Odds ratio adjusted for age, menopausal status, marital status, education, cigarette smoking, and number of children at the time of the questionnaire, age at first delivery, age at menarche, and maternal history of breast cancer.

Authors' conclusions: OC use for >10 years is associated with a twofold increased risk of breast cancer in women aged >55 years, but not in younger women.

Van Hoften et al[7] (2000)

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Marchbanks et al[8] (2002)	Oral contraceptives and the risk of breast cancer Case-control study	**Cases (C1):** Oral contraceptive (OC) use in women aged 35-64 years who have developed invasive breast cancer **Controls (C2):** OC use in women aged 35-64 who have not developed invasive breast cancer	Centres in Atlanta, Detroit, Philadelphia, Los Angeles, and Seattle, US	**C1**: 4,575 **C2**: 4,682	**Included (C1):** Women aged 35-64 years; resided in study locations; had invasive breast cancer diagnosed between 1994-1998; identified via registries. Younger women and black women were oversampled. **Included (C2):** Women without a diagnosis of invasive or in situ breast cancer from same locations as cases; identified randomly via telephone; matched to cases according to study site, race, and age	**Age (years, SD): C1**: 49.7±8.4; **C2**: 49.5±8.3 **Age at menarche (years, SD): C1**: 12.4±1.5; **C2**: 12.4±1.6 **Age at menopause (years, SD): C1**: 47.0±6.0; **C2**: 45.2±7.1 **Age at 1st term pregnancy (years, SD): C1**: 23.1±5.3; **C2**: 22.9±5.3 **No. term pregnancies (SD): C1**: 2.1±1.6; **C2**: 2.3±1.7 **Body-mass index: C1**: 25.5±5.6; **C2**: 25.8±5.9 **White race (%): C1**: 64.5; **C2**: 64.5 **Pre-/perimenopausal (%): C1**: 46.3; **C2**: 44.0; **postmenopausal: C1**: 33.7; **C2**: 34.1; **unable to classify: C1**: 20.0; **C2**: 21.9 **Family history of breast cancer (%): C1**: 17.0; **C2**: 9.7 **Current/previous HRT use (%): C1**: 38.0; **C2**: 41.3	Not applicable	Breast cancer risk according to current/former OC use; duration of OC use; age at 1st OC use; time since last OC use; type/dose of OC; subgroups of women (including family history of breast cancer) Conditional logistic regression; odds ratios

Results

Comparison of cases/controls for characteristics: 77% of C1 women and 79% of C2 women had used some type of OC. Significantly different distributions between **C1** and **C2** women were observed for age at menopause (P<0.01), age at 1st term pregnancy (P=0.02), number of term pregnancies (P<0.01), body-mass index (P=0.01), menopausal status (P=0.04), family history of breast cancer (P<0.01) and current/previous use of HRT (P<0.01).

Risk of Breast Cancer According to the Use of Combination Oral Contraceptives

Variable	Case Subjects (N=4575)	Controls (N=4682)	Odds Ratio (95& CI)
No use	1032	980	1.0
Any use	3497	3658	0.9 (0.8-1.0)
Current use	200	172	1.0 (0.8-1.3)
Former use	3289	3481	0.9 (0.8-1.0)‡
Duration of use			
<1 yr	782	822	0.9 (0.8-1.1)
1 to <5yr	1200	1280	0.9 (0.8-1.0)
5 to <10 yr	848	882	0.9 (0.8-1.0)
10 to <15yr	426	466	0.8 (0.7-1.0)‡
>15 yr	234	202	1.0 (0.8-1.3)
Age at first use			
<15 yr	72	79	0.9 (0.6-1.2)
15 to 19yr	1239	1272	1.0 (0.8-1.1)
20 to 24yr	1260	1369	0.9 (0.8-1.0)‡
25 to 29yr	587	592	0.9 (0.8-1.1)
30 to 34yr	209	239	0.8 (0.6-1.0) ‡
35 to 39 yr	84	67	1.2 (0.8-1.6)
>40yr	38	35	1.0 (0.6-1.6)

Variable	Case Subjects (N=4575)	Controls (N=4682)	Odds Ratio (95& CI)
Time since last use			
Current use	200	172	1.0 (0.8-1.3)
7 mo to <5yr	165	207	0.7 (0.5-0.9)
5 to <10yr	244	239	0.9 (0.8-1.2)
10 to <15yr	426	418	0.9 (0.8-1.1)
15 to <20yr	650	717	0.9 (0.7-1.0)
>20yr	1803	1899	0.9 (0.8-1.0)
High estrogen dose			
Any use	1082	1265	0.8 (0.7-0.9)
Current use	7	10	0.7 (0.2-0.9)
Former use	1074	1225	0.8 (0.7-0.9)‡
Low estrogen dose			
Any use	1460	1560	0.9 (0.8-1.0)
Current use	183	160	1.0 (0.8-1.3)
Former use	1267	1398	0.9 (0.8-1.0)

†Current use was defined as use of combination oral contraceptives within six months preceding the reference date.

‡The confidence interval does not include 1.0; some confidence limits were rounded to 1.0.

§A high estrogen dose was defined as 50µg or more of ethinyl estradiol or 75 µg or more of mestranol.

¶A low estrogen dose was defined as less than 50 µg of ethinyl estradiol or less than 75 µg of mestranol.

Ever-use, current/former use, duration of use, age at 1st use, interval since last use; estrogen dose: There was little evidence that OCs increase breast cancer risk in any of these categories. For current OC users, the odds ratio was 1.0 (95% CI, 0.8-1.3) and for previous users was 0.9 (95% CI, 0.8-1.0). Breast cancer risk did not increase with longer durations of use, with higher doses of estrogen, or among women who had begun using OCs at a young age. Former use was associated with a small but significant reduction in RR among the older women. There was a nonsignificant RR of 1.5 among the older women who were currently using low dose estrogen, compared with older women who had never used OCs.

Subgroup analysis: Results for subgroups of women (family history of breast cancer, body-mass index, menopausal status) according to ever-use and current use of OCs were generally similar to the results of the overall analysis. There were also no consistent differences in risk between white and black women. Results, however, did differ significantly according to geographic location.

Authors' conclusions: Current or former OC use is not associated with an increased breast cancer risk in women aged 35-64 years, nor is starting OC use at a young age. Use of OCs in women with a family history of breast cancer is also not associated with an increased risk of breast cancer.

Marchbanks et al[8] (2002)

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Narod et al (2002)[9]	Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers Matched case-control study	**Cases (C1):** Oral contraceptive (OC) use in women with a mutation in the BRCA1 or BRCA2 gene with invasive breast cancer (BC) **Controls (C2):** OC use in women with a mutation in the BRCA1 or BRCA2 gene without invasive breast cancer	52 centres in 11 countries: US, Canada, Israel, Poland, Netherlands, Norway, Italy, UK, Austria, Sweden and France	**C1**: 1,311 **C2**: 1,311	**Included:** women with BRCA1 or BRCA2 mutations **Excluded (all):** women with incomplete OC history, missing information on ovarian cancer/ oophorectomy status/ reproductive history; women born before 1920 **Excluded (C1):** women diagnosed with BC before 1970; diagnosed with ovarian cancer before BC; who had oophorectomy before BC diagnosis	**Age (mean ± SD): C1**: 47.3 (±10.0); **C2**: 46.2 (±10.3) **Ovarian cancer (%): C1**: 10.7; **C2**: 10.7 **BRCA1 mutation (%): C1**: 74.8; **C2**: 74.8. **BRCA2 mutation (%): C1**: 25.2; **C2**: 25.2 **Country of residence (%): C1** and **C2** (equal percentages): US 45.8; Canada 22.8; Israel 7.7; Poland 6.7; Netherlands 6.1; Norway 4.5; Italy 2.8; UK 1.1; Austria 1.1; Sweden 1.1; France 0.3 **Ethnicity (%): C1**: Black 2.1; French Canadian 7.6; Jewish 31.6; Other non-whites 0.8; Other whites 57.4; missing 0.4. **C2**: Black 1.1; French Canadian 7.4; Jewish 29.8; Other non-whites 0.5; Other whites 61.1; missing 0.1	Data collected between 1977-2001	Risk of breast cancer associated with OC use Student's *t* test; conditional logistic regression
Results								
OC use: OCs had been used by 69.7% of **C1** women and by 68.0% of **C2** women. The mean duration of OC use was 5.3 years in **C1** women and 5.0 years in **C2** women (P=0.27).								

Breast cancer risk and OC use: The odds ratio (OR) for ever users of OCs, adjusting for parity and ethnicity, was 1.20 (95% CI, 1.02-1.40) for BRCA1 mutation carriers and 0.94 (95% CI, 0.72-1.24) for BRCA2 mutation carriers, compared to never users.

BRCA1 mutation carriers only:

Breast cancer risk and duration of OC use: For each additional year of OC use, the OR increased by a factor of 1.02 (95% CI, 1.00-1.03; P=0.02) relative to never users. For those who used OCs for 5 or more years, the adjusted OR was 1.33 (95% CI, 1.11-1.60; P=0.002), compared to never users.

Breast cancer risk and ever use of OCs before age 30: The OR was 1.29 (95% CI, 1.09-1.52), compared to never users. For each additional year of OC use before age 30, the OR increased by 3% (OR=1.03; 95% CI, 1.01-1.05), compared to never users.

Breast cancer risk and ever use of OCs according to age at breast cancer diagnosis: The OR was 1.38 (95% CI, 1.11-1.72) for women diagnosed with BC before age 40, compared to never users.

Breast cancer risk according to year of 1st OC use: More **C1** women (38.8%) compared to **C2** women (33.6%) reported 1st OC use before 1975 (OR=1.42; 95% CI, 1.17-1.75; P<0.001).

Authors' conclusions: Results suggest that OC use is not associated with increased BC risk in BRCA2 mutation carriers, although the authors note that data on these women were limited. Among BRCA1 mutation carriers, those who reported 5 or more years of OC use, reported OC use before age 30, or who first used OCs before 1975, appeared to have an increased risk of early-onset breast cancer.

Table 7.4: Breastfeeding

Author(s) Study	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**
Bernier et al (2000) Breastfeeding and risk of breast cancer: a meta-analysis of published studies	To evaluate the relation between breastfeeding and breast cancer	Meta-analysis MEDLINE; Excerpta Medica (EMBASE) 1980-1998 Fixed effect model (Greenland); random effect model (DerSimonian and Laird); Cochran's Q statistic	**Included:** case-control and cohort studies published between 1980-1998; presented primary data; English or French language **Excluded:** studies with no separate data on parous and nulliparous women	23 case-control studies	Number of cases/controls reported for individual studies Ages/age ranges reported for individual studies. Ethnicity not reported, although study site listed by individual study.	Breast cancer risk in ever versus never breastfeeding women Breast cancer risk according to menopausal status at time of diagnosis in ever versus never breastfeeding mothers Breast cancer risk according to breastfeeding duration
Result						

Breast cancer risk in ever versus never breastfeeding women: Combined OR was 0.90 (95% CI, 0.86-0.94) using fixed effect model, and 0.84 (95% CI, 0.78-0.91) using random effect model. Results suggest a slight but significant protective effect of ever- versus never-breastfeeding for breast cancer. Excluding 5 studies which were potential sources for heterogeneity, analyses found similar ORs.

Breast cancer risk according to menopausal status at time of diagnosis in ever versus never breastfeeding mothers: A significant decrease in the combined OR of breast cancer for women who were non-menopausal at the time of diagnosis (n=10 studies) was observed (random effect OR=0.81; 95% CI, 0.72-0.91). No significant decrease in OR was observed for menopausal women (n=9 studies).

Breast cancer risk according to breastfeeding duration: A significant decrease in combined OR for breast cancer risk was observed only in women who breastfed for at least 12 months, relative to women who had never breastfed (random effect OR=0.72; 95% CI, 0.65-0.80). Pooled ORs for 3 categories of duration (1-6 months, 7-12 months, >12 months) suggested a trend towards decreasing risk of breast cancer with increasing duration of breastfeeding (chi-squared for trend P<0.0005).

Authors' conclusions: Findings suggest a slight but significant reduction of breast cancer risk in women who had ever breastfed. This decreased risk appeared to be related to duration, as women who breastfed for >12 months were at lower risk than those who breastfed for a shorter duration. This effect was present in women who were not menopausal at the time of breast cancer diagnosis. The authors discuss various limitations associated with meta-analysis.

Further information: The authors discuss aspects of methodological quality of included studies, although individual studies do not appear to have undergone systematic quality assessment.

Author(s) Study	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)**	**Outcome(s)**
Lipworth et al (2000) History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature	To critically evaluate the epidemiological evidence that a history of breast feeding may decrease the risk of breast cancer	Systematic review MEDLINE 1966-1998 Not applicable	**Included:** studies which included more than 200 cases; which controlled for number of full-term pregnancies and age at 1st birth	25 case-control studies, 1 cohort study and 2 'retrospective assessment s' Breast- feeding Study periods reported for individual studies	Numbers of cases/controls reported for individual studies Information on age/age ranges not provided Ethnicity of cases/controls not reported, although study location provided for individual studies	Breast cancer risk and ever-breastfeeding, duration of breastfeeding, mean duration of breast feeding per child, number of children breast fed, cessation of breastfeeding
Results						

Breast cancer risk and ever breastfeeding: Evidence of an inverse association between ever breastfeeding and breast cancer risk is limited and inconclusive, with findings suggestive of either no association, or a definite, but modest, protective effect. Among studies which found a protective effect, RRs for parous women who have ever breast fed ranged from 0.54 to just under 1.0, compared to women who had never breast fed.

Breast cancer risk and number of children breast fed: Two studies found that the more children a women breast fed, the lower her breast cancer risk, with a significant reduction in risk of 60% in women who breast fed ≥4 children in one study, and a 43% reduction in the other in women who breast fed 1-2 children. However, 4 studies found no trend of decreasing risk with increasing number of children breast fed.

Breast cancer risk and duration of breastfeeding: In studies which found a reduction in risk with increasing duration of breastfeeding in parous women, adjusted ORs for premenopausal women who breast fed for at least
12 months ranged from 0.21-slightly below 1.0, compared to parous women who never breast fed. Other studies found no such similar reduction in risk. Overall however, there appears to be evidence for a protective effect on breast cancer risk among women in non-Western societies with long durations of breastfeeding.

Breast cancer risk and mean duration of breastfeeding per child: Four studies have failed to show any significant association between breast cancer risk and mean months of breast feeding per child, with only 1 study reporting a statistically significant trend of decreasing risk.

Breast cancer risk and cessation of breastfeeding: Two studies found that women who stopped breastfeeding because of 'insufficient milk' had an elevated risk of breast cancer. Four other studies, however, found no evidence to support this association. There was also no evidence to support an association between breast cancer risk and exposure to lactation suppressants.

Patterns of breast cancer risk among parous women by menopausal status: In most studies, any protective effect of breastfeeding was strong among, or confined to, premenopausal women, with adjusted ORs ranging from 0.58-1.14, relative to never-breastfeeders. Evidence, however, for an inverse relation between breastfeeding and postmenopausal status is limited, with many studies reporting no association.

Authors' conclusions: The evidence, although not conclusive, points to a relatively weak protective effect of breastfeeding on breast cancer risk, limited to premenopausal women. The authors note that study populations were drawn from different geographic areas and cultures, with different definitions of 'long-term breastfeeding', and this factor, as well as potential for other confounding factors, makes comparison of study findings difficult.

Further information: The authors note that included studies were evaluated for bias, confounding and chance, although further details are not provided.

Author(s) Study	Research question(s)	Review type Databases used Time period covered	Study inclusion/ exclusion criteria	Number/type of studies Interventions Follow-up period	Characteristics of participants: Total sample number Age	Outcome(s)
Collaborative Group on Hormonal Factors in Breast Cancer (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease	To examine the relation between breastfeeding and breast cancer	Meta-analysis Not reported Not reported Mantel-Haenszel stratification technique	**Included:** case-control and cohort studies with at least 100 women with invasive breast cancer which recorded information on reproductive factors/use of hormonal preparations	47 published and unpublished case-control and cohort studies (authors state this is >80% of world-wide data) Breastfeeding Not applicable	50,302 women with invasive breast cancer (cases); 96,973 women without breast cancer (controls) Cases: average age of diagnosis 50.1 years. Other details of age/age ranges not reported Ethnicity not reported, although studies carried out in 30 countries world-wide	Breast cancer risk of breastfeeding by parity Breast cancer risk by duration of breastfeeding Effect of other potential confounding factors (including family history of breast cancer)
Results						

Comparison of characteristics of cases and controls: Cases had on average fewer births than controls (2.2 vs 2.6, respectively) and a greater proportion of cases were nulliparous (16% vs 14%, respectively). Proportion of parous women who had ever breastfed was lower in cases than in controls (71% vs 79%, respectively). Average lifetime duration of breastfeeding was shorter in cases compared to controls (9.8 vs 15.6 months). Only 7% of cases and 15% of controls reported lifetime durations of breastfeeding longer than 30 months.

Breast cancer risk of breastfeeding by parity/duration of breastfeeding: In women who had never breastfed, each birth reduces breast cancer RR by 7.0% (P<0.0001). RR of breast cancer decreased by 3.4% (P<0.0001) for each child breastfed. After stratifying by parity, lifetime duration of breastfeeding, study, age, age at 1st birth and menopausal status, RR of breast cancer was significantly reduced by 4.3% for each year of breastfeeding (CI, 2.9-5.8; P<0.0001). Adjustment for other potential confounding factors (including whether from developed or developing countries; family history of breast cancer) did not alter the size of these associations.

Authors' conclusions: Breast cancer risk is significantly reduced for each year that a women breastfeeds, in addition to a reduction in risk for each birth. The lack/short duration of breastfeeding in developed countries has public health implications in view of the high incidence of breast cancer in these countries.

Further information: Details of how studies were identified and quality assessed not provided; methods in these respects are reportedly described in previous publications by the authors.

Table 7.5: Other reproductive/fertility issues

Induced abortion

Author(s) **Study**	***Research question(s)***	**Review type** **Databases used** **Time period covered** **Data analysis**	***Study inclusion/ exclusion criteria***	**Number/type of studies** **Interventions** ***Follow-up period***	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**

Brind et al (1996) Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis	To assess the association between breast cancer risk and history of induced abortion	Meta-analysis; narrative review MEDLINE 1966-1996 Multiple logistic regression analysis; weighted averages	**Included:** published studies using search terms 'abortion', 'breast' and 'cancer'; studies relating to induced abortion only; English, Japanese, Portuguese and Russian languages	28 observational studies describing 23 independent studies Induced abortion Not stated	Total numbers of participants not reported; numbers recruited into individual studies reported in narrative review. No information on characteristics of combined sample reported	Breast cancer risk and history of induced abortion Subgroup analysis according to parity
Results						
Breast cancer risk and any induced abortion exposure (n=21 studies): Breast cancer risk was significantly increased, with an overall odds ratio (OR) of 1.3 (95% CI, 1.2-1.4). **Breast cancer risk and induced abortion according to parity:** Breast cancer risk was significantly increased in nulliparous women (OR=1.3; 95% CI, 1.0-1.6), in parous women who underwent abortion before 1st-term pregnancy (OR=1.5; 95% CI, 1.2-1.8), and in women who underwent abortion after 1st term pregnancy (OR=1.3; 95% CI, 1.1-1.5). **Authors' conclusions:** Induced abortion increases breast cancer risk regardless of parity or timing of abortion relative to the 1st term pregnancy. The authors state that the consistently positive associations found amongst studies in terms of induced abortion and breast cancer incidence rule out the possibility that the association results from bias or any other confounding variable. **Further information:** Included studies did not undergo systematic quality assessment, although the authors state that provision of a narrative review should aid readers in assessing the quality of individual studies. The authors discuss induced abortion in terms of a surgical procedure only.						

Table 7.6: Alcohol consumption

Author(s) Study	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)**	**Outcome(s)**
Longnecker et al (1988) A meta-analysis of alcohol consumption in relation to risk of breast cancer	To evaluate the relationship between alcohol consumption and risk of breast cancer	Meta-analysis MEDLINE 1966-1987 Weighted least-squares regression; *F* tests; separate analyses for case-control and cohort studies	**Included:** published epidemiological studies which evaluated the relation between alcohol consumption and an increased risk of breast cancer	12 case-control and 4 cohort studies Alcohol Not reported	Total numbers of cases/controls not reported; numbers reported for individual studies only Ages not reported Ethnicity not reported	Breast cancer risk by intake and ever-consumption of alcohol
Results						

Intake of alcohol and breast cancer risk:

Case-control studies (n=12): There was a statistically significant dose-response relation between alcohol consumption and breast cancer risk (P=0.01). The risk of breast cancer associated with an alcohol intake of 24 g of absolute alcohol/day (approximately 2 drinks/day) relative to non-drinkers was 1.4 (95% CI, 1.0-1.8). At lower levels of alcohol consumption (6-12 g/day), there is a weak or modest association, although 95% CIs generally include 1.

Cohort studies (n=4): There was a statistically significant dose-response relation between alcohol consumption and breast cancer risk (P<0.05). The risk of breast cancer associated with alcohol intake of 24 g of absolute alcohol/day (approximately 2 drinks/day) relative to non-drinkers was 1.7 (95% CI, 1.4-2.2). At lower levels of alcohol consumption (6-12 g/day), there weak or modest association, although 95% CIs generally (as with case-control studies) include 1.

Ever-consumption of alcohol and breast cancer risk: The results of 6 case-control studies showed an overall risk estimate of breast cancer for ever consuming alcohol compared with never 1.1 (95% CI, 1.0-1.2).

Authors' conclusions: Findings are strongly supportive of an association between alcohol consumption and breast cancer risk. However, the authors note that the increased risk should not be considered separately from the protective effect of alcohol against cardiovascular disease reported elsewhere.

Further information: Search strategies were not reported. Quality scoring of methods/data analysis of studies carried out by 2 investigators, who were also blinded to authors' names and study results. The authors reanalysed the data excluding studies which scored lowest in quality and found results similar to main analyses. They also included data from 3 unpublished studies and found that their conclusions did not alter.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**
Steinberg et al (1991) Alcohol and breast cancer risk – putting the current controversy	To assess the association between alcohol consumption and breast cancer risk in women.	Systematic review MEDLINE, Cancerlit, Excerpta Medica 1975-1990 Not applicable	**Included:** published case-control and cohort studies that dealt with alcohol and breast neoplasms **Excluded:**	6 cohort and 20 case-control studies Alcohol Follow-up (cohort studies only) ranged from 4	Total sample number for all studies not provided. Numbers of cases/controls provided for each study separately. Details of populations studied provided for	Breast cancer risk according to alcohol consumption

into perspective			abstracts/letters describing case-control/cohort studies; correlation studies	years to median of 26 years (one study did not state follow-up period)	each study separately. No further characteristics supplied.	

Results

Risk of breast cancer and alcohol consumption:

Cohort studies (n=6): 3 of these studies compared overall breast cancer risk in drinkers and non-drinkers; only 1 of them observed a significant association with a RR of breast cancer among drinkers of 1.5 (95% CI, 1.1-2.2). Five of these studies found breast cancer risk to be significantly increased in women with 'high' levels of alcohol intake (definitions varying across studies). Highest RR in any category of alcohol intake in these studies was 3.18 (95% CI 1.14-8.85) in women with an intake of >6 drinks/day. One study observed small decrease in breast cancer risk with increasing alcohol consumption.

Case-control studies (n=20): 11 studies compared breast cancer risk in drinkers vs non-drinkers, 5 of which found a significant positive association (RRs varied from 1.2-2.5). 8/11 studies found a significant dose-response gradient with increasing alcohol intake. 4 studies which did not find a significant overall association between alcohol intake and breast cancer risk found a significant increase among women who drank more than a specified amount daily. 1 study reported a significant decrease in risk with intake of ≥5 grams of alcohol/day.

Authors' conclusions: There is insufficient evidence to support a causal relationship between alcohol consumption and breast cancer risk.

Further information: Details of search strategy not provided. Quality assessment of included studies not undertaken; however, Bradford Hill criteria were applied to studies to determin whether differences in study results were related to methodological differences.

Author(s) Study	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**

Longnecker (1994) Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review	To evaluate the association between alcohol consumption and risk of breast cancer in women	Meta-analysis/ systematic review MEDLINE; abstracts presented at Society for Epidemiologic Research in previous 5 years 1966-Sept 1992 Dose-response curves/slopes; weighted least-squares regression; fixed-effects model; random-effects model	**Included:** case-control and cohort studies; results presented in manuscripts, letters, abstracts; English language	Total 38 studies: 10 cohort and 28 case-control studies Alcohol Not reported	No information on participant characteristics provided	Breast cancer risk according alcohol intake

Results

Breast cancer risk according to alcohol intake:

Meta-analysis: For all studies combined, the relative risks for 13g of alcohol/day (approx. 1 drink) ranged from 0.57-2.07. Trend in effect was significantly positive for 15 studies, significa negative for 3 studies and nonsignificant for 20 studies. The RRs of breast cancer associated with intake of 1, 2 or 3 drinks/day (random-effects model) were 1.11 (95% CI, 1.07-1.16), 1.24 CI, 1.15-1.34) and 1.38 (95% CI, 1.23-1.55), respectively. The slope for the random-effects model was 0.0083 (SE=0.0015) per gram of alcohol daily. Variation in size of association by stud design (cohort vs case-control) was not evident.

Qualitative review: Evidence for effect modification was not strong for any factor except perhaps for estrogen replacement therapy, although study data is limited for this association.

Authors' conclusions: There is strong evidence of a dose-response relation between alcohol consumption and breast cancer risk. However, the slope of the dose-response curve was quit modest, with eg, an 11% increase in breast cancer risk from 1 alcoholic drink per day compared with non-drinkers. There was no explanation for the marked variation in results across studies.

Further information: Search strategy not reported.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)**	**Outcome(s)**

		covered **Data analysis**		**period**	**Ethnicity**	
Smith-Warner et al (1998) Alcohol and breast cancer in women: a pooled analysis of cohort studies	To assess the risk of invasive breast cancer and alcohol intake, and to evaluate whether dietary and non-dietary factors modify the association	Meta-analysis Not reported Not reported Pooled analysis consistent with each study's original design; Kaplan-Meier curves; random-effects model	**Included:** prospective studies which had at least 200 incident breast cancer cases; assessment of long-term intake of foods; validation study/ instrument of diet assessment method **Excluded:** case-control studies	6 prospective studies Alcohol; dietary factors Between 3-7 years	Total sample 322,647 women, including 4,335 women (cases) diagnosed as having invasive breast cancer Age ranges reported for individual studies, overall range 34-93 years Ethnicity not reported	Breast cancer risk according to alcohol intake/type of alcoholic drink Breast cancer risk according to alcohol intake by potential effect modifiers: menopausal status; family history of breast cancer; HRT use; body mass inde age at menarche; parity; age at 1st birth; history of benign breast disease; oral contraceptive use; education; height; fibre intake; fat intake; smoking
Results						
Breast cancer risk according to alcohol intake: Alcohol consumption was positively associated with risk of invasive breast cancer; intake of 30 to less than 60 g/day (about 2-5 drinks per gave a RR of 1.41 (95% CI, 1.18-1.69) compared with non-drinkers. The association was weaker for women who consumed 60 g/day or more (≥4 drinks per day) compared with non-drinkers (RR=1.31; 95% CI, 0.86 1.98). Tests for heterogeneity between studies were not statistically significant in any of the consumption categories. Association between alcohol and breast cancer was linear for alcohol intakes of <60 g/day (reported by >99% of women), with a pooled RR of 1.09 (95% CI, 1.04-1.13; P=0.71 for heterogeneity among studies) for an increment of 10 g/day of alcohol (about 0.75-1 drink). **Breast cancer risk and type of alcoholic drink:** Consumption of beer, wine, or spirits did not strongly influence risk estimates, with breast cancer risk increasing by 11% (95% CI, 1.04-1.19), 5% (95% CI, 0.98-1.12) and 5% (95% CI, 1.01-1.10), respectively, for daily increases of 10 g/day. **Breast cancer risk for alcohol intake by levels of other breast cancer risk factors:**						

Pooled Multivariate Relative Risks for a 10-g/d Increment in Total Alcohol Intake by Levels of Other Breast Cancer Risk Factors		
Factor	**Relative Risk (95% Confidence Interval)**	**P for Interaction**
Menopausal status		
Premenopausal	1.00 (0.87-1.15)	.49
Postmenopausal	1.05 (1.01-1.10)	
Maternal history of breast cancer		
No	1.07 (1.03-1.11)	.22
Yes	0.98 (0.85-1.14)	
History of breast cancer in sister		
No	1.08 (1.04-1.12)	.74
Yes	1.11 (0.96-1.29)	
Hormone replacement therapy use		
Never	1.09 (1.03-1.14)	.80
Past	1.09 (1.00-1.18)	
Current	1.06 (0.98-1.16)	
Body mass index, kg/m2		
<21	1.02 (0.91-1.13)	
>21-23	1.07 (1.00-1.14)	.31
>23-25	1.11 (1.04-1.18)	
>25-29	1.04 (0.97-1.11)	

>29	1.12 (1.02-1.22)	

No statistically significant pooled interactions between breast cancer risk for each category were observed. P values for other interactions were 0.52 for age at menarche, 0.45 for parity 0.48 for age at 1st birth, 0.81 for history of benign breast disease, 0.12 for oral contraceptive use, 0.33 for education, 0.70 for height, 0.25 for fibre intake, 0.18 for fat intake, and 0.31 for smoking.

Authors' conclusions: Alcohol intake is associated with a linear increase in invasive breast cancer risk in women. The alcohol and breast cancer association was not modified by other fa

Further information: Details of search strategies and how studies were identified were not reported. Systematic quality assessment of included studies does not appear to have been ca out.

Smith-Warner et al (1998)

Author(s) Study	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**
Ellison et al (2001) Exploring the relation of alcohol consumption to risk of breast cancer	To assess the relationship between alcohol consumption and breast cancer risk in women	Meta-analysis MEDLINE Jan 1966-October 1999 Dose-response curves; weighted quadratic spline regression; linear regression model	**Included:** published studies which were based on original data; reported alcohol intake as grams/day; presented data on incident cases of breast cancer or breast cancer mortality; reported point estimates and estimate of variability for primary outcome	42 cohort and case- control studies on breast cancer incident cases; 2 studies on breast cancer mortality Alcohol Reported as <10 years/≥10 years	Breast cancer incidence studies: 41,477 cases; Breast cancer mortality studies: 3,283 cases. Numbers of cases also provided for individual studies Details of age/ethnicity of women not reported	Breast cancer risk according to alco intake Associations between breast cancer risk and alcohol intake according to different study characteristics Breast cancer mortality according t alcohol intake
Results						

Risk of breast cancer and alcohol consumption: There appeared to be a monotonic increase in risk with increasing alcohol consumption. In comparison to non-drinkers, women consumi g/day (approx. one-half drink) had a 4.9% increased risk (95% CI, 1.03-1.07), and those consuming 12g/day (approx 1 drink) and 24 g/day (approx 2 drinks) had 10% (95% CI, 1.06-1.14) an 21% (95% CI, 1.13-1.30) increased risks, respectively.

Associations between breast cancer risk and alcohol intake according to different study characteristics: RR estimates were 7% greater in hospital-based case-control studies than in coh studies or community-based case-control studies; 3% greater in studies published prior to 1990 than published after that date; and 5% greater in studies conducted outside of US than in Cohort studies with <10 years follow-up had risk estimates
11% higher than cohort studies with longer follow-up periods. No significant difference was observed by menopausal status or type of alcohol consumed.

Breast cancer mortality and alcohol consumption (2 studies): Estimated RR of breast cancer mortality was slightly below 1.0 for up to 6 g/day. RRs at 6, 12 and 24 g/day were 0.98, 1.15 1.16, respectively.

Authors' conclusions: There is a modest relation of alcohol consumption to breast cancer risk, which is even lower with longer-term follow-up in cohort studies.

Further information: The authors note that the quality of included studies varied widely, although details of a systematic quality assessment are not reported. Search strategy not report

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis

Vachon et al (2001)	Investigation of alcohol intake and family history on breast cancer risk in the Minnesota Breast Cancer Family Study Cohort study	**Cohort I (C1):** alcohol use as a risk factor for breast cancer in sisters, daughters, nieces and granddaughters of breast cancer patients **Cohort 2(C2):** alcohol use as a risk factor for breast cancer in women who married into breast cancer families	Mayo Clinic, Rochester, Minnesota, US	**C1**: 5042 women (sisters: 575; daughters: 555; granddaughters: 1,512; nieces: 2,400) **C2**: 3990 women **Total:** 9032 **Number of surrogates (C1+C2):** 2,974. Both cohorts were from 426 multigenerational families	**Included:** Women aged >18 years. **C1 women**: sisters, daughters, nieces, granddaughters of breast cancer patients. Surrogates also used where relatives were deceased/unable to provide data. **C2 women**: spouses (marry-ins) of corresponding 1st- and 2nd- degree relatives of those family members. **Excluded:** families where breast cancer patient was diagnosed <1940; where most/all relatives of breast cancer patient were deceased at baseline.	Approx. 80% of surrogates were 1st-degree relatives No further information provided on characteristics of participants	Not reported	Breast cancer risk of alc intake by family history breast cancer Subgroup analysis of br cancer risk of alcohol in in families at high risk o familial breast cancer (i families that had ≥3 bre and/or ovarian cancers Cox proportional hazar regression
Results								

Breast cancer risk and lifetime alcohol use (ever or never) in all women: Ever use was associated with a 22% increased risk (95% CI, 0.99-1.50). Size of risk did not increased with increasing frequency of alcohol consumption. Compared to non-drinkers, there were nonsignificant increases in risk in the less than weekly, weekly and daily drinker categories (RRs=1.23, 1.14 and 1.28, respectively).

Breast cancer risk and frequency of alcohol intake by relationship to breast cancer patient: C1 women: among 1st-degree relatives, daily drinkers had a significantly increased risk comp with non-drinkers (RR=2.45 [95% CI, 1.20-5.02]). This increase was less evident among 2nd-degree relatives who reported daily alcohol intake (RR=1.27 [95% CI, 0.73-2.22]). **C2 women**: There was no increase in breast cancer risk in women who married-in and reported daily alcohol intake (RR=0.90 [95% CI, 0.42-1.90]). An interaction of family history with alcohol intake also suggested when analyses restricted to self-respondents only (ie no surrogates), although this was not statistically significant (RR=2.29; P=0.27 for 1st-degree relatives who reported d alcohol intake).

Subgroup analysis of high-risk families: Findings were similar to findings based on all 426 families (Pinteraction=0.07)

Authors' conclusions: Alcohol-associated breast cancer risks may be modified by genetic susceptibility.

Further information: The authors note that their findings may have been affected by quality of surrogate data, recall bias, precision of exposure assessment, generalisability and other fac There were also low numbers and wide confidence intervals for some of the comparisons. The authors thus suggest caution in interpretation of these data.

Author (s) **Study**	**Research Question**	**Review type** **Databases used** **Time period covered**	**Study Inclusion/ Exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of** **participants: Total sample** **number**	**Outcome (s)**
Collaborative Group on Hormonal Factors in Breast Cancer	The relationship between breast cancer and the consumption of alcohol and/or tobacco	Collaborative reanalysis N/A – 80% of worldwide data	Case control and cohort studies with at least 100 women with incident invasive breast cancer and recorded information on reproductive factors and on use of hormonal factors	65 epidemiological studies (63 published) 53 studies used in analyses presented information on alcohol/tobacco consumption	Women with breast cancer (invasive) – cases women without breast cancer – controls 66426 cases, 126953 controls From 65 studies alcohol information 58515 cases, 95067 controls (from 53 studies) Average age at diagnosis 52.1 years 48 (of 53) studies conducted in developed countries	Relative risks (with standard err floated standard errors) in term breast cancer

Results

Relative risk[a] of breast cancer in relation to reported intake of alcohol, according to smoking history

g per day alcohol consumption (median)	Never-smoker relative risk[a] (FSE)	Ever-smoker relative risk[a] (FSE)	All women relative risk[a] (FSE)
0 (0)	1.00 (0.015)	1.00 (0.018)	1.00 (0.012)
<5 (2)	1.01 (0.020)	1.01 (0.020)	1.01 (0.014)
5-14 (8)	1.01 (0.023)	1.05 (0.021)	1.03 (0.015)
15-24 (18)	1.19 (0.048)	1.09 (0.035)	1.13 (0.028)
25-34 (29)	1.22 (0.056)	1.19 (0.047)	1.21 (0.036)
35-44 (39)	1.18 (0.093)	1.40 (0.077)	1.32 (0.059)
≥45 (58)	1.49 (0.110)	1.46 (0.072)	1.46 (0.060)

[a]Calculated as floating absolute risk (FAR), with corresponding floated standard error (FSE), and stratified by study, age, parity, age at first birth and, for 'all women', by smoking history (s Methods).

In each group the relative risk of breast cancer increased significantly with increasing intake of alcohol, increasing by the same amount, 7.1%, for each additional 10g per day intake of alc ($p<0.00001$ in each group).

The effect of adjusting for 11 other potential confounding factors (race, education, family history of breast cancer, age at menarche, height, weight, BMI, breastfeeding, use of hormonal preparations and age at and type of menopause) did not materially alter the magnitude of the increase in the relative risk of breast cancer associated with increasing levels of alcohol inta

Breast cancer in relation to tobacco consumption

22 255 cases, 40 832 controls reported drinking no alcohol – for these women the risk of breast cancer in ever smokers did not differ significantly from that in never smokers

(RR 1.03, SE 0.023, NS). Among women who reported drinking alcohol, the findings for smoking were difficult to disentangle from the effects of the alcohol itself.

Ever smokers compared to never smokers – no stratification of amount of alcohol – RR 1.09, after stratification – RR 1.05.

Since it is not possible to eliminate residual confounding among drinkers, results concerning tobacco consumption are restricted to women who reported drinking no alcohol at all, where such confounding should be minimized.

Compared to never smokers the relative risk of breast cancer was 0.99 (SE 0.03) for current smokers and 1.07 (SE 0.03) for

past smokers. The relationship between smoking and breast cancer was substantially confounded by the effect of alcohol.

Effect of additional adjustment for various factors on the relative risk of breast cancer associated with alcohol and tobacco consumption

	Per cent increase (SE) in the relative risk of breast cancer per 10g per day alcohol intake	Relative risk (SE) of breast cancer in ever-smokers, compared to never-smokers for women who reported drinking no alcohol
After stratification for study, age, parity, age at first birth and, for analyses concerning alcohol, tobacco consumption	7.1% (0.8%)	1.03 (0.02)
After additional stratification for:		
race	7.2% (0.8%)	1.03 (0.02)
education	7.3% (0.8%)	1.04 (0.03)
mother or sister with breast	7.2% (0.8%)	1.02 (0.03)
cancer age at menarche	7.4% (0.8%)	1.04 (0.03)
height	7.5% (0.8%)	1.02 (0.03)
weight	7.2% (0.8%)	1.04 (0.03)
body mass	6.9% (0.8%)	1.04 (0.03)
index	6.9% (0.8%)	1.02 (0.02)
	6.6% (0.8%)	1.02 (0.03)

Table 7.7: Smoking

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**
Palmer et al (1993) Cigarette smoking and the risk of breast cancer	To evaluate whether there is a causal relationship between cigarette smoking and breast cancer risk	Systematic review Details of databases searched not provided Up to Sept 1992 Not applicable	**Included:** published epidemiological studies **Excluded:** studies of prevalent disease; case-control studies where patients with smoking-related diagnoses included in control series	14 case-control and 5 cohort studies Active smoking Details of follow- up periods given for individual studies	Numbers of cases/controls provided for individual studies Age ranges provided for cohort studies only Details of ethnicity not provided	Breast cancer risk associated with ex- smokers, current smokers, age at commencement of smoking, and highest categories of smoking intensity or duration
Results						

Breast cancer risk and heavy smoking: Most of the RR estimates for the heaviest smoking category in each of the studies were in the range of 0.9-1.2, with many estimates slightly above 1.0 (more so in case-control studies). Only 2 of the smaller studies had evidence of a dose-response effect.

Breast cancer risk and smoking according to menopausal status: In 9 studies, RRs for the heaviest smoking categories for premenopausal or younger women were close to 1.0, ranging from 0.67-1.3. In 4 studies, RRs ranged from 1.5-2.1, but only one study found a statistically significant effect. **Other subgroup analyses:** similar RRs were noted for risk factors such as parity, family history of breast cancer and body mass index.

Breast cancer risk and age at commencement of smoking: In 8 studies, RRs for youngest category of age at commencement for all smokers relative to never smokers ranged from 1.07-1.30. In 2 studies, RRs for women who began smoking in early teens were 1.8 and 1.7, and were close to 1.0 in 2 other studies.

Authors' conclusions: Cigarette smoking does not appear to reduce breast cancer risk, and there is also little evidence to suggest that cigarette smoking increases risk. Most studies found either no association or very small positive associations for ever smoking, current smoking or heavy smoking. In the studies with positive associations, the increases were about 20-30%. There is inconsistent evidence about whether women who begin smoking in their early teens are at increased risk. The authors note the possibility of bias and confounding amongst studies.

Further information: No systematic quality of assessment of included studies was carried out. Details of search strategies and how studies were identified are not provided.

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis

Couch et al (2001)	Cigarette smoking increases risk for breast cancer in high-risk breast cancer families Historical cohort study	**C1** (cases): Breast cancer risk of ever smoking in families at high-risk of breast cancer **C2** (controls): Breast cancer risk of never smoking in families at high-risk of breast cancer	Mayo Clinic Cancer Centre, Rochester, Minnesota, US	**C1**: 1,891 **C2**: 2,246 Participants are from 132 high-risk breast cancer families (defined as families with 3 or more members affected with breast or ovarian cancer)	**Included:** sisters, daughters, granddaughters, nieces and marry-ins from 132 high-risk families. Data also collected from surrogates where cases had died since last contact (95% surrogates degree relatives)	**Parity/age at 1st birth (%):** Nulliparous: **C1**: 10.3; **C2**: 11.0. 1-2, ≤20 yrs: **C1**: 13.3; **C2**: 5.1. 1-2, >20 yrs: **C1**: 26.6; **C2**: 29.0. 3+, ≤20 yrs: **C1**: 24.1; **C2**: 19.4. 3+, >20yrs: **C1**: 25.6; **C2**: 35.9 **Age at menarche (mean yrs, SD): C1**: 13.0 (1.6); **C2**: 12.9 (1.5) **Menopausal status:** Premenopausal (%): **C1**: 30.6; **C2**: 27.3. Menopause <44 yrs: **C1**: 27.3; **C2**: 21.7. Menopause 45-50 yrs: **C1**: 25.5; **C2**: 27.1. Menopause >50yrs: **C1**: 16.6; **C2**: 24.0 **Oral contraceptive use (%):** 0 yrs: **C1**: 41.1; **C2**: 57.1; ≤4 yrs: **C1**: 30.4; **C2**: 23.2; >4 yrs: **C1**: 28.6; **C2**: 19.7	From between 1944-1952 followed through to 1996	Breast cancer risk and smoking status (ever vs never) in self- and surrogate-responders Breast cancer risk and age at smoking initiation, cigarettes/day, number of pack-years smoked in a life-time (self-responders only) Cox proportional hazards regression
Results								

Smoking history of family members: Among smokers (self-respondents only), there were no notable differences across relationship categories in age at initiation, cigarettes/day, or pack-years of tobacco exposure. Ever- smokers had a slightly earlier age at menopause and were more likely to have used oral contraceptives and to drink more alcohol than nonsmokers.

Breast cancer risk and smoking status by relationship to breast cancer patient: Among sisters and daughters, those who ever smoked were at 1.8-fold increased breast cancer risk (95% CI, 1.2-2.7) compared to never- smokers. No association was observed in nieces, granddaughters or marry-ins. When analysis was restricted to self-responders the association in sisters and daughters was even stronger (RR=2.4; 95% CI, 1.2-5.1).

Breast cancer risk and age at initiation of smoking and levels of smoking: No clear pattern with either aspect was observed (data not shown in paper).

Breast cancer risk and smoking status in highest-risk families (defined as 5 or more cases of breast and/or ovarian cancer: n=35): Among sisters and daughters, those who ever smoked were at 5.8-fold increased risk
(95% CI, 1.4-23.9) compared with never-smokers. No increased breast cancer risk observed in nieces and granddaughters.

Authors' conclusions: Study findings suggest that smoking may significantly increase breast cancer risk in sisters and daughters of women with breast cancer from high-risk families. The authors discuss potential for bias and confounding, although they discount the likelihood of any influence on results.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of** **participants: Total sample number** **Age** **(mean/SD/range)**	**Outcome(s)**

Khuder et al (2001) Smoking and breast cancer: a meta-analysis	To assess the relationship between smoking and breast cancer	Meta-analysis MEDLINE; Cancer Abstracts 1966-Dec 2001 (MEDLINE); 1980-2001 (Cancer Abstracts) Cochran's Q statistics; chi- squared test; t-tests; fixed- effect model; random effects model; Kendal ? rank correlation test for publication bias	**Included:** published studies **Excluded:** studies where data was missing; where subjects/data presented in other studies	31 case-control and 9 cohort studies published between 1984 and 2001	Numbers of cases/controls provided for individual studies Details of age and ethnicity not provided	Breast cancer risk and ever smoking, current smokers, former smokers, stratified by type of study and menopausal status. Breast cancer risk and number of cigarettes smoked per day, duration of smoking, and age at start of smoking
Results						

Qualitative review of included studies: 30 studies reported a positive association between ever smoking and breast cancer, 11 of which were statistically significant. 8 studies reported a negative association between smoking and breast cancer, with RRs ranging from 0.73-0.95, two of which were statistically significant.

Breast cancer risk and ever smoking, current smoking and former smoking: Combined RR for ever smokers was 1.10 (95% CI, 1.02-1.18); for current smokers was 1.11 (95% CI, 1.01-1.22); and for former smokers was
1.10 (95% CI, 1.00-1.21). Stratification for premenopausal status found combined RRs of 1.21 (95% CI, 1.08-1.36) and 1.30 (95% CI, 1.19-1.51) for ever smokers and former smokers, respectively. The RR for postmenopausal breast cancer was 1.07 (95% CI, 1.02-1.19) and 1.10 (95% CI, 1.03-1.18) for ever smokers and former smokers, respectively.

Breast cancer risk and number of cigarettes smoked/day: Combined RR associated with the lowest smoking category (1-10 cigarettes/day) was 1.03 (95% CI, 1.01-1.06). RR associated with the highest smoking category
(40+ cigarettes/day) was 1.30 (95% CI, 1.05-1.61). A significant dose-response trend was obtained (P<0.01).

Breast cancer risk and duration of smoking: Combined RR associated with the lowest duration (1-19 years) was 1.03 (95% CI, 1.02-1.04) and for highest duration (30+ years) was 1.12 (95% CI, 1.07-1.17). A significant dose-response trend was observed (P<0.01).

Breast cancer risk and age at start of smoking: Combined RR for starting smoking at a younger age (mean 14 years) was 1.14 (95% CI, 1.06-1.23) and 1.04 (95% CI, 0.95-1.13) at an older age (mean 31 years).

Authors' conclusions: Study findings suggest that cigarette smoking slightly increases breast cancer risk, with a higher risk in premenopausal women and in those who started smoking at an early age. Statistical tests showed no relation between RR and study size, nor evidence of bias due to study size; also RRs were increased for both case-control and cohort studies.

Further information: A systematic quality assessment of included studies was not carried out, although studies were tested for publication bias. Studies were reviewed by 2 independent reviewers. It is noted that there are errors in CI ranges reported in the text compared to corresponding ranges reported in 2 of the tables.

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis

Band et al (2002)	Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer Case-control study	**Cases:** effect of smoking on pre- and postmenopausal women with breast cancer **Controls:** effect of smoking on pre- and postmenopausal women without breast cancer	Data from British Columbia cancer registry, Canada	**Premenopausal:** cases: 318; controls: 340 **Postmenopausal:** cases: 700; controls: 685	**Included:** **Cases:** all women aged <75 years with BC diagnosed between 1 June 1988-30 June 1989, listed on cancer registry; Canadian citizens with no previous history of BC **Controls:** population age-matched (in 5-year age groups) women from 1989 British Columbia provincial voters list; no BC diagnosed <30 June 1989	**Premenopausal:** **Age % (years):** <30: cases: 2; controls: 4. 30-39: cases: 18; controls: 21. 40-49: cases: 64; controls: 59. ≥50: cases: 17; controls: 16 **Pregnancy, ever (%):** cases: 88; controls: 86 **BC in 1st degree relative (%):** cases: 16; controls: 7 **Ethnicity (%):** Caucasian: cases: 90; controls: 91. Other: cases/controls: 8. Unknown: cases: 2; controls: 1 **Postmenopausal:** **Age % (years):** 40-49: cases: 2; controls: 3. 50-59: cases: 26%; controls: 27. 60-69: cases: 50; controls: 47. 70-79: cases: 22; controls: 24 **Pregnancy, ever (%):** cases: 88; controls: 89 **BC in 1st degree relative (%):** cases: 20; controls: 12 **Ethnicity (%):** Caucasian: cases: 95; controls: 96. Other: cases/controls: 4. Unknown: cases/controls: 1	Not reported	Breast cancer risk and effect of smoking in premenopausal and postmenopausal women, according to never/ever smoking; number of cigarettes smoked/day; years of smoking; pack- years; time of smoking initiation in terms of menarche, 1st pregnancy and 1st full-term pregnancy Conditional logistic regression model
Results								

Premenopausal women:

Smoking initiated within 5 years of menarche was associated with a statistically significant increase in breast cancer risk in ever-pregnant women who smoked before their 1st pregnancy (OR=1.69; 95% CI, 1.13-2.51; P=0.01). In nulliparous premenopausal women (n=39 cases, 49 controls), breast cancer risk was significantly increased in women who smoked ≥20 cigarettes/day (OR=7.08; 95% CI, 1.63-30.8; P=0.009) and ≥20 pack-years (OR=7.48; 95% CI, 1.59-35.2; P=0.01)

Postmenopausal women:

None of the smoking variables was associated with a statistically significant increase in breast cancer risk. Adjusted OR was significantly reduced in ever-pregnant women who initiated smoking after a 1st full-term pregnancy (OR=0.64; 95% CI, 0.42-0.98; P=0.04). In women whose body mass index (BMI) increased from age 18 to current, and whose current BMI was ≥21, smoking initiated after a 1st full-term pregnancy was associated with a reduced breast cancer risk (OR=0.49; 95% CI, 0.27-0.89; P=0.02).

Authors' conclusions: Study findings show that the effect of smoking on breast cancer risk differs between pre- and postmenopausal women. In premenopausal women, risk is raised in those who smoke before a 1st pregnancy, but only when smoking is initiated within 5 years of onset of menarche, and among nulliparous women. In postmenopausal women, smoking is not associated with an increased breast cancer risk, but is associated with a significantly reduced risk in women who started to smoke after a 1st full-term pregnancy and whose BMI increased since early adulthood.

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis

Terry et al (2002)	Cigarette smoking and breast cancer risk: a long latency period? Prospective cohort study	**C1** (cases): Breast cancer risk of current smoking in women **C2** (cases): Breast cancer risk of former smoking in women **C3** (controls): Breast cancer risk of never smoking in women	Data from Canadian National Breast Screening Study (NBSS). Outcomes ascertained through Canadian Cancer Database and National Mortality Database (Statistics Canada)	89,807 women **C1**(current smokers): 19,942 **C2** (former smokers): 23,002 **C3** (never smokers): 46,863	**Included:** women taking part in NBSS RCT; recruited between 1980-1985; aged 40-59 at recruitment	**Age (mean years): C1**:48.1; **C2**: 48.6; **C3**: 48.8 **Parity (mean): C1**: 2.5; **C2**: 2.4; **C3**: 2.6 **Age at menarche (mean years): C1**, **C2** and **C3**: 12.8 **OC use (%): C1**: 62.9; **C2**: 63.3; **C3**: 54.3 **HRT use (%): C1**: 27.9; **C2**: 25.4; **C3**: 24.4 **Family history of BC (%): C1**: 12.6; **C2**: 12.1; **C3**: 12.0 **Postmenopausal (%): C1**: 37.4; **C2**: 36.1; **C3**: 37.3	Follow-up until date of diagnosis of BC, date of death or end of follow-up period (31 Dec 1993). Mean follow-up was 10.6 years.	Breast cancer risk and the association with cigarette smoking Cox proportional hazards models
Results								

Comparisons across study groups: **C1** women were younger and slightly leaner than **C2** and **C3** women, and less likely to have completed post-secondary education. **C1** women also had a higher % of HRT use, a lower level of alcohol consumption, and were more likely to have a family history of breast cancer than **C2** and **C3** women. **C1** women reported smoking mean 18.5 cigarettes/day, while **C2** women reported smoking mean 15.4 cigarettes/day.

Breast cancer risk and smoking: Age-adjusted RR for **C1** women was 1.15 (95% CI, 1.05-1.27) and for **C2** women was 1.00 (95% CI, 0.91-1.10), compared to **C3** women. Multivariate RRs were similar, with RR for **C1** women being 1.14 (95% CI, 1.03-1.27) and for **C2** women, 0.99 (95% CI, 0.90-1.09).

Breast cancer risk and duration of smoking: Women who had smoked for 40 years or longer had about a 60% increased breast cancer risk compared to **C3** women (RR=1.61; 95% CI, 1.19-2.19).

Breast cancer risk and smoking intensity (pack-years)/duration of smoking: Women who smoked 30-39 cigarettes/day or 40+ cigarettes/day were at increased risk of breast cancer compared to **C3** women (RR=1.21; 95% CI,
1.04-1.42 and RR=1.37; 95% CI, 1.15-1.62, respectively). Women who smoked 20 or more cigarettes per day over 40 years or more were at particularly high risk (RR=1.83; 95% CI, 1.29-2.61) compared to **C3** women.

Breast cancer risk and age at commencement of smoking/years since stopping smoking: There were no clear associations with breast cancer risk.

Influence of other variables on results: There was no evidence for an effect in the associations found with any of the smoking measures according to menopausal status, physical activity, alcohol use, family history of breast cancer, body mass index, HRT and OC use, parity or age at menarche (data not provided in paper).

Authors' conclusions: Study findings suggest that smoking of very long duration and high intensity may be associated with increased breast cancer risk.

Table 7.8: Obesity

Meta analysis/systematic review extraction table

Author (s)	**Research question**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Study design** **Interventions** **Follow-up period**	**Numbers randomised** Randomisation method Numbers incl in results analysis **(Confirm ITT analysis or % included in results)**	**Total sample number Age (mean/SD/range) Male/female Ethnicity**	**Out**
Harvie et al (2003)	The effect of central rather than general obesity on breast cancer risk. To assess the effect of waist or waist-hip ratio on risk of breast cancer in pre- or post-menopausal women. Whether adjustments for weight and/or BMI modified the relationship between	Systematic review Cochrane library (2001) Medline (1966-Oct 2002) Embase (1980-Oct 2002) Cancer Lit (1975-Oct 2002) Bibliographies of cancer organisations also used Experts contacted No language	Cohort or case control studies – provided separate analyses of relationship between waist and breast cancer risk in pre- and/or post- menopausal women undertaken. Case control studies only included if waist and hip measurement had been made before commencing treatment for breast cancer	8 papers in final analysis 5 cohort studies: 721705 person years observation 453 premenopausal women with breast cancer 2684 post-menopausal women with breast cancer 3 case control studies 276 pre-menopausal cases, 758 controls 390 post-menopausal cases, 1071 controls		

	waist or waist-hip ratio and breast cancer risk. Whether use of HRT modified the relationship between waist or waist-hip ratio and breast cancer risk.	restrictions Unadjusted relative risks calculated Adjusted risks calculated Relative risks in random effects meta-analyses where appropriate Sensitivity analyses of cohort data Chi-squared test for heterogeneity	Odds ratio or relative risk information required. Cohort studies mean 3.2-10.1 year			

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/trea clinician), investigator's conclusions and reviewers conclusions if different from investigators

Post menopausal women:

4 cohort studies – pooled relative risk for incidence of post-menopausal breast cancer incidence 0.61 (95% CI 0.52-0.73) for lowest compared with highest waist quintile (adjusted data) Unadjusted cohort data: relative risk 0.57 (95% CI 0.47-0.17)
Data for women who had never taken HRT: relative risk 0.57 (95% CI 0.43-0.63)
No relationship between waist and breast cancer risk in post-menopausal women using maximally adjusted data (RR 0.95, 95% CI 0.62-1.43) or in case control data (RR 1.1, 95% CI 0.66-1.83)

Waist-hip ratio:

5 cohort studies
Relative risk quartile smallest WHR compared with largest, adjusted data, 0.76 (95% CI 0.67-0.86) Unadjusted data RR 0.71, 95% CI 0.61-0.84
Women who had never taken HRT, RR 0.64 95% CI 0.47-0.86
No significant relationship between WHR and breast cancer risk using maximally adjusted data (RR 0.89, 95% CI 0.73-1.08) or in case control data (RR 0.55, 95% CI, 0.26-1.17)

Pre menopausal women:
Waist:
2 cohort studies
Relative risk, lowest compared with highest waist quartiles, adjusted data 1.09 (95% CI 0.77-1.55) Unadjusted data RR 1.09, 95% CI 0.77-1.54
Case control data RR 0.9, 95% CI 0.55-1.49

Waist-hip ratio:
3 cohort studies
Relative risk quartile smallest WHR compared with largest, adjusted data 0.83 (95% CI 0.61-1.13) Unadjusted data RR 0.85, 95% CI 0.63-1.15
Maximally adjusted cohort data RR 0.63, 95% CI 0.45-0.88) Case control data RR 0.37, 95% CI 0.21-0.66

Authors conclusions:
Post menopausal women:
Pooled results (cohort, adjusted but not for weight or BMI) suggest 39% lower risk of breast cancer in women with smallest waist and 34% lower risk in women with smallest WHR Women who had never taken HRT had a similar relationship between central obesity and risk to overall group
Adjustment for BMI attenuated relationship between waist and WHR and risk

Pre menopausal women:
Pooled results suggest waist or WHR have little if any effect on risk of breast cancer
Adjustment for BMI altered this with a 42% relative reduction in women with the smallest WHR Adjustment for BMI produced a relationship between central obesity and risk.

7.13 The effectiveness of chemoprevention for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer

7.13.1 Review Question

What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer

7.13.2 Background

Drugs such as Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer for women who are at high risk of the disease. Both drugs are approved by the US FDA (Food and Drug Administration) but not EMA (European Medical Agency) for reducing breast cancer risk. However, even in the USA use of both drugs for breast cancer prevention is uncommon. Poor uptake is likely to be due to concerns over side effects of treatment and uncertainties around who should be offered chemoprevention.

All drugs have side effects and risk which are particularly important when drugs are being used to prevent other diseases. Tamoxifen, which is effective in pre and postmenopausal women, can cause blood clots and cancer of the lining of the womb. Raloxifene and aromatase inhibitors are only effective in postmenopausal women. Raloxifene, unlike Tamoxifen, does not appear to prevent non-invasive breast cancer. Aromatase inhibitors increase the risk of osteoporosis and bone fracture and can sometime cause intolerable muscle and joint aches and pains.

7.13.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women with a family history of breast, ovarian or related (prostate/pancreatic) cancer **And/or** Women at risk of breast cancer based on the results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53)	Chemoprevention • Tamoxifen • Raloxifene • Aromatase Inhibitors	Each Other No chemoprevention	• Development of Cancer(1) • Adverse Events(2) • Health Related Quality of life • Overall Survival • Cost Effectiveness (3)

7.13.4 Relative importance of these outcomes?

The most important outcome for this topic was considered to be the development of cancer and whether the cancer was invasive or DCIS.

Adverse events associated with treatment were considered to be a second outcome and the GDG recommend that when searching the evidence relating to adverse events, the population should not be limited to women at risk but should encompass the whole breast cancer population as the adverse events are not specific to women at risk and therefore we would be throwing out potentially relevant evidence by limiting the population.

7.13.5 How the information will be searched

Searches: *(To be Completed by subgroup lead)*	
Can we apply date limits to the search	This topic is an update of the original CG14/41 guideline and therefore the searches will be limited to only evidence published since the cut-off point for searches conducted in the old guideline.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	The GDG requested that no RCT filter be applied as some of studies have looked at risk/benefit models which may be relevant but would be thrown out by such a limit
List useful search terms.	Tamoxifen Raloxifene Aromatase Inhibitor – I think only 1 has been published to date using an AI 'Family history' was not considered to be a useful search term. 'Breast cancer (chemo) prevention' likely to pull up the studies done
Any other information	To ensure that all relevant published information is identified, an update search will be conducted towards the end of guideline development and any new data added to the body of evidence.

7.13.6 The review strategy

Any additional information to be added by subgroup lead

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	• Women with a family history of breast, ovarian or related (prostate/pancreatic) cancer • Women at risk of breast cancer based on the results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53)

	• All women with breast cancer when examining evidence for adverse events related to Tamoxifen. • Invasive versus DCIS

7.13.7 Search results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-current	1977	272	27/09/2011
Premedline	2003-current	57	6	27/09/2011
Embase	2003-current	4108	192	28/09/2011
Cochrane Library	2003-current	345	28	28/09/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2003-current	1598	95	28/09/2011

Total References retrieved (after duplicates removed): 407

Medline search strategy for Part One *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
7. 5 or 6
8. exp Prostatic Neoplasms/
9. (prostat$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
10. 8 or 9
11. exp Pancreatic Neoplasms/
12. (pancrea$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
13. 11 or 12
14. 4 or 7 or 10 or 13
15. (familial or family histor$).tw.
16. (heredit$ or inherit$ or predispos$).tw.
17. exp Genetics/
18. genetic$.tw.
19. (gene or genes or mutation$).tw.
20. Genetic Screening/
21. exp Genetic Predisposition to Disease/
22. exp Neoplastic Syndromes, Hereditary/
23. Genetic Counseling/
24. exp Genetic Techniques/
25. (BRCA1 or BRCA2 or TP53).tw.
26. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
27. ((high adj risk) or (increas$ adj risk)).tw.
28. or/15-27
29. 14 and 28

30. 4 and 29
31. exp Chemoprevention/
32. (chemoprevent$ or chemoprophyla$).tw.
33. exp Tamoxifen/
34. exp Raloxifene/
35. exp Aromatase Inhibitors/
36. aromatase inhibitor$.tw.
37. (reduction adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
38. (exemestane$ or aromasin$).tw.
39. anastr?zol$.tw.
40. letrozol$.tw.
41. or/31-40
42. 30 and 41
43. limit 42 to yr="2003 -Current"

Notes:

As this was an update topic then the date limits were from when the searches in the previous guideline finished in 2003.

A search filter to exclude animal studies was added to Embase to reduce the number of hits.

Part two:

At the request of the GDG, an additional search was run considering the adverse effects (as outcome) of tamoxifen in women with breast cancer.

An adverse effects search filter was used (BMJ Clinical Evidence) – see below.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-current	2583	535	05/10/2011
Premedline	2003-current	96	29	05/10/2011
Embase	2003-current	7819	651	19/10/2011
Cochrane Library	2003-current	1225	187	11/10/2010
Web of Science (SCI & SSCI) and ISI Proceedings	2003-current	1759	302	11/10/2011

Total References retrieved (after duplicates removed): 954

Medline search strategy for Part Two

1. exp Breast Neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. Carcinoma, Intraductal, Noninfiltrating/
4. Carcinoma, Lobular/
5. Carcinoma, Medullary/

6. exp mammary neoplasms/
7. or/1-6
8. (breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
9. (mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
10. 8 or 9
11. 7 or 10
12. exp Chemoprevention/
13. (chemoprevent$ or chemoprophyla$).tw.
14. exp Tamoxifen/
15. tamoxifen.tw.
16. exp Raloxifene/
17. raloxifene.tw.
18. exp Aromatase Inhibitors/
19. aromatase inhibitor$.tw.
20. (reduction adj2 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
21. (exemestane$ or aromasin$).tw.
22. anastr?zol$.tw.
23. letrozol$.tw.
24. or/12-23
25. 11 and 24
26. (ae or to or po or co).fs.
27. (safe or safety).tw.
28. side effect$.tw.
29. ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).tw.
30. exp product surveillance, postmarketing/
31. exp adverse drug reaction reporting systems/
32. exp clinical trials, phase iv/
33. exp poisoning/
34. exp substance-related disorders/
35. exp drug toxicity/
36. exp abnormalities, drug induced/
37. exp drug monitoring/
38. exp drug hypersensitivity/
39. (toxicity or complication$ or noxious or tolerability).tw.
40. exp Postoperative Complications/
41. exp Intraoperative Complications/
42. or/26-41
43. 25 and 42
44. limit 43 to yr="2003 -Current"

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search

Medline	27/09/2011-09/07/2012	227	22	09/07/2012
Premedline	27/09/2011-09/07/2012	6	4	09/07/2012
Embase	09/2011-07/2012	84	3	09/07/2012
Cochrane Library	09/2011-07/2012	9	2	09/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	09/2011-07/2012	331	8	09/07/2012

Premedline: 1 new reference added 10/09/2012

Total References retrieved (after de-duplication): 35

Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	27/09/2011-09/07/2012	224	53	09/07/2012
Premedline	27/09/2011-09/07/2012	6	3	09/07/2012
Embase	09/2011-07/2012	152	23	09/07/2012
Cochrane Library	09/2011-07/2012	26	13	09/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	09/2011-07/2012	114	28	09/07/2012

Premedline: 1 new reference added 10/09/2012

Medline: 1 new reference added 17/09/2012

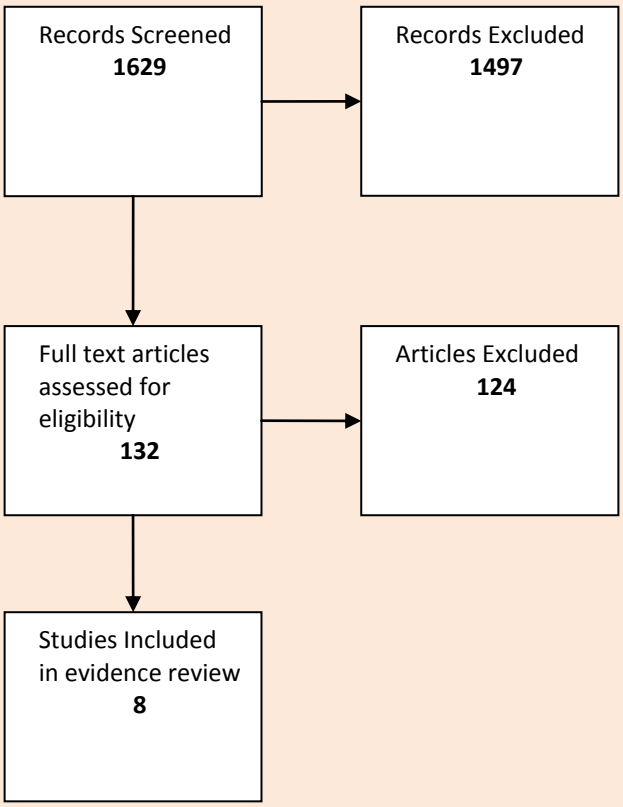
Embase: 1 new reference added 17/09/2012

Embase: 2 new references added 24/09/2012

Premedline: 2 new references added 24/09/2012

Total number of references (after de-duplication):96

7.13.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=2)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=4)
Prospective cross sectional study (n=0)
Case Series Studies (n=1)
Qualitative Study (n=1)

Table 7.9: Summary of Included Studies

Study	Study Type	Population	Aim	Intervention	Comapriso n	Outcomes
Cuzick et al (2007	Randomised Controlled Trial	N=7154 Tamoxifen=3579 Placebo=3575	To provide updated analysis of the IBIS_I trial comparing tamoxifen and placebo for breast cancer prevention in high risk women	Tamoxifen	Placebo	• Breast Cancer Occurence • Death • Endometrial Cancer Occurrence • Thromboembolic and Cardiovascular Events • Side Effects
Fisher et al (2005)	Randomised Controlled Trial	Initial Participants Randomised =13388 Included in initial analysis=13175	To provide updated findings from the P-1 trial after 7 years of follow-up	Tamoxifen	Placebo	• Invasive breast cancer occurrence • Reduced incidence of ischemic heart disease • Bone fractures
Vogel et al (2006)	Randomised Controlled Trial	N=19747 randomised Tamoxifen=9726 analysed Placebo=9745 analysed	To compare the relative effects and safety of Raloxifene and Tamoxifen on the risk of developing invasive breast cancer and other disease outcomes	Tamoxifen	Raloxifene	• Invasive breast cancer • Endometrial cancer • In situ breast cancer • Cardiovascular disease • Stroke • Pulmonary embolism • DVT

						• Transient ischemic attack • Osteoporotic fractures • Cataracts • Death • Quality of Life
Amir et al (2011)	Systematic Review and meta-analysis	7 studies giving a total population of 30,023 patients Total population relevant to topic =11,163	To evaluate and compare serious and/or life threatening adverse events reported in randomised trials comparing different adjuvant endocrine therapy strategies in postemenopausal women with early stage breast cancer	Aromatase Inhibitor	Tamoxifen	• Cardiovascualr Disease • Cerebrovascular disease • Venous Thrombosis • Bone Fracture • Endometrial Carcinoma • Hypercholestoremia
Land et al (2006)	Randomised Controlled Trial	N=1983 Tamoxifen=973 Raloxifene=1010	To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes	Tamoxifen	Raloxifene	• Health Related Quality of Life • Depressive Symptom • Sexual Functioning
Nelson et al (2009)	Systematic Review	N=14 studies included in the review	To summarise the benefits and harms of tamoxifen citrate, raloxifene and tibolone to reduce the risk of primary breast cancer	Tamoxifene Raloxifene		• Adverse Events
Vicus et al (2009)	Retrospectiv e Matched Case Control Study	N=154 cases N=500 controls	To assess whether Tamoxifen treatment of primary breast cancer and for the prevention of contralateral breast cancer is associated with	Tamoxien		• Risk of ovarian Cancer

			an increase in the subsequent risk of ovarian cancer among women with a BRCA1 mutation			
Goss et al (2011)	Randomised Controlled Trial	N=4560 Exemestane=2285 Placebo=2275	To detect relative reduction in invasive breast cancer in women randomised to exemestane	Exemestane + Placebo Exemestane + Coelecoxib	Placebo + Placebo	• Incidence of invasive breast cancer • Combined incidence of invasive and non-invasive (DCIS) breast cancer • Incidence of receptor negative breasct cancer • Incidence of combined atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ • Number of clinical breast biopsies • Clinical Features • Adverse cardiovascular events including mysocardial infarction or coronary heart diesease resulting in death • Overall cancer incidence • Side effect profile and safety • Health related and menopause specific qualities of life

7.13.9 Evidence Statements

Incidence of Breast Cancer

High quality evidence from two randomised trials (Fisher et al 2005 and Cuzick et al al, 2007; GRADE profile 7.1) suggests the incidence of breast cancer is lower in patients given tamoxifen than in those given a placebo (RR 0.65; 95% CI, 0.56-0.74).

High quality evidence from one randomised trial (Vogel et al, 2006; GRADE Profile 7.3) suggests tamoxifen and raloxifene have similar effectiveness when used as prophylaxis for breast cancer (RR 1.02; 95% CI, 0.82-1.28).

Very low quality evidence from a single randomized trial (Goss et al, 2011; GRADE profile 7.5) suggests the incidence of breast cancer is lower in patients given tamoxifen compared with those given a placebo (HR 0.35; 95% CI, 0.18-0.70).

Incidence of Endometrial Cancer

There is high quality evidence from a systematic review (Nelson et al, 2009; GRADE profile 1) that the incidence of endometrial cancer is higher in patients treated with prophylactic tamoxifen than in those given placebo (RR 2.13; 95% CI, 1.36-3.32).

There is moderate quality evidence (Nelson et al, 2009; GRADE profile 2) of uncertainty about the relative incidence of endometrial cancer in those given prophylactic raloxifene compared to those given placebo (RR 1.14; 95% CI, 0.65-1.98). This uncertainty is due to the low number of incident cases of endometrial cancer in the review. [DOWNGRADED EVIDENCE – CHECK GRADE PROFILE]

There is moderate quality evidence from one randomised trial (Vogel et al, 2006; GRADE Profile 3) of uncertainty about the relative incidence of endometrial cancer in patients who received tamoxifen compared to those given raloxifene (RR 0.62; 95% CI, 0.35-1.08). This uncertainty is due to the low number of incident cases of endometrial cancer in this trial.

High quality evidence, from one systematic review (Amir et al, 2011; GRADE profile 4), suggests the incidence of endometrial cancer is significantly lower in patients treated with an aromatase inhibitor than in those given tamoxife (OR 0.22, 95% CI, 0.11-0.46). [CHECK WITH SUE ABOUT GRADE PROFILE 4]

Thromboembolic Events

There is high quality evidence (Nelson et al, 2009; GRADE profiles 1 and 2) that thromboembolic events are more common in patients treated with tamoxifen or raloxifene when compared with placebo. For tamoxifen versus placebo RR = 1.93 (95% CI, 1.41-2.64) and for raloxifene versus placebo RR = 1.60 (95% CI, 1.15-2.23) .

High quality evidence (Vogel et al, 2006; GRADE Profile 3) suggests that thromboembolic events are more common in patients treated with tamoxifen than in those given raloxifene (RR 0.70; 95% CI, 0.54-0.91).

There is high quality evidence (Amir et al, 2011; GRADE Profile 4) of that thromboembolic events are less common during prophylaxis with an aromatase inhibitor than with tamoxifen (OR 0.57; 95% CI, 0.46-0.64).

Fractures

High quality evidence suggests that fractures are less likely with prophylactic tamoxifen that with placebo (Fisher et al 2006; GRADE Profile 1; RR 0.68; 95% CI, 0.51-0.92) or with an aromatase inhibitor (Amir et al, 2011; GRADE Profile 4; OR 0.68; 95% CI, 0.60-0.76). High quality evidence from a trial of tamoxifen versus raloxifene (Vogel et al, 2006; GRADE profile 3) suggests no difference in the relative fracture rates of the two treatments (RR 0.92; 95% CI, 0.69-1.22).

Health Related Quality of Life

There is moderate quality evidence (GRADE profile 7.3) from one qualitative assessment conducted as part of a randomised trial comparing raloxifene and tamoxifen(Land et al, 2006) both mental and physical health component scores declined over the 60 months of assessment and no significant difference was observed between the treatment groups: MCS p=0.23 and PCS p=0.21.

7.13.10 Evidence Summaries

Breast Cancer

Two trials comparing Tamoxifen with placebo, reported breast cancer incidence and the rate was lower in the Tamoxifen arm of both trials (Cuzick et al (2007) and Fisher et al (2005)). Cuzick et al (2007) reported a risk ratio of 0.73 (95% CI 0.58-0.91, p=0.004) for all breast cancer (Invasive and DCIS) and Fisher et al reported a risk ratio of 0.57 (95% CI 0.46-0.7) for invasive breast cancer and a risk ratio of 0.63 (95% CI, 0.45-0.89) for non-invasive breast cancer.

Pooled analysis of the data from both trials resulted in a statistically significantly lower rate of breast cancer (invasive and non-invasive) in the Tamoxifen group versus the placebo group: Pooled Risk Ratio=0.65, 95% CI, 0.56-0.74.

From one high quality randomised trial comparing Tamoxifen and Raloxifene (Vogel et al, 2006), there was no significant difference in the incidence of either invasive or non-invasive breast cancer between women receiving Tamoxifen or Raloxifene: Invasive breast cancer Risk Ratio=1.02, 95% CI, 0.82-1.28, Non-invasive breast cancer risk ratio=1.40, 95% CI, 0.98-2.00.

From one randomised trial of low quality (GRADE assessment) comparing Exemestane with placebo (Goss et al, 2011), cumulative breast cancer incidence was significantly lower in the exemestane arm compared with the placebo arm (HR=0.35, 95% CI, 0.18-0.70; p=0.002)

Endometrial Cancer

From one high quality systematic review comparing Tamoxifen with Placebo(Nelson et al, 2009) there were more cases of endometrial cancer in the tamoxifen arm compared with placebo: Pooled Risk Ratio=2.13, 95% CI, 1.36-3.32 (3 trials).

The same review (Nelson et al, 2009) compared Raloxifene with placebo and reported there was significant difference in risk of endometrial cancer for patients taking Raloxifene compared with placebo: Risk Ratio=1.14, 96% CI, 0.65-1.98

From one high quality randomized trial comparing Tamoxifen with Raloxifene (Vogel et al, 2006), there was no statistically significant difference between the two treatments in relation to the incidence of uterine cancer: Risk Ratio=0.62, 95% CI, 0.35-1.08.

From one systematic review comparing aromatase inhibitors and tamoxifen (Amir et al, 2011), there was a statistically significant reduction in relative odds of endometrial cancer between the use of aromatase inhibitor and tamoxifen: OR= 0.22, 95% CI, 0.11-0.46, p<0.001.

The absolute risk difference between the treatments was -0.4% and the number needed to harm was -258.

Thromboembolic Events

From one high quality systematic review (Nelson et al, 2009) there were more thromboembolic events (deep vein thrombosis and pulmonary embolism) in the tamoxifen arm compared with placebo: Risk Ratio=1.93, 95% CI, 1.41-2.64 (4 trials)

From one systematic review (Nelson et al, 2009), more thromboembolic events (deep vein thrombosis, pulmonary embolism and other unspecified thromboembolic events) were recorded in the Raloxifene group compared with placebo: Risk Ratio=1.60, 95% CI, 1.15-2.23

A statistically significant difference was observed between treatments in relation to the incidence of thromboembolic events, with more events recorded in the Tamoxifen arm than in the Raloxifene arm: Risk Ratio=0.70, 95% CI, 0.54-0.91.

From one systematic review comparing aromatase inhibitors with tamoxifen (Amir et al, 2011), the use of aromatase inhibitors was associated with a decreased odds of venous thrombosis compared with tamoxifen: OR=0.57, 95% CI, 0.46-0.64, p<0.001.

The absolute risk difference between the treatments was -1.3% and the number needed to harm was -79.

Coronary Heart Disease Events

From one high quality systematic review (Nelson et al, 2009), no difference was observed between tamoxifen and placebo for risk of coronary heart disease events (myocardial infarction, acute coronary syndrome and severe angina): Risk Ratio=1.36, 95% CI, 0.89-2.08 (4 trials)

From one systematic review (Nelson et al, 2009), raloxifene did not increase the risk of coronary heart disease events (myocardial infarction, acute coronary syndrome and severe angina) compared with placebo: Risk Ratio=0.96, 95% CI, 0.67-1.38.

From one trial comparing Tamoxifen and Raloxifene (Vogel et al, 2006) there was no statistically significant difference in overall ischaemic heart disease events between the treatment groups: Risk Ratio=1.10, 95% CI, 0.85-1.43

From one systematic review comparing aromatase inhibitor and tamoxifen (Amir et al, 2011), there was a statistically significant association between the use of aromatase inhibitor and cardiovascular disease compared with tamoxifen: OR=1.30, 95% CI, 106-1.61, p=0.01

The absolute risk difference between the groups was -0.1% and numbers needed to harm was -0.974.

All Fractures

From one high quality randomized trial (Fisher et al, 2005) there was a reduction in hip, spine and radius fractures in the tamoxifen group compared with placebo: Risk Ratio= 0.68, 95% CI, 0.51-0.92.

From one randomised trial comparing Tamoxifen and raloxifene (Vogel et al, 2006), no significant difference was observed between the treatments for rates of hip, spine and Colles fractures of the wrist: Risk Ratio=0.92, 95% CI, 0.69-1.22

From one systematic review (Amir et al, 2011), the use of aromatase inhibitors was associated with increased odds of bone fractures compared with tamoxifen: OR=1.48, 95% CI, 1.31-1.67, p<0.001.

The absolute risk difference between the groups was 2.2% and numbers needed to harm was 46.

Cataracts

From one high quality systematic review (Nelson et al, 2009), tamoxifen did not increase the risk of cataract surgery compared with placebo: Risk Ratio=1.25, 95% CI, 0.93-1.67 (2 trials).

From one systematic review (Nelson et al, 2009), raloxifene did not increase the risk of cataract surgery compared to placebo: Risk Ratio=0.93, 95% CI, 0.84-1.04.

Significantly more women in the tamoxifen arm developed cataracts compared with the Raloxifene arm (Vogel et al, 2006) : Risk Ratio=0.79, 95% CI, 0.68-0.92

Other Second Cancers

From one systematic review (Amir et al, 2011), there was no statistically significant difference in the odds of developing secondary cancers for aromatase inhibitors versus tamoxifen: OR=1.05, 95% CI, 0.90-1.23, p=0.51.

Ovarian Cancer

One small case control study (Vicus et al, 2009) assessed the risk of ovarian cancer in BRCA1 mutation carriers with primary breast cancer who were treated with Tamoxifen to prevent contralateral breast cancer, reporting no significant difference in risk of ovarian cancer between cases and controls: OR=0.78, 95% CI, 0.46-1.33, p=0.36.

Health Related Quality of Life

From one qualitative assessment conducted as part of a randomised trial comparing raloxifene and tamoxifen(Land et al, 2006) both mental and physical health component scores declined over the 60 months of assessment and no significant difference was observed between the treatment groups: MCS p=0.23 and PCS p=0.21.

Symptom Severity

From one qualitative assessment conducted as part of a randomised trial comparing raloxifene and tamoxifen (Land et al, 2006), patients in the raloxifene group experienced significantly greater musculoskeletal problems (p=0.002), dyspareunia (p<0.001) and weight gain (p<0.001). Patients in the tamoxifen arm experienced significantly greater vasomotor symptoms (p<0.001), bladder problems (p<0.001), gynaecological problems (p<0.001) and leg cramps (p<0.001).

GRADE Profile 7.1: What is the effectiveness of Tamoxifen versus Placebo for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Tamoxifen	Placebo	Relative (95% CI)	Quality
All Breast Cancer: Cuzick et al (2007); Fisher et al (2005) (follow-up 5-7 years)									
2	randomised trials	serious[1]	no serious inconsistency[2,3]	no serious indirectness	no serious imprecision[4]	347/10260 (3.4%)	538/10282 (5.2%)	Rate Ratio 0.65 (0.56 to 0.74)[5]	HIGH
Endometrial Cancer: Nelson et al (2009) (follow-up median 4 years)									
3	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	79/7682 (1%)	31/7719 (0.4%)	Rate Ratio 2.13 (1.36 to 3.32)	HIGH
Thromboembolic Events: Nelson et al (2009) (follow-up median 4 years)									
4	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	123/14198 (0.9%)	63/14223 (0.4%)	Rate Ratio 1.93 (1.41 to 2.64)	HIGH
Stroke: Nelson et al (2009) (follow-up median 4 years)									
4	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	59/14198 (0.4%)	43/14223 (0.3%)	Rate Ratio 1.36 (0.89 to 2.08)	HIGH
All Fractures: Fisher et al (2006) (follow-up mean 74 months)									
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	80/6597 (1.2%)	116/6610 (1.8%)	Rate Ratio 0.68 (0.51 to 0.92)	HIGH
Ovarian Cancer: (Vicus et al, 2009)									
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	not enough information in the paper to complete this section				VERY LOW

[1] Both included studies were large randomised trials, employing adequate methodology to randomise patients and subsequently analyse data. Both of the included studies are updated results of trials which have been previously reviewed and included in the original guideline. One study however was unblinded after the initial trial results were published.

[2] The two included randomised trials compared tamoxifen with placebo

[3] Trials varied in relation to follow-up times, women enrolled in the trials and in method of assessment of outcomes of interest, and these factors would be

expected to affect the outcome of the trials, however overall, no inconsistency was observed in the individual trial results and therefore the studies were not downgraded.

[4] Large numbers randomised together with an extended period of follow-up mean that it is unlikely that the results are imprecise.

[5] RR refers to Rate Ratio (number of observed events divided by the total number of observed event-specific person-years at risk)

[6] Not a randomised trial and small numbers in the study

GRADE Profile 7.2: What is the effectiveness of Raloxifene versus Placebo for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Raloxifene	Placebo	Relative (95% CI)	Quality
Thromboembolic Events: Nelson et al (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	162/10173 (1.6%)	85/7633 (1.1%)	Rate Ratio 1.60 (1.15 to 2.23)	HIGH
Endometrial Cancer: Nelson et al (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	Serious[2]	none	30/7860 (0.4%)	22/4081 (0.5%)	Rate Ratio 1.14 (0.65 to 1.98)	MODERATE
Cataracts/Cataract surgery: Nelson et al (2006) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	665/10117 (6.6%)	551/7600 (7.3%)	Rate Ratio 0.93 (0.84 to 1.04)	HIGH
Coronory Heart Disease Events: Nelson et al (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	297/8554 (3.5%)	256/6760 (3.8%)	Rate Ratio 0.96 (0.67 to 1.38)	HIGH

[1] Trials varied in relation to follow-up times, women enrolled in the trials and in method of assessment of outcomes of interest, and these factors would be expected to affect the outcome of the trials, however overall, no inconsistency was observed in the individual trial results and therefore the studies were not downgraded.

[2]There were very few events recorded and the confidence interval crosses 0 therefore the results are considered to be imprecise as it is unclear whether there is treatment effect or not.

GRADE Profile 7.3: What is the effectiveness of Tamoxifen versus Raloxifene for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Tamoxifen	Raloxifene	Relative (95% CI)	Quality
Breast Cancer (Invasive): Vogel et al (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	163/9726 (1.7%)	168/9745 (1.7%)	Rate Ratio 1.02 (0.82 to 1.28)[4]	MODERATE
Breast Cancer (non-invasive): Vogel et al (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	57/9726 (0.6%)	80/9745 (0.8%)	Rate Ratio 1.40 (0.98 to 2)[4]	MODERATE
Uterine Cancer: Vogel et al (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	36/9726 (0.4%)	23/9745 (0.2%)	Rate Ratio 0.62 (0.35 to 1.08)[4]	MODERATE
Thromboembolic Events: Vogel et al (2006) (follow-up median 47 months)									
1	randomised trials[5]	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	141/9726 (1.4%)	100/9745 (1%)	Rate Ratio 0.70 (0.54 to 0.91)	HIGH
All Fractures: Vogel et al (2006) (follow-up median 47 months[5])									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	0/0 (0%)	0/0 (0%)	Not estimable	HIGH
Cataracts: Vogel et al (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	394/8334 (4.7%)	313/8329 (3.8%)	Rate Ratio 0.79 (0.68 to 0.92)	HIGH
Ischaemic Heart Disease: Vogel et al (2006) (follow-up median 47 months[5])									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	114/9726 (1.2%)	126/9745 (1.3%)	Rate Ratio 0 (0 to 0)	HIGH

Health Related Quality of Life: Land et al (2006)							
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[7]	No data	MODERATE

[1] Large, multicentre, double blind randomised trial. Randomisation method used was the biased coin minimisation method with stratification of age, race/ethinicity, history of LCIS and 5 year predicted risk of breast cancer.
[2]Due to the small number of events reported, the confidence intervals cross the line of no effect and therefore there is a degree of uncertainty over the true effect.
[3] Large numbers in the trial together with an extended period of follow-up mean that it is unlikely that the results are imprecise (N=19747 patients randomised and 19471 patients analysed) despite the low number of events observed.
[4] RR relates to Risk Ratio (number of observed events divided by the total number of observed event-specific person-years at risk)

[5] Minimum follow-up=64 months; Maximum follow-up=77 months
[6]Although the study was designed as a randomised trial, the entire trial population did not complete in the quality of life assessments and the numbers completing the questionnaires declined at each assessment from baseline

GRADE Profile 7.4: What is the effectiveness of Aromatase Inhibitor versus Tamoxifen for the reduction of breast cancer incidence in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Aromatase Inhibitor	Tamoxifen	Relative (95% CI)	Quality
Endometrial Cancer: Amir et al (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[3]	HIGH
Venous Thrombosis: Amir et al (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[4]	HIGH
Cardiovascular Disease: Amir et al (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[5]	HIGH
Bone Fractures: Amir et al (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[3]	HIGH
Other Secondary Cancers: Amir et al (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[6]	HIGH

[1] Although the population for these trials included women with breast cancer and not just unaffected women with family history, there was an a priori decision to include such trials on the basis that the adverse effects of treatment will not differ in the different populations. Therefore this will not be downgraded for indirectness.

[2] Numbers not reported and the rates reported in the systematic review are for all comparisons combined, not just AI versus Tamoxifen so these cannot be used to work out the number of events.

[3] $p<0.001$

[4] OR is for two trials comparing AI (anastrozole and letrozole) with Tamoxifen only.

[5] p=0.01
[6] p=0.83

GRADE Profile 7.5: What is the effectiveness of Aromatase Inhibitor (Exemestane) versus Placebo for the reduction of breast cancer incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aromatase Inhibitor	Placebo	Relative (95% CI)	
Invasive Breast Cancer Incidence (Goss et al, 2011) (follow-up median 35 months; Mammography[1])										
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	11/2285 (0.5%)[5]	32/2275 (1.4%)[6]	HR 0.35 (0.18 to 0.70)[7]	VERY LOW

[1] Annual mammography was performed equally in both groups
[2] Short follow-up time (median 3 years)
[3] BRCA carriers were specifically excluded from the study and patients with a previous history of breast cancer were included.
[4] The number of events recorded during the study was small (n=66)
[5] Annual incidence rate for invasive breast cancer was reported as being 0.19%
[6] Annual incidence rate for invasive breast cancer was reported as being 0.55%
[7] Favouring Exemestane over placebo

7.13.11 Evidence Tables

Citation: Cuzick J (2007) Long term results of Tamoxifen prophylaxis for breast cancer – 96 month follow up of the randomized IBIS-I trial. Journal of the National Cancer Institute 99;4:272-282

Design: Randomised Trial

Country: UK but included patients from Europe, Australia and New Zealand

Setting: Follow-up

Aim: The study is an updated analysis of the IBIS-I trial which compared Tamoxifen and placebo in the prevention of breast cancer in women at high risk of breast cancer.

Inclusion criteria
(Inclusion in the original trial as reported in the updated analysis)

Women with risk factors for breast cancer indicating at least a two-fold relative risk for women 45-70 years, a fourfold relative risk for women 40-44 years or a 10 fold risk for women 35-39 years.

Women were eligible from 45 years if they had:
A mother or sister diagnosed with breast cancer before the age of 50 years
Two first or second degree relatives with breast cancer at any age
A first degree relative with breast cancer at any age and either were nulliparous or had a previous hyperplastic benign legion.

Women were eligible from aged 40 years if they had:
Atypical ductal or lobular hyperplasia
A first degree relative with bilateral breast cancer at any age
Two first or second degree relatives with breast cancer, one of whom was diagnosed before the age of 50years.

Women were eligible from 35 years if they had:
Lobular carcinoma in situ
Two first degree relatives with breast cancer, both diagnosed before the age of 50 years

Any women with an estimated 10 year risk of 5% or more based on a complex model were eligible as risk equivalent following approval by the study chairman.

Exclusion criteria
(Exclusion from the original trial as reported in the updated analysis)

Previous invasive cancer (excluding non-melanoma skin cancer)
Previous deep vein thrombosis or pulmonary embolism
Current users of anticoagulants
Wished to become pregnant

Sample Size
No details provided as part of the update study

Randomisation Method

Randomisation was double blind (patients and investigators)
Performed by telephone or fax at the IBIS central office in London for the UK and Europe and at the central centre in Sydney for Australia and New Zealand.

Population
N=7154
Placebo=3575
Tamoxifen=3579

Study Duration
Recruitment from April 1992-March 2001
5 years active treatment for the original study with a median follow-up of 8 years (no range given) for the updated analysis.

Interventions

Tamoxifen 20mg/day versus placebo

Outcomes
Breast Cancer Occurrence
Deaths
Endometrial Cancer Occurrence
Thromboembolic and Cardiovascular Events
Side Effects

Results

The cut-off date for this analysis was April 1, 2006 for a median follow-up of 95.6 months.
A total of 57128 woman-years of follow-up (28573 in the placebo group and 28555 in the Tamoxifen group) 35704 woman-years were accrued during the active treatment phase and 21424 woman-years were accrued in the follow-up phase.
Additional follow-up represents a median addition of more than 46 months and almost double woman-years at risk since the first report.
Cumulative numbers of women years of randomised treatment were 14009 (placebo) and 12772 (Tamoxifen)
In total, 4861 (67.9%) of women completed the full 5 years of treatment of whom 2574 were in the placebo arm and 2287 were in the Tamoxifen arm.

Breast Cancer
337 breast cancers (invasive or DCIS) were reported before the cut-off date.
Incidence rate in the Tamoxifen group was 27% lower than the placebo group: RR=0.73, 95% CI=0.58-0.91, p=0.004.
The annual incidence rate was 6.82 per 1000 women-years in the placebo group and 4.94 per 1000 woman-years in the Tamoxifen group.
The estimated absolute reduction in cumulative incidence after 10 years of follow-up after 10 years of follow-up was 1.7% (6.4% in the placebo group to 4.7% in the Tamoxifen group) representing a 1.5fold greater reduction than the estimated absolute risk reduction of 1.1% after 5 years (from 3.3% in the placebo group to 2.2% in the Tamoxifen group).
The reduction in incidence for all breast cancers in the Tamoxifen arm was 32% during the active treatment phase (years 0-4) and 18% during the follow-up years.
Incidence rates of ER positive invasive breast cancers in the Tamoxifen group were 26% lower than in the placebo group during the active treatment years and 44% lower during the follow-up years.
The 1.4% reduction in absolute risk of ER positive breast cancer after 10 years of follow-up was almost 3

times as large as the 0.5% reduction seen at year 5.
There was no clear evidence for subgroup specific differences in treatment effects as evidenced by a statistically significant result from a test for heterogeneity (result not presented) (subgroups analysed included age, menopausal status, HRT use, ER status, ER/PR status. Grade, nodal status and tumour size).
The incidence of ER negative invasive cancers was not reduced in the Tamoxifen arm compared with the placebo arm however the incidence of ER positive cancers was 34% lower in the Tamoxifen arm: RR=0.66, 95% CI=0.5 -0.87 (no p value).

Deaths
A total of 24 deaths from breast cancer were recorded, 11 in the Tamoxifen arm and 13 in the placebo arm: RR=0.85, 95% CI=0.34-2.05
There was no statistically significant difference in the number of deaths in the two arms though there were more deaths in the Tamoxifen arm (n=65) compared with the placebo arm (n=55): RR=1.18, 95% CI=0.81-1.73

Endometrial Cancer
17 endometrial cancers were reported in the Tamoxifen arm compared with 11 in the placebo arm: RR=1.55, 95% CI=0.68-3.65
The incidence rate for endometrial cancer was 0.59 per 1000 women-years in the Tamoxifen arm versus 0.38 per 1000 in the placebo arm.
12 of the endometrial cancers in the Tamoxifen arm and 3 in the placebo arm were detected during the active treatment phase (p=0.02).
There was no significant difference in the number of women with endometrial cancer who were taking HRT (10 in the Tamoxifen group versus 5 in the placebo group; p=0.21).

Thromboembolic and Cardiovascular events
The number of thromboembolic events was statistically significantly higher in the Tamoxifen group (n=117 events) versus the placebo group (n=68 events) RR=1.72, 95% CI=1.27-2.36.
The incidence rates were 4.1 per 1000 woman-years in the Tamoxifen group and 2.38 per 1000 woman-years in the placebo group.
The number of deep vein thrombosis, pulmonary embolism or retinal vein thrombosis events in the Tamoxifen arm (n=68) was almost double that of the placebo group (n=37): RR=1.84, 95% CI=1.21-2.82
There were almost 3 times as many superficial thromboplebitis events in the Tamoxifen arm (n=23) compared with the placebo arm (n=8): RR=2.88, 95% CI=1.24-7.44
There was no significant difference between the groups in relation to non-specific thrombotic events: RR=1.13, 95% CI=0.62-2.08
The excess of thromboembolic events was found only in the active treatment phase.
There were no statistically significant differences between the treatment groups in the rates of cerebrovascular events or cardiovascular events.

Side Effects
Statistically significantly more women in the Tamoxifen arm reported gynaecological or vasomotor side effects. The increase was observed only during active treatment: RR=1.2, 95% CI=1.16-1.25 with no significant difference in the follow-up phase: RR=1.06, 95% CI=0.99-1.12
Significantly more women in the placebo arm reported any breast complaint versus women in the Tamoxifen arm with reductions seen in both the active treatment and follow-up phases: RR=0.77, 95% CI=0.7-0.84
The incidence of multiple cysts was lower in the Tamoxifen arm compared with the placebo arm and this was true for both the active treatment: RR=0.29, 95% CI=0.19-0.44 and the follow-up phase: RR=0.61, 95% CI=0.4-0.94
Statistically significant reductions in headaches were reported in the Tamoxifen arm though the numbers

were small (32.7% versus 35.3%): RR=0.93, 95% CI=0.87-0.99, p=0.02 again, these differences were only observed during the active treatment phase: RR=0.85, 95% CI=0.79-0.92, p<0.0001.

General comments
This study is an update of trial and for this reason the paper does not report all the details of the study methodology and outcomes thus making it difficult to accurately assess the study quality.

Citation: Fisher B et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study Journal of the national cancer institute 97;22:1652-1662

Design: Randomised Controlled Trial

Country: USA

Setting: Follow-up

Aim: to provide updated findings from the P-1 trial after 7 years of follow-up (average follow-up was 74 months)

Inclusion criteria
Women at increased risk of breast cancer because:
they were aged 60 years or older
they were aged 35-59 years with a 5 year predicted risk for breast cancer of at least 1.66% (according to Gail index)
had a history of lobular cancer in situ (LCIS)
Note Inclusion criteria are taken from the evidence tables from CG14 (original familial guideline).

Exclusion criteria
Women with breast cancer who were pregnant of who had a history of deep vein thrombosis or pulmonary embolism
Women taking oral contraceptives or hormonal therapy during the trial
Note Exclusion criteria are taken from the evidence tables from CG14 (original familial guideline).

Sample Size
No details provided in the update publication or in the original guideline evidence table.

Randomisation Method
Performed centrally and was double blinded for the original analysis/results and stratified by age, race, history of LCIS and 5 year predicted breast cancer risk.

After the trial results were published (1998), all women and their physicians were informed as to whether they had received Tamoxifen or placebo and women in the tamoxifen group were given the option to continue for a total of 5 years and patients in the placebo group were given the option of taking Tamoxifen for 5 years or to be randomised to the STAR trial (Tamoxifen versus Raloxifene).

Population
Initial participants randomized: N=13388 (from CG14 evidence table)
Included in initial analysis: N=13175 (from CG14 evidence table)

Study Duration
The original trial protocol included a 7 year follow-up plan and after the trial was unblinded the protocol was amended to extend follow-up beyond 7 years for women who had been assigned to the Tamoxifen group.

Interventions
Tamoxifen – 20mg daily for at least 5 years
Placebo

Outcomes
Primary Outcome: Occurrence of invasive breast cancer

Secondary Outcomes: reduced incidence of ischemic heart disease (fatal/non-fatal myocardial infarction, severe angina and acute ischemic syndrome) and bone fractures.

Results

Data included in the updated articles were based on information received and processed by the NSABP Biostatistical Centre as of March 31, 2005.

Due to the lack of follow-up data for patients in the placebo group after 7 years, all analyses were censored at 7 years.

All randomly assigned participants who were at risk and for whom follow-up data were available were included in the analysis.

A total of 113388 women recruited (n=6707 in placebo group and n=6681in Tamoxifen group)
Included in analysis=13207: Placebo=6610, Tamoxifen=6597

Follow up time
≥5 years=11152 (placebo=5550, Tamoxifen=5602); Average follow up time=73.8 months; total person years follow up=40648

≥6 years=10657 (placebo=5285, Tamoxifen=5372): Average follow up time=74.3 months; total person years follow up=40844

≥7 years=9310 (placebo=4379, Tamoxifen=4931): Average follow up time=74 months; total person years follow up=81492

Patient Characteristics
39% aged 35-49 years; 31% aged 50-59 years; 30% aged ≥60 years
96% white
37% had a hysterectomy prior to randomisation
6% with history of LCIS
9% with a history of atypical hyperplasia
57% had one first degree relative with breast cancer,16% had two and 3% had three or more
24.9% had a 5-year predicted risk of ≤2%, 58% had a 5-year predicted risk of 2.01%-5% and 17% had a 5-year predicted of more than 5%

Reduction in invasive and non-invasive breast cancer events
Through 7 years of follow-up the cumulative rate of invasive breast cancer was reduced from 42.5 per 1,000 women in the placebo group to 24.8 per 1,000 women in the Tamoxifen group (p<0.001): RR=0.57, 95% CI, 0.46-0.7
The incidence rate of invasive breast cancer was 0.27% less in the Tamoxifen group compared with the placebo group.
Tamoxifen reduced the risk of invasive breast cancer in all subgroups (age, history of LCIS, history of atypical hyperplasia, level of breast cancer risk).

Cumulative rate of non-invasive breast cancer (DCIS and LCIS) was reduced from 15.8 per 1000 women in the placebo group to 10.2 per 1000 women in the Tamoxifen group (p=0.008): RR=0.63, 95% CI=0.45-0.89.
The incidence rate of non-invasive breast cancer was 0.09% less in the placebo group compared with the Tamoxifen group (note: not clear whether this result is correct and the data are not shown in the paper – likely it should read 0.09% less in the Tamoxifen group)

Comparing the rates of occurrence of invasive breast cancer at yearly intervals showed that between years

2-5 the rates of tumours in women receiving Tamoxifen were reduced by approximately 50% versus women in the placebo arm. In year 6, the reduction was 29% and in year 7 the reduction was 14% (due to a decrease in the rate of breast cancer in the placebo group and not an increase in rate in the Tamoxifen arm).

Relation of tumour characteristics to reduction in breast cancer
The size distributions of invasive tumours were similar in both Tamoxifen and placebo groups.
The reduction in the rate of invasive cancer among Tamoxifen users was 39% for tumours ≤1cm, 43% for tumours 1.1-3cm and 49% for tumours >3.1cm.
The distribution of tumours according to nodal status was similar in the Tamoxifen and placebo groups.
Tamoxifen reduced the rate of node-negative cancer by 45% and node-positive cancer by 32%
81% of tumours in the placebo group were ER positive compared with 56% in the Tamoxifen group. There was a 62% reduction in the rate of ER+ invasive breast cancer in Tamoxifen group but no change in the rate of ER- breast cancer.

Reduction in Osteoporotic Fractures
There was a reduction in hip, spine and radius fractures in the Tamoxifen group compared with the placebo group: RR=0.68, 95% CI 0.51-0.92
89% of fractures were in women aged 50 years or older and Tamoxifen reduced the rate of fractures in that age group by 29%: RR=0.71, 95% CI 0.52-0.97
In women aged 49 years or younger, Tamoxifen reduced fractures by 53% RR=0.47, 95% CI 0.16-1.22

Ischaemic Heart Disease
There was no evidence that Tamoxifen increased ischemic heart disease: Overall RR=1.03, 95% CI 0.79-1.36

Uterine Cancer
There was a statistically significant increase in the risk of invasive endometrial cancer for women in the Tamoxifen group: RR=3.28, 95% CI 1.87-6.03, however this risk did not extend to women aged 49 years or younger – RR=1.42, 95% CI 0.55-3.81.
In women aged 50 years and older there was a statistically significant increase in the risk of endometrial cancer: RR=5.33, 95% CI 2.47-13.17

The cumulative rate of invasive endometrial cancer through 7 years of follow up was 4.68 per 1000 women in the placebo group versus 15.64 per 1000 women in the Tamoxifen group ($p<0.001$)

Thromboembolic Events
There was evidence that Tamoxifen increased the risk of stroke though this was not found to be statistically significant: RR 1.42, 95% CI 0.97-2.08
The incidence rate of stroke was 0.05% greater in the Tamoxifen group compared with the placebo group.
In women aged ≤49 years were not at increased risk of stroke if they received Tamoxifen: RR=1.13, 95% CI 0.39-3.36
Women aged ≥50 years receiving tamoxifen showed some evidence of an increased risk of stroke: RR=1.47, 95% CI 0.97-2.22
The risk of transient ischemic attacks was similar for both groups: RR=0.91, 95% CI 0.54-1.52
The incidence of pulmonary embolism was statistically significantly greater in the Tamoxifen group compared with the placebo group: RR=2.15, 95% CI 1.08-4.51
The overall risk of deep vein thrombosis was greater in the Tamoxifen group compared with the placebo group: RR=1.44, 95% CI 0.91-2.30

Cataracts
The rates of cataracts and cataract surgery was higher in the Tamoxifen arm compared with the placebo arm

with an incidence rate of cataract development of 27.75 per 1000 women in the Tamoxifen group versus 22.85 per 1000 women in the placebo arm: RR=1.21, 95% CI 1.10-1.34
In women who developed cataracts, the incidence rate of cataract surgery was 10.54 per 1000 women in the Tamoxifen group and 7.58 per 1000 in the placebo group: RR=1.39, 95% CI 1.19-1.63

Other Cancers
A total of 155 cancers at 18 sites other than breast and/or endometrium were reported in the placebo group versus 178 cancers at 21 sites in the Tamoxifen group, though the differences were not significant.

Causes of Death
Death rates were similar in both arms: RR=1.10, 95% CI 0.85-1.43

Adverse Events
Not reported as an outcome in the updated analysis

General comments
Due to the positive results for patients receiving Tamoxifen, the trial was unblinded and both patients and physicians were informed as to which arm of the trial they were in. Women in the Tamoxifen arm were given the option to continue for a total of 5 years and women in the placebo arm were given the option to begin taking tamoxifen.

Citation: Goss P et al (2011) Exemestane for Breast Cancer Prevention in Postmenopausal Women The New England Journal of Medicine 364;25:2381-2391

Design: Randomised Controlled Trial

Country: USA

Setting:

Aim: To detect a relative reduction in invasive breast cancer in women randomised to exemestane compared with women randomised to placebo.

Inclusion criteria
Women age 35 years and older if they were:
postmenpausal (aged over 50 years) with no spontaneous menses in the 12 months prior to randomisation
aged 50 years or younger with no spontaneous menses in the 12 months prior to randomisation and a follicle stimulating hormone level within the postmenopausal age or with prior bilateral oophorectomy

At least one of the following risk factors:
age 60 years or older
GAIL risk score greater than 1.66%
Prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ on breast biopsy
Prior ductal carcinoma in situ treated with mastectomy

Prior menopausal hormone therapies were allowed but not within 3 months of randomisation

Exclusion criteria
Prior invasive or ductal carcinoma in situ treated with lumpectomy
Were known carriers of the BRCA1 or BRCA2 gene
A history of other malignancies (except nonmelanoma skin cancer, treated in situ cancer of the cervix or other treated solid tumours with no evidence of disease for at least 5 years)
Uncontrolled hypothyroidism or hyperthyroidism
Chronic liver disease

Sample Size
Sample size estimate was based on as assumption of a rate of invasive breast cancer of 0.6% per year in the placebo group compared with a rate of 0.21% in the exemestane group.

A total of 38 cases of invasive breast cancer were required to detect a relative reduction of 65% in the exemestane group with a two sided 5% level and 90% power. A total sample size of 4560 women was required.

Randomisation Method
Stratification for use of low dose aspirin and GAIL risk score
Randomisation using a dynamic minimisation algorithm

Population
N=4560 (Exemestane = 2285 & Placebo = 2275)

Following randomisation, 15 women were deemed ineligible but were included in the primary intention to treat analysis.

Study Duration

Recruitment: February 11, 2004 – March 23, 2010
Clinical Data cut-off: November 5, 2010
Follow-up: Method imply a minimum follow up of 1.2 years and maximum follow up of 4.2 years

Interventions
25mg Exemestane plus placebo
25mg exemestane plus celecoxib
Placebo plus placebo

Outcomes
Primary Outcome
Incidence of invasive breast cancer

Secondary Outcomes
Combined incidence of invasive and non-invasive (DCIS) breast cancer
Incidence of receptor negative invasive breast cancer
Incidence of combined atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ
Number of clinical breast biopsies
Clinical fractures
Adverse cardiovascular events including myocardial infarction or coronary heart disease that resulted in death
Overall incidence of other cancers
Side effect profile and safety
Health related and menopause specific qualities of life

Results
Both arms were well balanced for race, body mass index, and breast cancer risk factors.
Prior menopausal hormone therapy use was recorded in 1310 women in the exemestane arm (57.3%) and in 1327 women in the placebo arm (58.3%)

At the time of clinical data cutoff, 735 women (32.8%) in the exemestane arm and 646 women (28.7%) in the placebo arm were no longer taking the study medication.
Reasons for discontinuation of treatment include toxic effects (15.4% in the exemestane group versus 10.8% in the placebo group, $p<0.001$) and patient refusal (6.9% versus 6%, $p=0.22$).

Median time from randomisation to off-protocol treatment was 10.2 months (range: 0.1-61.5) for exemestane and 14.2 months (range, 0.1-62.9) for placebo.

Compliance with protocol was approximately 85%.

Scheduled annual mammography was performed equally in both groups with 7.2% in the exemestane group and 7.7% in the placebo group, missing at least one scheduled mammography.

At a median of 35 months follow-up (range, 0-63.4) 43 invasive breast cancers were diagnosed, 11 in the exemestane group and 32 in the placebo group giving an annual incidence rate of 0.19% (95% CI, 0.08-0.30) in the exemestane arm and 0.55% (95% CI, 0.36-0.73) in the placebo arm: Hazard Ratio 0.35, 95% CI 0.18-0.7

Planned subgroup analysis

A hazard ratio <1 favours exemestane

Subgroup	HR (95% CI)	P value
Current aspirin use		
Yes	0.12 (0.01-0.92)	0.24
No	0.43 (0.21-0.91)	
GAIL risk score		
≤2%	0.34 (0.09-1.27)	0.92
>2%	0.36 (0.16-0.8)	
Age		
≥60 years	0.29 (0.12-0.73)	0.58
<60 years	0.44 (0.15-1.27)	
Body Mass Index		
<25	0.35 (0.09-1.29)	0.94
25-30	0.31 (0.10-0.94)	
>30	0.41 (0.13-1.3)	
Prior ADH, ALH or LCIS		
Yes	0.61 (0.20-1.82)	0.25
No	0.26 (0.11-0.64)	

Unplanned subgroup analysis
Invasive breast cancers according to prior use of menopausal hormone therapy: HR=0.3 (95% CI 0.11-0.81) for prior users and HR=0.41, (95% CI, 0.16-1.05) for prior non users
Continent of residence: HR=0.34 (95% CI, 0.16-0.71) for North America and HR=0.39 (95% CI, 0.07-1.99) for Europe

Annual incidence of invasive breast cancer plus ductal carcinoma in situ was 0.35% in the exemestane group and 0.77% in the placebo group HR=0.47 (95% CI, 0.27-0.79)
Combined lobular carcinoma in situ, atypical ductal hyperplasia and atypical lobular hyperplasia incidence rates was 0.2% in the exemestane group and 0.5% in the placebo group HR=0.36, 95% (CI, 0.11-1.12)
Number needed to treat to prevent one case of invasive breast cancer with exemestane therapy was 94 in 3 years and 26 in 5 years.

Adverse Events
Symptoms and adverse events occurred in 88% of women in the exemestane group versus 85% of women in the placebo group (p=0.003)
Arthritis (p=0.01) and hot flashes (p<0.001) were more common in the exemestane group.
Differences between the groups in the frequency of those with grade 2 or higher symptoms were modest:
Arthritis: 6.5% versus 4.0%
Hot flashes: 18.3% versus 11,9%
There were no significant differences between the two groups in prespecified secondary end points including new diagnosis of osteoporosis or cardiovascular events.
The proportion of women in each group who were prescribed bisphosphonate therapy was similar for both groups (24.5% in the exemestane arm versus 24.1% in the placebo arm). Clinical fracture rates were similar in both groups.
There were no significant differences in the number of cancers (apart from breast cancer) or the time to cancer detection (2.2% versus 2.0% and 1.8 years versus 1.6 years)
No significant differences were detected between the two groups with respect to hypercholesterolemia, hypertriglyceridemia, abnormal liver function tests, acne, alopecia, rash, weight gain or hair loss.

Quality of Life

Compliance in completing the QoL questionnaire at each follow-up visit was 92.9-97.4% in the exemestane group and 94.3%-97.5% in the placebo group. There were no between group differences in overall health related quality of life responses on comparison of of the distributions of worsened, stabled and improved scores despite worsened menopause specific QoL in those taking exemestane.
General comments Study drug and funding support were provided by Pfizer but the sponsor had no role in the design of the study, accrual, management or data analysis. Quality of life was measured using the Medical Outcomes Study 36 item short form health survey and Menopause specific Quality of life questionnaire (MENQOL). Trial limitations include a relatively short follow-up time (median was 3 years) and a small total number of breast events.

Citation: Vogel VG et al (2006) Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial *JAMA* 295;23:2727-2741

Design: Randomised Controlled Trial

Country: USA

Setting: Almost 200 centres across the USA

Aim: to compare the relative effects and safety of raloxifene and Tamoxifen on the risk of developing invasive breast cancer and other disease outcomes

Inclusion criteria

- A five year predicted breast cancer risk of 1.66% based on the GAIL model
- ≥35 years and postmenopausal
- Not taking Tamoxifen, raloxifene, hormone therapy, oral contraceptives or androgens for at least the 3 months prior to randomisation
- Not taking warfarin or cholestyramine
- No history of stroke, pulmonary embolism or deep vein thrombosis
- No history any malignancy diagnosed in the five years prior to randomisation except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
- No uncontrolled atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension
- No psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day.
- Post-menopausal women aged ≥35 years or older with a history of LCIS treated by local excision only

Exclusion criteria
None specifically listed – implied by the inclusion criteria

Sample Size
No details given

Randomisation Method
Biased coin minimisation method with stratification for age, race/ethnicity, history of LCIS, 5 year predicted risk of breast cancer

Population
N=19747 randomised
Tamoxifen: n=9872 with 146 lost to follow up leaving **n=9726 analysed**
Raloxifene: n=9875 with 128 lost to follow up and 2 found not to be at risk of breast cancer leaving **n=9745 analysed.**

Study Duration

Accrual began July 1, 1999 and finished on November 4th, 2004 (64 months total)

Cut-off date for analyses was December 31st, 2005 (13 months later)

Minimum follow-up – 64 months
Maximum follow-up – 77 months
Median follow-up – 47months (3.9 years)
Standard deviation – 19 months (1.6 years)

Interventions
Tamoxifen 20md/day for 5 years maximum
Raloxifene 60mg/day for 5 years maximum

Outcomes

- *Primary Endpoint:* Invasive breast cancer
- *Secondary endpoints:* endometrial cancer, in situ breast cancer, cardiovascular disease, stroke, pulmonary embolism, DVT, transient ischemic attack, osteoporotic fractures, cataracts, death and quality of life.

Results

Follow-up
6 months after treatment initiation and every 6 months thereafter for 5 years
After 5 years, follow-up occurred annually.

Invasive breast cancer
No difference was observed between the effect of Tamoxifen and raloxifene on the incidence of invasive breast cancer with 163 cases of invasive breast cancer recorded in the Tamoxifen group and 168 in the raloxifene group.
A rate of 4.30 per 1000 person years in the Tamoxifen group and 4.41 per 1000 person years in the Raloxifene group:
RR=1.02, 95% CI0.82-1.28, log-rank p=0.96
The cumulative incidence through 72 months was 25.1 per 1000 person years for Tamoxifen and 24.8 per 1000 person years for Raloxifene (log-rank p=0.83)
HR= 0.98, 95% CI 0.79-1.21(method 7, Excel workbook using cumulative incidence log-rank p value)

No difference was observed between the effects of Tamoxifen and Raloxifene on subgroup analysis (age, history of LCIS, history of atypical hyperplasia, 5-year predicted breast cancer risk, no of first degree relatives with breast cancer).
No differences were observed between the effects of Tamoxifen and Raloxifene in relation to tumour characteristics (tumour size, nodal status, oestrogen receptor level).

Non-invasive breast cancer
There were 57 cases of non-invasive breast cancer in the Tamoxifen group and 80 cases in the Raloxifene group.
A rate of 1.51 per 1000 person years in the Tamoxifen group and 2.11 per 1000 person years in the Raloxifene group
RR=1.40, 95% CI 0.98-2.00

The cumulative incidence through 6 years was 8.1 per 1000 person years in the Tamoxifen group and 11.6 per 1000 person years in the Raloxifene group (log-rank p=0.52)
HR= 0.71, 95% CI 0.51-1.00(method 7, Excel workbook using cumulative incidence log-rank p value)

Uterine Cancer, uterine hyperplasia and hysterectomy
There was no statistically significant difference between the two treatments in relation to the incidence of uterine cancer with 36 cases in the Tamoxifen group and 23 cases in the raloxifene group.
Annual incidence rates were 2.00 per 1000 person years in the Tamoxifen arm and 1.25 per 1000 person years in the Raloxifene arm.
RR=0.62, 95% CI 0.35-1.08
The cumulative incidence rates through 7 years were 14.7 per 1000 person years for Tamoxifen and 8.1 per 1000 person years for raloxifene (log-rank p=0.07).
HR= 0.62, 95% CI 0.37-1.04(method 7, Excel workbook using cumulative incidence log-rank p value)

In patients not diagnosed with uterine cancer, there was a statistically significant difference in the incidence of uterine hyperplasia with 84 cases in the Tamoxifen group and 14 in the raloxifene group.
RR=0.16, 95% CI 0.09-0.29
HR cannot be calculated as log rank p value not reported for this outcome

A statistically significant difference in the number of hysterectomies performed in women no diagnosed with endometrial cancer with 244 hysterectomies performed in the Tamoxifen arm and 111 in the raloxifene arm.
RR=0.44, 95% CI 0.35-0.56
HR cannot be calculated as log rank p value not reported for this outcome

Other invasive malignancies
No statistically significant difference between treatments was observed in relation to any other cancer.

Ischemic Heart Disease
No statistically significant difference in overall ischemic heart disease events was observed with 114 events in the Tamoxifen arm and 126 events in the Raloxifene arm.
RR= 1.10, 95% CI 0.85-1.43
HR cannot be calculated as log rank p value not reported for this outcome
No significant difference was observed between treatments for separate events including myocardial infarctions, severe angina and acute ischemic syndrome

Stroke and thromboembolic events
53 strokes were recorded in the Tamoxifen arm compared with 51 in the raloxifene arm.
No significant difference was observed between the treatments in relation to transient ischemic events with 41 events in the Tamoxifen arm and 50 in the raloxifene arm
RR=1.21, 95% CI 0.79-1.88
HR cannot be calculated as log rank p value not reported for this outcome

A statistically significant difference was observed between the treatment groups in relation to the incidence of thromboembolic events with 141 events in the Tamoxifen arm compared with 100 in the raloxifene arm.
RR=0.70, 95% CI 0.54-0.91.
Cumulative incidence at 6 years was 21.0 per 1000 in the Tamoxifen arm and 16.0 in the raloxifene arm (log-rank p=0.01).
HR= 1.4, 95% CI 1.08-1.81(method 7, Excel workbook using cumulative incidence log-rank p value)

Pulmonary embolism (54 events in Tamoxifen arm versus 35 events in Raloxifene arm)

RR=0.64, 95% CI 0.41-1.00

DVT (87 events in Tamoxifene arm versus 65 events in Raloxifene arm)
RR=0.74, 95% CI 0.53-1.03

Fractures
No significant difference was observed between the treatments for rates of hip, spine and Colles fractures of the wrist with 104 patients in the Tamoxifen arm and 96 patients in the raloxifene arm experiencing one of these fractures.
RR=0.92, 95% CI 0.69-1.22

Hip fractures (26 in Tamoxifen arm versus 23 in raloxifene arm)
RR=0.88, 95% CI 0.48-1.60

Spine fractures (53 in tamoxifen arm versus 52 in raloxifene arm
RR=0.98, 95% CI 0.65-1.46

Colles fractures (27 in Tamoxifen arm versus 23 in raloxifene arm
RR=0.85, 95% CI 0.46-1.53

Cataracts
In patients who were cataract free at baseline (n=16663), a total of 707 developed cataracts during the course of follow-up, 394 in the Tamoxifen arm versus 313 in the raloxifene arm.
RR=0.79, 95% CI 0.68-0.92
Cumulative incidence at 6 years was 77.9 per 1000 person years for Tamoxifen and 56.3 per 1000 person years for raloxifene (log-rank p=0.002).
HR= 1.26, 95% CI 1.09-1.47(method 7, Excel workbook using cumulative incidence log-rank p value)

Cataract Surgery (260 in Tamoxifen arm versus 215 in raloxifene arm)
RR=0.82, 95% 0.68-0.99

Deaths
101 deaths were recorded in the Tamoxifen arm for a rate of 2.64 per 1000 person years compared with 96 in the raloxifene arm for a rate of 2.49 per 1000 person years.
RR=0.94, 95% CI 0.71-1.26
HR cannot be calculated as log rank p value not reported for this outcome

General comments

Citation: Land SR et al (2006) Patient reported symptoms and quality of life during treatment with Tamoxifen or raloxifene for breast cancer prevention: The NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial *Journal of the American Medical Association* 295;23:2742-2751

Design: Randomised Controlled Trial

Country: USA

Setting: Almost 200 centres across the USA

Aim: to compare the relative effects and safety of raloxifene and Tamoxifen on the risk of developing invasive breast cancer and other disease outcomes

Inclusion criteria

- A five year predicted breast cancer risk of 1.66% based on the GAIL model
- ≥35 years and postmenopausal
- Not taking Tamoxifen, raloxifene, hormone therapy, oral contraceptives or androgens for at least the 3 months prior to randomisation
- Not taking warfarin or cholestyramine
- No history of stroke, pulmonary embolism or deep vein thrombosis
- No history any malignancy diagnosed in the five years prior to randomisation except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
- No uncontrolled atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension
- No psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day.
- Post-menopausal women aged ≥35 years or older with a history of LCIS treated by local excision only

Exclusion criteria

None specifically listed – implied by the inclusion criteria

Sample Size

The protocol specified sample size of 1670 evaluable participants provides a power of >99% of the repeated measures of variance of 2 primary end-points at a 2 sided significance level of 0.25 assuming a meant treatment difference equal to one half of an SD.
It was estimated that accrual of 2000 patients would yield adequate data, allowing for study attrition or missing data.

Randomisation Method

Biased coin minimisation method with stratification for age, race/ethnicity, history of LCIS, 5 year predicted risk of breast cancer

Population

N=1983
Tamoxifen : n=973
Raloxifene: n=1010

Study Duration

Accrual between January 4th, 2000 and May 31st 2001

Interventions

Tamoxifen 20md/day for 5 years maximum

Raloxifene 60mg/day for 5 years maximum
Outcomes Health related QoL Depressive Symptoms Sexual Functioning
Results No significant differences in baseline characteristics were observed between the two groups of women participating in the QoL substudy. Characteristics of those participating in QoL substudy were comparable with women accrued for the main trial though there was a 3% excess of women with atypical hyperplasia among non participants and a 3% excess of women with hysterectomy among participants. 12.9% of QoL forms in the Tamoxifen arm and 10.6% in the raloxifene arm were completed after treatment discontinuation. QoL form completion was 95% at baseline and ranged from 76%-86% at all time points from 6-60 months Symptom checklist form completion was 99% at baseline and ranged from 83% to 95% for other time points. QoL missing data forms were submitted for 41% for reasons including staff error, participant refusal, participant failed to show up for follow-up visit, participant withdrew consent and participant failed to respond to telephone or mail request. **QoL Outcomes** Both mental health and physical health component scores declined modestly over the 60 months of assessment and no significant difference was observed between the treatment groups: MCS p=0.23 and PCS p=0.21. Significant differences in favour of raloxifene were observed in 2 of the SF-36 subscales: role physical p=0.03, mean difference = 2.4, effect size 0.1 social function p=0.02, mean difference 1.0, effect size 0.1 Mean CES-D score worsened after study initiation in both treatment groups but no significant difference was observed between the groups (p=0.61) The percentage of women reporting sexual activity was significantly higher in younger women (aged <60 years): **OR=0.55, 95% CI 0.46-0.66, p<0.001** Treatment was also significant in favour of Tamoxifen: **OR=1.22, 95% CI 1.01-1.46, p=0.04** In those reporting sexual activity, participants in the raloxifene arm experienced significantly greater difficulty in sexual interest (MD=0.096 p=0.009); greater difficulty with sexual arousal (MD=0.081, p=0.028); sexual enjoyment (MD=0.078, p=0.032) but no significant difference in the ability to experience an orgasm (p=0.21). **Symptom Severity** Patients in the raloxifene group experienced significantly greater musculoskeletal problems (p=0.002), dyspareunia (p<0.001) and weight gain (p<0.001). Patients in the tamoxifene arm experienced significantly greater vasomotor symptoms (p<0.001), bladder problems (p<0.001), gynaecological problems (p<0.001) and leg cramps (p<0.001). Overall vasomotor symptoms diminished with age and younger patients in the raloxifene arm had less severe vasomotor symptoms. Analysis of percentages of women reporting to be at least moderately bothered by their symptoms at 6 months showed a small difference in vasomotor symptoms among women aged <60 year: 32% in the Tamoxifen arm versus 23% in the raloxifene arm.

The proportion of women who experienced a unit increase in severity of vasomotor symptoms was significantly greater among those in the Tamoxifen group (p<0.001) and the effect of Tamoxifen was significantly greater among women aged <60 years (p=0.002 for interaction) and without a hysterectomy (p=0.002 for interaction).

Leg cramps also showed a difference: 32% in the Tamoxifen arm and 24% in the raloxifene arm
The effect of Tamoxifen on leg cramps was slightly stronger in younger women (p=0.049), white women (p=0.01) and in those without a hysterectomy (p=0.03).

Patients in the Tamoxifen arms reported being bothered by bladder problems 5% more often than those in the raloxifene arm.
A total of 1646 (17.95%) in the Tamoxifen group versus 1086 (11.83%) in the raloxifene group experienced a unit increase in bladder problems.
For dyspareunia, only treatment (p=0.03) and age (p=0.004) were significant
A total of 1153 (12.66%) participants in the Tamoxifen group versus 1387 (15.2%) in the raloxifene group experienced a unit increase in dyspareunia.

General comments

Analysis was performed with an intent to treat approach including all women with follow-up assessments available

Health related QoL was measured using the Medical Outcomes Study Short Form-36 (SF-36) which has 8 individual subscales:

- Physical functioning
- Role function-physical
- Bodily pain
- Social functioning
- Emotional well being
- Role function emotional
- Vitality
- General health perceptions

Depressive symptoms were measured using the Centre for Epidemiological Studies Depression Scale (CES-D)

Sexual functioning was assessed using a modified Medical Outcomes Study Sexual Functioning Scale

Symptom information was collected using a modified symptom checklist

Citation: Vicus D et al (2009) Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers *Gynaecological Oncology* 115;1:135-137

Design: Retrospective Matched Case Control Study

Country: Numerous

Setting: clinical genetic centres in eight participating countries including the UK

Aim: To assess whether Tamoxifen treatment of primary breast cancer and for the prevention of contralateral breast cancer is associated with an increase in the subsequent risk of ovarian cancer among women with a BRCA1 mutation.

Inclusion criteria
Women carrying a deleterious mutation in the BRCA1 gene

Exclusion criteria
Women who were diagnosed with ovarian cancer before breast cancer
Women for whom data on key variables were missing (Tamoxifen use, year of breast or ovarian cancer diagnosis, oophorectomy or year of oophorectomy).
Women with BRCA2 mutation

Sample Size
N/A

Randomisation Method
N/A

Population
N=154 cases and 560 controls
154 matched sets

For each case 1 or more controls were selected, matched on date of birth, age at diagnosis of breast cancer and country of residence.

Study Duration
N/A

Interventions
Tamoxifen

Outcomes
Risk of ovarian cancer

Results
No differences observed in average year of birth or age at diagnosis between cases and controls
Approximately 20% of all patients had been treated with Tamoxifen
Multivariate analysis was adjusted for radiotherapy, chemotherapy, breast cancer, surgery, age at diagnosis of breast cancer, oral contraceptive use, hormone replacement therapy use and parity
OR for ovarian cancer associated with Tamoxifen =0.78, 95% CI 0.46-1.33, p=0.36

General comments
No statistically significant difference in ovarian cancer risk observed between cases and controls

Citation: Amir E (2011) Toxicity of adjuvant endocrine therapy in post menopausal breast cancer patients: A systematic review and meta-analysis *Journal of the National Cancer Institute* 103;17:1299-1309

Design: Systematic Review and Meta-analysis

Country: N/A

Setting: Literature based review of published randomised trials

Aim: to evaluate and compare serious and/or life threatening adverse events reported in randomised trials comparing different adjuvant endocrine therapy strategies in postmenopausal women with early stage breast cancer.

Inclusion criteria
Randomised phase III clinical trials comparing aromatase inhibitors with Tamoxifen as initial adjuvant therapy in postmenopausal women with early stage breast cancer
Trials with treatment duration of 5 years in total
Published articles and abstracts presented at annual meetings were included in the meta-analysis

Exclusion criteria
Studies with treatment duration longer than 5 years
Studies conducted in pre/peri-menopausal women
Studies which did not compare aromatase inhibitors to Tamoxifen
Review articles
Cost effectiveness studies
Early analyses of trials

Sample Size
N/A

Randomisation Method
N/A

Population
N=7 studies with a total of 30023 patients

Study Duration
MEDLINE: 1996-April, 2010
EMBASE: 1980-2010
ASCO Annual Meetings: 2000-2009
San Antonio Breast Cancer Symposium Annual Meetings: 2000-2009

Interventions
5-years of aromatase inhibitor (AI) versus Tamoxifen
Tamoxifen for 2-3 years followed by AI for 2-3 years versus 5-years of Tamoxifen
Tamoxifen for 2-3 years followed by AI for 2-3 years versus 5 years of an AI

Outcomes
Cardiovascular Disease (myocardial infarction, angina, cardiac failure)
Cerebrovascular disease (cerebrovascular accident, transient ischaemic attack)
Venous thrombosis (any venous thromboembolic event)
Bone Fracture (any)
Endometrial Carcinoma alone and other secondary cancers (invasive cancer excluding endometrial cancer

and contralateral breast cancer)
Hypercholestoremia

Results
Two trials compared up-front AI's to up-front Tamoxifen (Anastrozole versus Tamoxifen) with a combined total population of 11,163 patients.

Four publications (5 trials) compared switching from Tamoxifen to AI and Tamoxifen alone with a combined total population of 9,094 patients.
A single trial compared switching from Tamoxifen to AI and AI alone with a population of 9,766 patients.

Cardiovascular Disease
A statistically significant association between the use of aromatase inhibitor and cardiovascular disease was observed compared with Tamoxifen: **OR=1.30, 95% CI 1.06-1.61, p=0.01**

No statistically significant association between Tamoxifen followed by AI and cardiovascular disease was observed: **OR=1.15, 95% CI 0.93-1.41, p=0.2**

A statistically significant association was observed between AI use and cardiovascular disease in the single trial comparing Tamoxifen and AI with AI alone: **OR=1.37, 95% CI 1.05-1.79, p=0.02**

Increased odds of cardiovascular events in the AI groups versus Tamoxifen group were seen in all treatment cohorts though the magnitude was numerically but not statistically significantly lower for the cohort where AI's were administered after 2-3 years of Tamoxifen: **OR=1.15 versus 1.30 versus 1.37, subgroup differences p=0.53.**

Pooled analysis of data for all three comparisons showed that longer duration AI use was associated with a statistically significant increase in the odds of developing cardiovascular disease compared with Tamoxifen alone or shorter duration of AI: **OR=1.26, 95% CI 1.10-1.43, p<0.001**
In absolute terms, 4.2% of patients in the aromatase inhibitor group and 3.4% of patients in the Tamoxifen group suffered a cardiovascular event: **Absolute Risk Difference=0.8%, NNTH=132**

Cerebrovascular Disease
No significant difference in the odds of cerebrovascular disease between treatment groups was observed: **OR=1.01, 95% CI 0.81-1.26, p=0.93**
Tamoxifen versus AI OR=0.84, 95% CI 0.62-1.14, p=0.28
Tamoxifen to AI versus Tamoxifen OR=1.01, 95% CI 0.62-1.64, p=0.97
Tamoxifen to AI versus AI OR=1.45, 95% CI 0.94-2.23, p=0.09
Cerebrovascular disease was an uncommon side-effect occurring in 1.4% of patients in the AI group and 1.5% of patients in the Tamoxifen group: **Absolute Risk Difference= -0.1%, NNTH= -0.974**

Venous Thrombosis
Longer duration of AI use was associated with decreased odds of venous thrombosis compared with Tamoxifen: **OR=0.55, 95% CI 0.46-0.64, p<0.001**
Tamoxifen versus AI OR=0.57, 95% CI 0.46-0.71, p<0.001
Tamoxifen to AI versus Tamoxifen OR=0.57, 95% CI 0.40-0.80, p=0.001
Tamoxifen to AI versus AI OR=0.46, 95% CI 0.32-0.65, p<0.001
The incidence of venous thrombosis was 1.6% in the AI group and 2.8% in the Tamoxifen group: **Absolute Risk Difference= -1.3%, NNTH=-79**
Test for subgroup differences showed no statistically significant difference between Tamoxifen to AI versus

AI alone suggesting the relative harm of Tamoxifen was not reduced by switching to AI (p=0.67)

Bone Fractures
An increased odds of bone fractures was observed for longer duration of AI use compared with Tamoxifen use: **pooled OR=1.47, 95% CI 1.34-1.61, p<0.001**
After adjustment for differential survival between AI group and Tamoxifen group: **OR=1.45, 95% CI 1.33-1.60, p<0.001.**
Tamoxifen versus AI OR=1.48, 95% CI 1.31-1.67, p<0.001
Tamoxifen to AI versus Tamoxifen OR=1.44, 95% CI 1.15-1.80, p=0.001
Tamoxifen to AI versus AI OR=1.48, 95% CI 1.21-1.80, p<0.001
Absolute fracture incidence was 7.5% in the AI group and 5.2% in the Tamoxifen group: **Absolute Risk Difference=2.2%, NNTH=46**

Endometrial Carcinoma
Longer duration of AI was associated with a 66% reduction in the relative odds of endometrial cancer compared with Tamoxifen: **OR=0.34, 95% CI 0.22-0.53, p<0.001**
Tamoxifen versus AI OR=0.22, 95% CI 0.11-0.46, p<0.001
Tamoxifen to AI versus Tamoxifen OR=0.46, 95% CI 1.15-1.80, p=0.03
Tamoxifen to AI versus AI OR=0.41, 95% CI 0.17-0.98, p=0.05
Endometrial cancer occurred in 0.1% of the AI group and in 0.5% of the Tamoxifen group: **Absolute Risk Difference=-0.4%, NNTH=-258**

Other Second Cancers
No statistically significant difference in odds of developing secondary cancers was observed on pooled analysis: **OR=0.98, 95% CI 0.85-1.14, p=0.83**
Tamoxifen versus AI OR=1.05, 95% CI 0.90-1.23, p=0.51
Tamoxifen to AI versus Tamoxifen OR=0.61, 95% CI 0.41-0.93, p=0.02
The absolute rates of other cancers were 4.7% for AI patients and 4.8% for Tamoxifen patients.
The difference between the AI only and Tamoxifen then AI was statistically significant suggesting that switching from Tamoxifen to AI may reduce the odds of developing secondary cancers (p=0.02).

Hypercholesterolemia
Pooled analysis showed that longer duration of AI use was associated with a statistically significant increase in the odds of hypercholesterolemia compared with Tamoxifen: **OR=2.36, 95% CI 2.15-2.60, p<0.001**
Tamoxifen versus AI OR=3.14, 95% CI 2.78-3.55
Tamoxifen to AI versus Tamoxifen OR=1.27, 95% CI 1.01-1.59, p=0.04
Tamoxifen to AI versus AI OR=1.71, 95% CI 1.38-2.13, p<0.001
Test for subgroup differences for AI versus Tamoxifen to AI were significant suggesting that shorter duration of AI might reduce odds of hypercholesterolemia (p<0.001).

General comments

References (systematic reviews)

Boccardo F et al (2006) Switching to anastrozole versus continued Tamoxifen treatment of early breast cancer: updated results of the Italian Tamoxifen anastrozole (ITA) trial *Ann. Ocol* 17;suppl 7:vii0-vii4

Coates AS et al (2007) Five years of letrozole compared with Tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine responsive breast cancer: update of study BIG 1-98 *Journal of Clinical Oncology* 25;5:486-492

Jakesz R et al (2005) Switching of postmenopausal women with endocrine responsive early breast cancer to anastrozole after 2 years adjuvant Tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial *Lancet* 366;9484:455-462

Forbes JF et al (2008) Effect of anastrozole and Tamoxifen as adjuvant treatment for early stage breast cancer: 100 month analysis of the ATAC trial *Lancet Oncology* 9;1:45-53

Coombes RC et al (2007) Survival and safety of exemestane versus Tamoxifen after 2-3 years of Tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial *Lancet* 369;9561:559-570

Aihara T et al (2010) Phase III randomised adjuvant study of Tamoxifen alone versus sequential Tamoxifen and anastrozole in Japanese postmenopausal women with hormone responsive breast cancer: N-SAS BC03 study *Breast Cancer Res Treat* 121;2:379-387

Van de Velde CJ (2011) Adjuvant Tamoxifen and exemestane in early breast cancer (TEAM); a randomised phase III trial *Lancet* 377;9762:321-331

Citation: Nelson HD (2009) Systematic Review: comparative effectiveness of medications to reduce risk for primary breast cancer Annals of Internal Medicine 151;10:703-715

Design: Systematic Review

Country: N/A

Setting: Literature based review of randomised trials

Role of Funding: The Agency for Healthcare Research and Quality provided the initial key questions and copyright release for the review but did not participate in the literature search, data analysis or interpretation of the results.

Aim: to summarise the benefits and harms of Tamoxifen citrate, raloxifene and tibolone to reduce the risk of primary breast cancer through addressing 5 key questions:

1. In adult women without pre-existing breast cancer what is the comparative effectiveness of tamoxifen, raloxifene and tibolone when used to reduce the risk of breast cancer on improving short and long term outcomes including invasive breast cancer, non-invasive breast cancer, breast cancer mortality, all cause mortality and osteoporotic fractures
2. What is the evidence for harms of tamoxifen, raloxifene and tibolone when used to reduce breast cancer risk (thromboembolic events, cardiovascular events, metabolic disorders, musculoskeletal symptoms, foetal health, genitourinary outcomes, other breast outcomes, other cancer, ophthalmologic disorders, gastrointestinal/hepatobiliary disorders and other adverse events impacting quality of life.
3. How do outcomes for tamoxifen, raloxifene and tibolone vary by heterogeneity in subpopulations (age, menopausal status, hysterectomy status, use of exogenous oestrogen, level of risk for breast cancer, ethnicity and race, metabolism status and risk for thromboembolic events).
4. What is the evidence that harms or secondary potential benefits listed above affect treatment choice, concordance, adherence and persistence to treatment with tamoxifen, raloxifene and tibolone when used to reduce risk for primary breast cancer
5. What methods, such as clinical risk assessment models, have been used to identify women who could benefit from medications to reduce risk for primary breast cancer

Inclusion criteria

Benefits/Benefits among population subgroups
Randomised, double blind, placebo controlled trials of tamoxifen, raloxifene or tibolone used to reduce breast cancer risk
Head to head trials of breast cancer prevention which include direct comparisons of tamoxifen, raloxifene or tibolone
Trials report breast cancer results as primary or secondary outcomes
Trials enrol women without pre-existing breast cancer and can include pre or post-menopausal women, U.S and non U.S. patients
English language publications

Harms/Harms among population subgroups
Randomised double blind, placebo controlled trials of tamoxifen, raloxifene or tibolone designed for multiple types of outcomes
Head to head trials of breast cancer prevention which include direct comparisons of tamoxifen, raloxifene or tibolone

Observational studies designed for multiple types of outcomes that report results for women using tamoxifen, raloxifene or tibolone and compares results with a nonuser group or between these drug use groups
Studies enrol women without pre-existing breast cancer and can include women of all ages, pre or post-menopausal status, U.S and non-U.S.
Health Outcomes
English Language

Exclusion criteria
Benefits/Benefits among population subgroups
Non RCT
Studies not about risk reduction for breast cancer
Women with pre-existing breast cancer, known precursor conditions or known carriers of BRCA1/BRCA2 and other breast cancer susceptibility mutations
Drugs other than Tamoxifen, raloxifene or tibolone
No breast cancer results
Laboratory or animal studies
Non-English language studies

Harms/Harms among population subgroups
Women with pre-existing breast cancer, known precursor conditions or known carriers of BRCA1/BRCA2 and other breast cancer susceptibility mutations
Drugs other than tamoxifen, raloxifene or tibolone
No harms results
Intermediate results rather than health outcomes
Laboratory of animal studies
Non-English language studies

Sample Size
Minimum study participant numbers ≥100

Randomisation Method
Only double blind trials are included in the review

Population
N=7 trials reporting adverse events associated with Tamoxifen and Raloxifene
N=4 Tamoxifen versus Placebo
N=2 Raloxifene versus Placebo
N=1 Tamoxifen versus Raloxifene

Study Duration
Literature searches were conducted from date of inception of relevant database to January 2009
Included studies should be ≥3 months in duration

Interventions
Of interest to this topic:
Tamoxifen
Raloxifene

Outcomes
Of interest to this topic were outcomes relating to harms of treatment (Adverse events)

Limitations/Bias

- Differences in trial designs resulted in different groups of women being enrolled into the individual trials.
- Mean age of participants at entry ranged from 47years to 51 years in the tamoxifen trials and from 67-68 years in the raloxifene trials; risks for adverse events such as thromboembolic events and stroke increase with age and therefore the age range across the trials may influence the results.
- Follow-up times varied across the individual trials
- Similar outcomes were reported across the individual trials though method of assessment varied and the diagnostic criteria for several outcomes were not well described in the trials.
- In 3 trials, women using oestrogen were included, the use of which could potentially confound outcomes such as thromboembolic events.

Results

There were more thromboembolic events in patients taking tamoxifen and raloxifene versus placebo but risk returned to normal following tamoxifen discontinuation in two trials.
Tamoxifen Risk Ratio=1.93, 95% CI 1.41-2.64 (4 trials)
Raloxifene Risk Ratio=1.60, 95% CI 1.15-2.23 (2 trials)
From one head to head trial comparing Tamoxifen and Raloxifene, raloxifene caused fewer thromboembolic events (STAR trial, data not provided)

Tamoxifen and Raloxifene did not increase the risk of coronary heart disease events in placebo controlled trials (measured as myocardial infarction, acute coronary syndrome and severe angina).
Tamoxifen and Raloxifene did not increase the incidence of stroke in placebo controlled trials.
Tamoxifen Risk Ratio=1.36, 95% CI 0.89-2.08 (4 trials)
Raloxifene Risk Ratio=0.96, 95% CI 0.67-1.38 (2 trials)
From one trial (RUTH), women assigned to Raloxifene had a higher stroke mortality than those assigned to placebo: Risk Ratio=1.49, 95% CI 1.00-2.24

In placebo controlled trials, there were more cases of endometrial cancer in women taking tamoxifen while raloxifene did not appear to increase the risk of endometrial cancer.
Tamoxifen Risk Ratio=2.13, 95% CI 1.36-3.32 (3 trials)
Raloxifene Risk Ratio=1.14, 95% CI 0.65-1.98 (2 trials)
From one head to head trial comparing Tamoxifen and Raloxifene, raloxifene was associated with fewer cases of endometrial hyperplasia (risk ratio=0.16, 95% CI 0.09-0.29) and fewer hysterectomies (Risk ratio=0.44, 95% CI 0.35-0.56) than Tamoxifen but did not reduce endometrial cancer: Risk Ratio=0.62, 95% CI 0.35-1.08.

No increased risk of cataract surgery was observed on pooled analysis of tamoxifen versus placebo trials: Risk Ratio=1.25, 95% CI 0.93-1.67 (2 trials)
Raloxifene did not increase the risk of cataracts or cataract surgery in placebo controlled trials: Risk Ratio for cataracts=0.93, 95% CI 0.84-1.04 (2 trials)
From one head to head trial, raloxifene was associated with fewer cataracts compared with tamoxifen: Risk Ratio 0.82, 95% CI 0.68-0.99

The most common side effects associated with tamoxifen include hot flashes and other vasomotor symptoms, vaginal discharge, itching or dryness while for raloxifene, vasomotor symptoms and leg cramps are most common.

General comments

The authors state in the review that the quality of included studies was assessed using GRADE methodology though no evidence of the results of GRADE assessments was provided.

7.13.12 Appendix 1: Evidence Tables from CG41 (2004)

Author (s)	Study Design	Type of intervention	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria	Participant characteristics	Follow-up period	Main ou Analysi
Fisher et al (1998)	Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study [Breast Cancer Prevention Trial; P-1 (BCPT; P-1)] Randomised controlled trial (double-blind)	**T1**: Tamoxifen (20mg daily) for at least 5 years **T2**: placebo	131 clinical centres throughout USA and Canada	**At start**: 13388 (**T1**: 6681; **T2**: 6707) **Included in analysis**: 13175 (**T1**: 6576; **T2**: 6599)	**Included**: women at increased risk of breast cancer (BC) because they were aged 60 years or older; were aged 35-59 years with a 5-year predicted risk for BC of at least 1.66% (according to Gail index); or had a history of lobular carcinoma *in situ* (LCIS). **Excluded**: women with breast cancer; who were pregnant; or who had a history of deep vein thrombosis or pulmonary embolism. Hormone therapy or oral contraceptive use was not permitted during the trial.	**Age:** 35-39 yrs: **T1**: 2.4; **T2**: 2.8 40-49 yrs: **T1**: 36.8; **T2**: 36.5 50-59 yrs: **T1**: 30.9; **T2**: 30.6 60-69 yrs: **T1**: 23.9; **T2**: 24.1 70 yrs & over: **T1**: 6.0; **T2**: 6.0 **Ethnicity:** White: **T1**: 96.5; **T2**: 96.4 Black: **T1**: 1.7; **T2**: 1.7 Other: **T1**: 1.8; **T2**:2.0 **No. 1st degree relatives with BC:** None: **T1**: 23.4; **T2**: 24.2 1 relative: **T1**: 57.1; **T2**: 56.5 2 relatives: **T1**: 16.3;**T2**: 16.5 3 or more: **T1**: 3.2; **T2**: 2.7 **Prior hysterectomy: T1**: 37.7; **T2**: 36.4 **History of LCIS: T1**: 6.3; **T2**: 6.2 **History of atypical hyperplasia in breast: T1**: 8.8; **T2**: 9.3 **5-yr predicted BC risk (%):** ≤2.00: **T1**: 24.9; **T2**: 25.2 2.01-3.00: **T1**: 31.3; **T2**: 30.8 3.01-5.00: **T1**: 26.1; **T2**: 27.1 ≥5.01: **T1**: 17.8; **T2**: 16.9 Groups reported as comparable at baseline, although no P values supplied.	Average follow-up of 47.7 months for both groups. 23.7% of **T1** women stopped treatment compared to 19.7% of **T2** women. 1.6% of women in each group were lost to follow-up.	**Primary** occurre **Second** reduced ischemi (fatal/n infarcti and acu syndron fracture **Analysi** basis. 2 tests of betwee by use o

Results

Primary outcome: A total of 368 invasive and non-invasive breast cancers occurred (**T1**: 124; **T2**: 244). Tamoxifen reduced the risk of invasive breast cancer by 49% (P<0.00001) with cumulative incidence through 69 months of follow-up 22.0 per 1000 women in **T2** and **T1**, respectively. Tamoxifen reduced the occurrence of oestrogen receptor (ER)-positive tumours by 69%, although no difference was observed in the occurrence of ER-negative tumours. The decreased women aged 49 years or younger (44% reduction), 50-59 years (51% reduction) and 60 years or older (55% reduction). Risk was also reduced in women with a history of LCIS (56% reduction) or atypical hyperplasia (86% reduction) and in category of predicted 5-year risk. Tamoxifen reduced the risk of non-invasive breast cancer by 50% (P<0.002).

Secondary outcomes: Tamoxifen did not alter the average annual rate of ischemic heart disease (**T1**: 71; **T2**: 62 [RR: 1.15, 95% CI: 0.81-1.64]); however, a reduction in hip, radius (Colles') and spine fractures was observed, although the di not reach statistical significance.

Adverse events: A greater proportion of **T1** women than **T2** women reported that hot flushes were 'quite a bit' or 'extremely' bothersome (45.7% compared to 28.7%, respectively). Similarly, 'moderately bothersome, or worse' vaginal reported by more **T1** women than **T2** women (29.0% compared to 13.0%). **Serious adverse events**: The occurrence of endometrial cancer, stroke, DVT, PE and new cataracts was more frequent in **T1** women compared to **T2** women, alt difference was statistically significant for endometrial cancer (**T1**: 36; **T2**: 15 [RR: 2.53, 95% CI: 1.35-4.97]), pulmonary embolism (**T1**: 18; **T2**: 6; RR: 3.01 [95% CI 1.15-9.27]) and new cataracts only (**T1**: 574; **T2**: 507 [RR: 1.14, 95% CI 1.01-1

	Placebo	Tamoxifen	Placebo	Tamoxifen	Risk Ratio	95% Confidence Interval
All Women	175	89	6.76	3.43	0.51	0.39-0.66
Age, y						
≤49	68	38	6.70	3.77	0.56	0.37-0.85
50-59	50	25	6.28	3.10	0.49	0.29-0.81
≥60	57	26	7.33	3.33	0.45	0.27-0.74
History of LCIS						
No	157	81	6.41	3.30	0.51	0.39-0.68
Yes	18	8	12.99	5.69	0.44	0.16-1.06
History of atypical hyperplasia						
No	152	86	6.44	3.61	0.56	0.42-0.73
Yes	23	3	10.11	1.43	0.14	0.03-0.47
5-y predicted breast cancer risk, %						
≤2.00	35	13	5.54	2.06	0.37	018-0.72
2.01-3.00	42	29	5.18	3.51	0.68	0.41-1.11
3.01-5.00	43	27	5.88	3.88	0.66	0.39-1.09
≥5.01	55	20	13.28	4.52	0.34	0.19-0.58
No. of first degree relatives with breast cancer						
0	38	17	6.45	2.97	0.46	0.24-0.84
1	90	46	6.00	3.03	0.51	0.35-0.73
2	37	20	8.68	4.75	0.55	0.30-0.97
≥3	10	6	13.72	7.02	0.51	0.15-1.55

Author (s)	Study Design	Type of intervention	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria	Participant characteristics	Follow-up period	Main outcome measu Analysis
Powles et al (1998)	Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial Randomised controlled trial (double-blind)	**T1**: Tamoxifen (20mg daily orally) **T2**: identical placebo (Orion Pharma)	Royal Marsden Hospital (UK) screening and symptomatic breast clinics	**At start**: 2494 (**T1**: 1250; **T2**: 1244) **Included in analysis**: 2471 (**T1**: 1238; **T2**: 1233)	**Included**: Women between 30-70 yrs; no clinical/screening evidence of breast cancer; at least one 1st degree relative aged <50 with breast cancer, or one 1st degree relative with bilateral breast cancer, or one affected 1st degree relative of any age + another affected 1st or 2nd degree relative; also women with history of a benign breast biopsy who had 1st degree relative with breast cancer was included. **Excluded**: women with history of any cancer or DVT or PE; premenopausal women considering further pregnancies or taking oral contraception.	**Median age (range):** **T1**: 47 (31-70); **T2**: 47 (30-70) **Under 50 years (no.):** **T1**: 774; **T2**: 749 **Pre/perimenopausal:** **T1**: 822; **T2**: 812 **Post menopausal:** **T1**: 416; **T2**: 421 **1st degree relative with breast cancer <50 yrs:** **T1**: 698; **T2**: 668 **2 or more relatives, any age, with breast cancer:** **T1**: 225; **T2**: 205 **Previous benign lump excised: T1**: 280; **T2**: 263 **On HRT at start:** **T1**: 187; **T2**: 202 Groups comparable at baseline, although no P-values supplied	Median follow-up of 70 months for both groups. Follow-up assessments every 6 months. Annual mammography. 320 (26%) women in **T1** discontinued treatment early, compared with 176 (14%) in **T2** (P<0.0005)	**Primary outcome**: occ breast cancer Kaplan-Meier and logr techniques. Cox prop hazards model

Results **Primary outcome**: There was no significant difference in the overall frequency of breast cancer in women on tamoxifen or placebo: **T1**: 34; **T2**: 36. Relative risk of breast cancer: 1.06 (95% CI 0.7-1.7; P=0.8). There were 4 deaths from breast cancer in **T1** and 1 in **T2**. **Prognostic factors for breast cancer-free survival**: nulliparous women had 2-fold increase in risk of breast cancer compared with women with children (RR 2.0 compared to RR 1.0 [95% CI 1.1-3.4, P=0.02]). Women already on HRT when they entered study had increased risk of breast cancer compared with non-users (RR 1.9 compared to RR 1.0 [95% CI 1.1-3.3, P=0.04]). Those women who started HRT while on trial had a significantly reduced risk of breast cancer (RR 0.4 compared to RR 1.0 [95% CI 0.2-0.7, P=0.01]). For all other confounding variables, the randomised treatment of tamoxifen or placebo was not predictive of breast cancer. **Adverse events (T1)**: hot flushes/other vasomotor symptoms; gynaecological problems including period irregularities, vaginal discharge, and benign abnormalities on US. **Clinically significant adverse events**: These were low with no significant differences between tamoxifen or placebo, although there were 4 cases of endometrial cancer in **T1** compared with 1 in **T2**.	

Univariate analysis of prognostic factors for breast-cancer-free survival in all 2494 participants

Variable	Relative risk of breast	95% CI	p
Age group			
<50	1.0		
≥50	1.1	0.7-1.8	0.6
Menopausal status			
Pre	1.0		
Peri	1.1	0.3-3.5	0.9
Post	1.0	0.6-1.6	
Number of first degree relatives with breast cancer			
1	1.0		
2	1.2	0.8-1.8	0.3
3	1.5	0.7-3.3	
Relatives aged <50 with breast cancer			
None	1.0		
1	1.1	0.7-1.5	0.7
2	1.2	0.6-2.3	
Relatives with bilateral breast cancer			
No	1.0		
Yes	1.2	0.5-3.0	0.7
Previous benign lump			
No	1.0		
Yes	0.8	0.1-6.9	0.8
Nulliparous			
No	1.0		
Yes	2.0	1.1-3.4	0.02
On HRT at randomisation			
No	1.0		
Yes	1.9	1.1-3.3	0.04
Started HRT during trial			
No	1.0		
Yes	0.4	0.2-0.7	0.01
Randomised treatment			
Tamoxifen	1.0		
Placebo	1.06	0.7-1.7	0.8

Author (s)	Study Design	Type of intervention	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Veronesi et al (1998)	Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women [Italian Tamoxifen Prevention Study] Randomised controlled trial (double-blind, placebo-controlled)	T1: Tamoxifen 20 mg per day orally for 5 years T2: placebo 20 mg per day orally for 5 years	55 participating centres: 51 in Italy; 2 in Brazil; 1 in Argentina; 1 in Greece. 96.7% participants were recruited in Italian centres.	At start: Total: 5408 (T1: 2700; T2: 2708) At end: Total: 3986 (T1: 1948; T2: 2038)	Included: healthy women aged 35-70 years who had had a total hysterectomy for reasons other than neoplasm. Women with a subtotal hysterectomy were included for a short time (91 cases (1.7%)). Excluded: women with severe concurrent illness; history of cardiac disease; endometriosis; suspected or certain previous DVT. HRT use was permitted during the trial.	Not reported by individual intervention group. No indication of comparability. For total sample: Median age: 51 years 98.3% had total hysterectomy; 26.3% had conservation of ovaries; 48.3% had bilateral oophorectomy; 18.6% had unilateral oophorectomy; 5.2% had no information. 18.2% had at least one 1st degree relative/aunt with breast cancer; 2.5% had 2 relatives; 0.3% had 3 relatives.	Median follow-up of 46 months. 1422 women dropped out of study (on own adverse event). 149 women completed 5 years of treatment.	Primary outcomes: reducti frequency and mortality ra histologically confirmed br cancer. Secondary outcomes: char cardiovascular variables; psychological assessment participants' lifestyle; asse cognitive capacity and its r to Alzheimer's disease. Logrank tests; simulation a Intention-to- treat analysis
Results								

Primary outcomes: In total, 41 cases of breast cancer occurred but differences between groups was not statistically significant (T1: 19; T2: 22 [P=0.6358]). Of the 41 cases of breast cancer, 30 used HRT (T1: 17; T2: 13 [P=0.44]). Nine women who developed breast cancer had used HRT at baseline and throughout the trial (T1: 1 out of 362 women; T2: 8 out of 390 women [P=0.0216 was no difference in the frequency of ER-positive breast cancer between the tamoxifen group (10 cases) and the placebo group (8 cases). Progesterone-receptor-positive cases were more fr although not significantly, in breast cancers occurring in the placebo group (10 cases) than in the tamoxifen group (6 cases). No deaths from breast cancer were observed in either group.

Secondary outcomes: Vascular events: in total, 56 women had 64 events of thrombophlebitis, phlebothrombosis, or embolus (or combination) (T1: 38; T2: 18 [P=0.0053]). 42 events were superficial phlebitis, with 9 women having a diagnosis of DVT (T1: 6; T2: 3). There were 14 cerebrovascular ischaemic events (T1: 9; T2: 5 [P=0.27]). Results for other secondary endpoints no reported.

Adverse events: 17 women had hypertriglyceridaemia (T1: 15; T2: 2 [P=0.0013]).

Author	Study Design	Type of intervention	Setting and location	Numbers randomised	Inclusion criteria/Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome meas Analysis
IBIS investigators (2002)	First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial *Lancet* **360**: 817-824 Double-blind placebo-controlled randomised trial	**T1**: Tamoxifen (20mg/day) **T2**: placebo	Centres in the UK, Australia, New Zealand and Europe. Recruitment carried out via family history clinics; relatives of women with breast cancer; breast screening centres; GPs; and the media.	**At start:** Total: 7139; T1: 3573; T2: 3566 **At data lock (5-year compliance estimation):** Total: 1796; T1: 837; T2: 959 **At data lock (still on treatment):** Total: 3334; T1: 1574; T2: 1760	**Included:** women aged 35-70 years; at least 2-fold RR of breast cancer for ages 45-70, 4-fold RR for ages 40-44 and approx. 10-fold RR for ages 35-39. (RRs estimated from family history of breast cancer; lobula carcinoma in situ; atypical hyperplasia; parity; benign biopsy) **Excluded:** women as above with a history of invasive cancer (except non- melanoma skin cancer), DVT or PE; currently using anticoagulants; with a life expectancy of <10 years; or who were/ intended to become pregnant.	**Mean (SD) age in yrs:** T1: 50.7 (7.0); T2: 50.8 (6.7) **Country of origin (% total sample):** UK: 60; Australia and New Zealand: 37; Europe: 3 **Postmenopausal (%):** T1: 49.3; T2: 48.8 **HRT use (%):** Before entry: T1: 41.1; T1: 40.5. During trial: T1: 40.4; T2: 39.2. Ever: T1: 51.7; T2: 50.0 **Hysterectomy (%):** All: T1: 34.5; T2: 36.0. Both ovaries retained: T1: 19.9; T2: 20.7. One ovary removed: T1: 6.4; T2: 5.8. Both ovaries removed: T1: 7.9; T2 9.2 Baseline comparability of treatment of groups not reported.	**Median follow-up:** 50 months (IQR 32-67) Women were followed up every 6 months during 5 years of active treatment; subsequently by annual questionnaire or clinical visit for up to 5 years.	**Primary outcome:** of breast cancer (inc ductal carcinoma in **Secondary outcome** frequency of other c thromboembolic eve cardiovascular event specific mortality Comparison of prop odds ratios; Fisher's values; two-sided P intention to treat an exclusion of 13 wom have breast cancer a

Results

	No. of cancers		Odds ratio (95% CI) tamoxifen vs placebo
	Placebo	Tamoxifen	
Total	101	69	0.68 (0.50-0.92)
Age (years)			
<50	39	25	0.64 (0.39-1.05)
≥50	62	44	0.70 (0.48-1.04)
HRT use			
During the trial	38	29	0.76 (0.47-1.23)
Before trial only	21	9	0.43 (0.20-0.91)
Never	42	31	0.73 (0.46-1.17)
Invasiveness			
Ductal carcinoma in situ	16	5	0.31 (0.12-0.83)
Invasive	85	64	0.75 (0.54-1.04)

Primary outcome: Total number of breast cancers was 170. Rate of breast cancers was 32% (95% CI 8-50) lower in T1 women than in T2 women (T1: 69; T2: 101; P=0.01). Reduction in risk
Tamoxifen apparent for both invasive breast cancer (64 vs 85; reduction 25%) and non- invasive breast cancer (5 vs 16; reduction 69%). Age and use of HRT did not significantly affect risk re
positive breast cancer developed in 44 T1 women compared to 63 T2 women, and ER-negative breast cancers in 19 T1 women compared to 19 T2 women. There were 4 deaths from breast c
each study group).

Secondary outcomes: Frequency of other cancers: a non-significant 2-fold excess of endometrial cancer in T1 women (11 vs 5 in T2 women; odds ratio 2.20 [95% CI 0.80-6.06)] P=0.2). No e
that endometrial cancer was linked to HRT. Cancers other than breast and endometrium equally distributed between T1 and T2 women with no significant differences in frequency of cance
between groups. Thromboembolic events: Rate of events was about 2.5 times higher in T1 women than T2 women (95% CI 1.5-4.4; P=0.001). 25 (42%) of these events occurred within 3 mon
major surgery/immobility, with 20 in the T1 group (P=0.004). Cardiovascular events: No significant differences between the groups. Cause-specific mortality: Death rate from all causes signifi
higher in T1 women than T2 women (25 vs 11; P=0.028). Increases are for cancers other than breast, pulmonary embolisms, other vascular causes and cardiac deaths.

Adverse events: Major groupings of side-effects reported in both groups were gynaecological/vasomotor; headaches/migraines; all fractures; osteoporotic fractures; breast complaints; nail
(excluding cataracts); and cataracts. Gynaecological or vasomotor side-effects were significantly higher in T1 women (81.8% vs 67.7%; P<0.0001); breast complaints were significantly lower i
than T2 women (14.7% vs 18.9%; P<0.0001; and nail changes were significantly higher in T1 women than T2 women (4.1% vs 2.7%; P=0.0001).

Author's conclusions: Tamoxifen can reduce the risk of breast cancer in healthy women by about a third, although it appears to increase the all-cause death rate. Authors suggest that Tamo
be stopped and antithrombotic measures taken during and after major surgery/immobilisation. Tamoxifen is contraindicated in women at high risk of thromboembolic disease. Overall risk t
ratio for use of Tamoxifen in prevention is still unclear.

Author (s)	Study Design	Type of intervention	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Veronesi et al (2002)	Tamoxifen for breast cancer among hysterectomised women [update of Italian Tamoxifen Prevention Study] Lancet **359**: 1122-24 Randomised controlled trial (double-blind, placebo-controlled)	**T1**: Tamoxifen 20 mg per day orally for 5 years **T2**: placebo 20 mg per day orally for 5 years	55 participating centres: 51 in Italy; 2 in Brazil; 1 in Argentina; 1 in Greece. 96.7% participants were recruited in Italian centres.	At start: **Total**: 5408 **T1**: 2700 **T2**: 2708 At end: **Total**: 3509 **T1**: 1721 **T2**: 1788	**Included**: healthy women aged 35-70 years who had had a total hysterectomy for reasons other than neoplasm. Women with a subtotal hysterectomy were included for a short time (91 cases (1.7%). **Excluded**: women with severe concurrent illness; history of cardiac disease; endometriosis; suspected or certain previous DVT. HRT use was permitted during the trial.	Not reported by individual intervention group. No indication of comparability. **For total sample**: Median age: 51 years 98.3% had total hysterectomy; 26.3% had conservation of ovaries; 48.3% had bilateral oophorectomy; 18.6% had unilateral oophorectomy; 5.2% had no information. 18.2% had at least one 1st degree relative/aunt with breast cancer; 2.5% had 2 relatives; 0.3% had 3 relatives.	Median follow-up of 81.2 (IQR 66.0-87.2) months. **T1**: 979 women withdrew from study; 1217 completed 5 years of treatment; 504 still on Tamoxifen **T2**: 920 women withdrew from study; 1245 completed 5 years of treatment; 543 still on Tamoxifen	**Primary outcomes**: reduction in fr mortality rate for histologically co breast cancer. **Secondary outcomes**: changes to cardiovascular variables; psycholo assessment of participants' lifestyl assessment of cognitive capacity a relation to Alzheimer's disease. Logrank tests; simulation analysis. treat analysis.
Results								

Primary outcomes: There was no significant difference in the incidence of breast cancer between **T1** and **T2** women: breast cancer was diagnosed in 45 (1.7%) of 2708 controls (**T2**) and in 3
2700 women on Tamoxifen
(**T1**) (P=0.215). No deaths reported in the 79 women who developed breast cancer.

HRT: Cumulative frequency of breast cancer in women who never used HRT was 1.59% (1.00-2.19) for **T1** women and 1.59% (0.99-2.18) for **T2** women (P=0.986). Frequency of breast cance
women who used HRT at some time during trial was 0.92% (0.17-1.66) in **T1** women and 2.58% (1.30-3.85) in **T2** women. Of 79 women with breast cancer, 56 (71%) had never used HRT (ec
numbers of **T1**/**T2** women). Frequency of breast cancer significantly higher in **T2** women compared to **T1** women who had used HRT at baseline/during trial (17/791 on placebo vs 6/793 on
Tamoxifen; P=0.022). Difference remained significant when analysis restricted to 11 (3%) **T2** women and 3 (1%) **T1** women who were continuous users of HRT (P=0.048). Of 2620 (49%) of 5
women who had bilateral oophorectomy, Tamoxifen did not decrease frequency of breast cancer in those who had never taken HRT (10/821 **T1** women vs 10/886 **T2** women; P=0.86).

Secondary outcomes: 15 (1%) of **T1** women and 9 (0.3%) of **T2** women had cerebrovascular events; 5 (0.2%) from each group had myocardial infarction; 7 (0.3%) **T1** and 6 (0.2%) **T2** women
vein thrombosis; 2 (0.1%) **T1** and 1 (<0.1%) **T2** women had pulmonary embolism. All-cause deaths were 10/2700 (0.4%) of **T1** women compared to 20/2708 (0.7%) **T2** women. 59 (2.2%) of
and 53 (2.0%) of **T2** women had cancer diagnosed at sites other than the breast. Further secondary endpoints not reported.

Adverse events: Not reported.

Authors' conclusions: Tamoxifen did not significantly reduce the incidence of breast cancer in women at usual/slightly reduced risk of the disease. They suggest that use of HRT increases t
breast cancer, and Tamoxifen use in women using HRT reduces the risk of breast cancer to that of non-users of HRT. Interpretation of findings should be cautious, however, as women were
randomised to HRT, and there was a significant difference in age between women who never took HRT and those who took HRT at some point (mean 51.9% vs mean 50.5; P<0.0001).

Further information: See corresponding section in extraction for Veronesi et al (1998)

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion/Exclusion criteria	Characteristics of participants	Follow-up period Analysis	M m
Fallowfield et al (2001)	Tamoxifen for the prevention of breast cancer: psychosocial impact on women participating in two randomized controlled trial Prospective cohort study	**T1**: psychological and sexual functioning in women at high familial risk of breast cancer randomised to tamoxifen (20mg daily) for at least 5 years **T2**: psychological and sexual functioning in women at high familial risk of breast cancer randomised to placebo for at least 5 years	Royal Marsden Hospital tamoxifen RCT (TAMOPLA C), London; International Breast Cancer Intervention Study (IBIS), Manchester centre	**Total:** 488 **T1**: 254 **T2**: 234	**Included:** consecutive women at high familial risk of breast cancer recruited into the TAMOPLAC and IBIS trials (416 and 72 women respectively)	**Women recruited into TAMOPLAC and IBIS trials before data merge:** age, familial risk of breast cancer, use of HRT and psychosocial characteristics reported as similar, although more TAMOPLAC than IBIS women were premenopausal (P=0.02). **Median age (years/range):** **T1**: 46 (33-66); **T2**: 46 (33-67) **Premenopausal (%)**: **T1**: 51.0; **T2**: 51.8 **Postmenopausal or hysterectomy** (%): **T1**: 49.0; **T2**: 48.2 **HRT before trial entry (%):** **T1**: 20.6; **T2**: 22.6 **Family history of breast cancer (%): Mother: T1**: 73.7; **T2**: 72.7 **Sister: T1**: 32.1; **T2**: 33.8 **Psychosocial characteristics** reported as similar between **T1** and **T2** women.	Participants sent postal questionnaires every 6 months for 5 years. 71.1% of women returned at least 8 of 10 questionnaires. 46.9% returned all questionnaires. No difference in participation between **T1** and **T2** women (OR 1.00; 95% CI 0.68-1.49). **Analysis:** intention-to- treat; nonparametric tests; univariate analyses; random effects models. Unblinding of data conducted by independent statistician.	**P o** R M C A St (S G m cl Q 3 Se pl ac **O** ac ch sy

Results
Psychological morbidity: The proportion of women who scored above GHQ-30 threshold was between 22-30% during trial. Adjusting for time on study and baseline GHQ was a marginally significant effect favouring **T1** women (OR 0.72; 95% CI 0.53-1.00). Scoring above the threshold at 6 months was not associated with treatment group (**T1** 12.9%); and scoring above the threshold repeatedly was associated with pre-trial GHQ (P<0.001) but not with treatment group. **Anxiety:** Differences between **T1** and **T2** women's anxiety scores during the trial favoured tamoxifen, but this effect of treatment was not significant when baselines anxiet taken into account (P=0.09). **Sexual activity:** Approx. three-quarters of women who completed the SAQ during the trial were sexually active and there was no effect of treatment (OR [adjusted for base activity/time on study] 1.63; 95% CI 0.86- 3.08). In those women who reported frequency of sexual activity at trial entry 'as usual', there was no association between a reduction in sexual activity during trial and tr (adjusted OR 1.04; 95% CI 0.69-1.56). 'Pleasure' from sexual activity was not associated with treatment group (P=0.09). No differences between sexually active **T1** and **T2** women in vaginal dryness and pain/dis penetration. **Symptoms:** The number of problems reported was associated with anxiety; women with trait anxiety score of <40 reported a median of 6 symptoms compared to 9 among trait anxiety score of ≥40 (P<0.001). Number of symptoms not associated with age or treatment group. **T1** women were more likely to report night sweats (P=0.005), hot fl cold sweats (P=0.009) and vaginal discharge (P=0.45); **T2** women were more likely to report low energy (P=0.009), breast sensitivity/tenderness (P=0.005) and blurring of v **HRT use:** starting HRT use during trial was not associated with treatment group (20.5% of **T1** women vs 17.7% of **T2** women). **Tablet adherence:** Self-reported tablet adherence declined over time in both groups, with a reduced adherence associated with tamoxifen (OR 0.33; 95% CI 0.19-0.57). **Authors' conclusions:** No evidence of side effects affecting women's psychosocial and sexual functioning relating to long-term use of tamoxifen. Although women on tamo more likely to report vasomotor symptoms and vaginal discharge, these problems did not seem to have a major impact on psychological/sexual well-being.

Author(s) **Study**	**Research question(s)**	**Review type** **Databases used** **Time period covered** **Data analysis**	**Inclusion/ exclusion criteria**	**Number/type of studies** **Interventions** **Follow-up period**	**Characteristics of participants: Total sample number** **Age (mean/SD/range)** **Ethnicity**	**Outcome(s)**
Cuzick et al (2003) Overview of the main outcomes in breast-cancer prevention trials	To evaluate the effect of tamoxifen or raloxifene for the prevention of breast cancer	Overview/meta-analysis Not stated Not stated Fixed-effect model; Poisson regression; random-effects model to allow for heterogeneity	Stated as 'available data'	Tamoxifen as prophylaxis: 4 RCTs. Raloxifene as prophylaxis: 1 RCT. Tamoxifen as adjuvant therapy: 1 overview. 20 mg/day tamoxifen (prevention); 20-40 mg/day tamoxifen (adjuvant therapy); 60 mg or 120 mg/daily raloxifene Tamoxifen prevention trials: at least 5 years; Tamoxifen adjuvant trials: at least 3 years (mean 5 years); raloxifene: 4 years	Total sample numbers and populations reported for individual studies (see results section) Age/age ranges not reported Ethnicity not reported	Breast cancer incidence Endometria incidence Thromboembolic events C events All-cause mortality
Results						

Characteristics of included studies:

Breast-cancer prevention trials

Trial (entry dates)	Population	Number randomised	Agents (vs placebo) and daily dose	Intended duration of
Royal Marsden[4] (1986-96)	High risk, family history	2 471	Tamoxifen 20 mg	5-8 years
	>1.6% 5-year risk	13 388	Tamoxifen 20 mg	5 years
NSABP-P1[2] (1992-97)	Normal-risk, hysterectomy	5 408		5 years
	>2-fold relative risk	7 139	Tamoxifen 20 mg	5 years
Italian[5] (1992-97)	Normal-risk, postmenopausal women with osteoporosis	7 705		4 years
IBIS-I[1] (1992-2001)	Women with mostly ER-positive operable breast cancer in nine trials	14 170	20 mg Raloxifene 60 mg or 120 mg (three study groups) Tamoxifen 20-40 mg with or without chemotherapy in both groups	3 years or longer (average 5 years)
MORE[3] (1994-99)				

ER = oestrogen receptor

Breast cancer incidence: Combined data from tamoxifen prevention trials showed a reduction in breast cancer incidence of 38% (fixed effect model: 95% CI, 28-46; P<0.000
(random effects model: 95% CI,
16-48; P=0.0007). Combined data from adjuvant tamoxifen studies showed a reduction in incidence of 46% (95% CI, 31-57; P<0.0001). Data from raloxifene trial showed a 6
in incidence (95% CI, 44-78; P<0.0001). No significant heterogeneity between tamoxifen trials (P=0.09); however, raloxifene study results differed, leading to significant ove

heterogeneity (P=0.03).

ER-negative breast cancer incidence: No reduction in incidence (hazard ratio 1.22 [95% CI, 0.89-1.67; P=0.21])

ER-positive breast cancer incidence: Reduction of 48% in incidence (95% CI, 36-58, P<0.0001).

ER status of breast cancers in the tamoxifen prevention trials and other related studies (tamoxifen vs control)

	Royal Marsden	NSABP-P1	Italian	IBIS-I	All tamoxifen prevention trials	Adjuvant (5 years tamoxifen)	MORE (raloxifene vs. Placebo)
Number randomised	1238 vs 1233	6681 vs 6707	2700 vs 2708	3573 vs 3566	14 192 vs 14 214	7085 vs 7085	2557 + 2572 vs 25
ER status **(invasive only)**							
Positive	**31 vs 44**	**41 vs 130**	**19 vs 30†**	**44 vs 63**	**135 vs 267**	**NA**	**10/2 vs 31**
Negative	**17 vs 10**	**38 vs 31**	**14 vs 12†**	**19 vs 19**	**88 vs 72**	**NA**	**9/2 vs 4**

NA = Not available; Numbers of breast cancers given for two arms of raloxifene combined, so numbers should be divided by two (/2) to be comparable. †Includes DCIS (ductal carcinoma-in-situ).

Endometrial cancer incidence: Rates were increased with tamoxifen in all prevention trials (consensus RR=2.4 [95% CI, 1.5-4.0, P=0.0005]). Also increased risk in adjuvant t (hazard ratio 3.4 [95% CI, 1.8-6.4, P=0.0002]). Most of excess risk observed in women aged 50 years or older. No increase observed in raloxifene trial.

Venous thromboembolic events: These were increased in all studies, with RR of 1.9 (95% CI, 1.4-2.6, P<0.0001) in tamoxifen prevention trials. Similar RR in women under a at entry.

All-cause mortality: Much variation across studies. No effect in tamoxifen prevention trials (hazard ratio 0.90 [95% CI, 0.70-1.17, P=0.44]), but significant heterogeneity (P=

Authors' conclusions: Tamoxifen can reduce the risk of ER-positive breast cancer, however it is not recommended as prophylaxis except in women at very high risk with a l effects.

Further information: No details provided of how included studies were identified. No quality assessment of included studies.

7.14 Risk Reducing Mastectomy for Women with no Personal History of Breast Cancer

7.14.1 Evidence statements

- Risk reducing mastectomy reduces the risk of breast cancer. (III)
- There are case reports of breast cancer in women who have had sub-cutaneous mastectomy (nipple/areola sparing), and total mastectomy. (IV)
- Total mastectomy is likely to be more effective than sub-cutaneous mastectomy (nipple/areola sparing) in reducing the incidence of breast cancer. (IV)
- Risk reducing mastectomy will not prevent the development of all breast cancers. (III)
- At risk reducing mastectomy some women are found to have cancer. (IV)
- Various observational studies report a risk reduction for breast cancer of about 90% in populations of those considered as moderate or high risk and BRCA1 or BRCA2 gene carriers. (III)
- The majority of women undergoing risk reducing mastectomy are happy with their decision. (IV)
- For many women, cancer worry decreases after risk reducing mastectomy. (IV)
- A small proportion of women express regret about their decision for bilateral risk reducing mastectomy and would not choose this option again. These women were more likely to have had the option of risk reducing mastectomy raised by a clinician rather than by themselves.. (IV)
- The effectiveness of preoperative counselling has not been formally evaluated. (IV)

7.14.2 Summary: risk reducing mastectomy research

The overall findings from 2 observational studies and 3 decision analysis studies suggest that risk reducing subcutaneous/total mastectomy has a beneficial effect in terms of significantly reducing the risk of breast cancer in women with a family history of breast cancer, or with BRCA1 and BRCA2 mutations. One of the observational studies found that risk reducing mastectomy was also associated with a reduction in breast cancer mortality in women with a family history of breast cancer.

Results from 7 studies which evaluated various psychosocial outcomes after risk reducing mastectomy, two of which had lengthy follow-up periods, show that risk reducing mastectomy is associated overall with fairly high levels of satisfaction and reduced anxiety and psychological morbidity amongst women who undergo this procedure. A number of the studies suggest that the provision of pre-surgical multidisciplinary support was likely to have had a bearing on these findings. A minority of women, however, do express regrets and experience adverse psychosocial events following their surgery.

There is no clear evidence on the optimal surgical technique for risk reducing mastectomy.

7.14.3 Studies

Bilateral mastectomy may be used as a risk reducing measure in women at increased risk of breast cancer due to their family history. The aim of surgery is to remove the majority of the 'at risk' breast tissue with a corresponding reduction in breast cancer risk. This type of major intervention is one that will need considerable discussion and the women concerned may need time to consider this in detail to allow them to reach an informed decision that they are comfortable with.

Risk reducing mastectomy studies (effectiveness)

Meijers-Heijboer et al (2001)
The incidence of breast cancer after a mean follow-up of 3 years was compared in a Dutch prospective cohort study involving 76 women with BRCA1 or BRCA2 mutations who had undergone bilateral risk reducing mastectomy (total simple, including nipple), and a control group of 63 women with BRCA1 or BRCA2 mutations who underwent surveillance.

No cases of invasive breast cancer were observed in the women who had undergone risk reducing bilateral mastectomy whereas in the surveillance group, 8 invasive breast cancers were detected. Proportional hazards analysis showed that risk reducing mastectomy significantly (P=0.003) reduced the incidence of breast cancer (hazard ratio = 0.95% confidence interval, 0-0.36), although the length of follow-up is short. The authors do not report on postoperative complications.

Hartmann et al (1999)
This retrospective US cohort study studied the incidence of, and risk of death from, breast cancer after a median follow-up of 14 years among 639 women who had a family history of breast cancer and who had undergone bilateral subcutaneous or total risk reducing mastectomy. In the mastectomy group, women were divided into high (n=214) or moderate risk (n=425) subgroups, with most women in each subgroup having undergone subcutaneous mastectomy (89% and 90%, respectively). In the high risk group, the expected number of cases of breast cancer was determined, with 403 sisters of the high risk women used as controls to calculate the expected age-specific breast cancer rate. The Gail model was used to predict the expected incidence of breast cancer in the moderate risk women.

Study results show a reduction in the risk of breast cancer of 89.5% (P<0.001) in moderate risk women who had undergone risk reducing mastectomy, and in the high risk women, a reduction in risk of between 90-94%. All 7 breast cancers in the moderate and high risk groups developed in women who had undergone bilateral subcutaneous mastectomy, although the study was not sufficiently powered to detect a difference between this technique and total mastectomy. Postoperative complications were not reported. The incidence of death from breast cancer was nil in moderate risk women who had undergone risk reducing mastectomy, giving a risk reduction of 100% (95% confidence interval; 70-100). The number of deaths from breast cancer in the high risk women who had undergone risk reducing mastectomy was 2, giving a risk reduction of between 81-94%.

Other identified studies of relevance (extraction tables not provided)

Two US studies and 1 Dutch study were identified which used decision analysis to estimate, respectively: the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 or BRCA2 mutations (Schrag et al (1997); the effect of risk reducing oophorectomy and mastectomy in terms of survival, quality of life and cost-effectiveness in women with BRCA1 and

BRCA2 women (Grann et al (1998); and the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 mutations (van Roosmalen et al (2002). All 3 studies estimate life expectancy gains as a result of both types of risk reducing surgery in BRCA1 and/or BRCA2 women. However, as the findings of these studies are based on modelling techniques, the cohort studies summarised above will take precedence in terms of providing more robust evidence.

Hartmann et al (2001) carried out blood sample analyses on 176 of the 214 high-risk women who participated in their earlier US retrospective cohort study of bilateral risk reducing subtotal and total mastectomy. They analysed blood specimens to identify women with BRCA1 and BRCA2 mutations in order to estimate the carriers' probabilities of developing breast cancer. Results identified 26 women with alterations in BRCA1 and BRCA2, of whom none had developed breast cancer after a median of 13.4 years of follow-up. The authors conclude that risk reducing mastectomy is associated with a substantial reduction in incidence of subsequent breast cancer not only in women identified as having a high risk based on family history of breast cancer, but also in known BRCA1 and BRCA2 mutation carriers.

Pennisi et al (1989) published a statistical analysis of US registry data for 1500 women at high risk of breast cancer who had undergone risk reducing subcutaneous mastectomy. Their analysis found that of the 1500 women, 6 (0.4%) developed breast cancer, although 30% of women were lost to follow up over a mean period of 9 years. They conclude that risk reducing subcutaneous mastectomy is effective in reducing the incidence of breast cancer in high risk women. However, these results reflect a statistical data analysis only.

Risk reducing mastectomy studies (psychosocial outcomes)

Bebbington Hatcher & Fallowfield (2003)
This paper presents the results of qualitative interviews with sixty women who opted for bilateral risk reducing mastectomy and twenty who declined. The women had been referred to centres because of a family history. Those who underwent surgery interviewed pre-operatively and then at 6 and 18 months post-operatively. Those who did not undergo the surgery had an initial interview and then another interview 18 months later. Findings from the interviews were discussed in terms of anxiety; surgery; reconstruction; sexual impact; information; gene testing; support. In these categories there were both positive and negative experiences described by those interviewed. In terms of conclusions the authors argued that there was a clear need for information written specifically for this group of women. They also argued that many of the women needed emotional support. The interviews discussed

Bebbington Hatcher et al (2001)
The authors compared psychological and sexual morbidity in 2 cohorts of UK women (total number 154) with a family history of breast cancer who either chose or declined bilateral risk reducing mastectomy, with psychosocial questionnaires administered preoperatively and at 6 and 18 months. The authors do not report on surgical status (whether subcutaneous or total mastectomy was carried out), although 81% of women received implants. Results showed that women who underwent risk reducing mastectomy showed a reduction in psychological morbidity from baseline to 6 and 18 months ($P<0.001$), whereas in women who declined risk reducing surgery, no comparably significant reduction was observed ($P=0.11$). Similarly, a reduction in anxiety from baseline to 18 months was observed in women who chose risk reducing mastectomy ($P=0.001$), compared to no significant reduction in anxiety over time in women who declined risk reducing surgery ($P=1.00$). Findings also showed that risk reducing mastectomy did not have a detrimental impact on body image or sexual functioning, with no differences in the median score of 4.0 (range 0-

30) and no change over time (median change 0, 95% CI, 0-1; P=0.84). However, the authors reported differences between the 2 groups in terms of coping strategies and risk perceptions, notably that women who choose surgery have a higher perception of their breast cancer risk. The authors do not measure the effect of presurgical counselling on psychological morbidity.

Frost et al (2000)

In this questionnaire survey based on Hartmann et al's study (Hartmann et al 1999), the authors evaluated satisfaction and psychosocial function in 572 US women with a family history of breast cancer who had undergone bilateral risk reducing mastectomy, with a mean follow-up of 14.5 years. Most women (89%) had undergone subcutaneous mastectomy with reconstruction. Findings showed that 70% of women reported that they were either satisfied or very satisfied with their risk reducing mastectomy; 74% reported a reduction in emotional concern about developing breast cancer; and 67% stated that they would be likely to choose a risk reducing mastectomy again. Levels of satisfaction were not influenced by age, length of time since surgery, whether women were in the high or moderate risk group, or whether surgery had involved a simple or subcutaneous mastectomy. For some women, however, risk reducing mastectomy was associated with adverse psychosocial effects: 36% reported diminished or greatly diminished satisfaction with their body appearance; and adverse effects were reported in terms of emotional stability (9%), stress (14%), self-esteem (18%), sexual relationships (23%) and feelings of femininity (25%). 18% of women said that they would be unlikely to undergo risk reducing mastectomy if they had the choice again. The authors do not report whether women received counselling prior to surgery.

Hopwood et al (2000)

Postoperative mental health and body image concerns were evaluated in 52 UK women with $\geq$1:4 lifetime risk of breast cancer who, following multidisciplinary counselling within a strict confidential protocol, had undergone risk-reducing mastectomy with a mean follow-up of 11 months. Most women underwent risk reducing mastectomy and reconstruction using a tissue expansion technique and implants. Data collected from questionnaires and interviews showed that most women experienced only minor changes in body image and low levels of psychological distress, and both appeared stable over time. Mean scores were fairly similar for women who underwent risk reducing mastectomy with reconstruction compared to those who had no reconstruction. The authors note, however, that some women (7 of 45 interviewed) required further psychiatric support; these women were more likely to have had surgical complications.

Josephson et al (2000)

Satisfaction with bilateral risk reducing mastectomy (simple, including nipple) and immediate breast reconstruction (IBR) was evaluated in 15 Swedish women with an average lifetime risk of breast/ovarian cancer of >20%. All the women received genetic and surgical counselling, but no psychological evaluation or support. Data from semi-structured interviews which mostly took place at least 1 year post-surgery showed that none of the women regretted having risk reducing mastectomy, with the major benefit perceived as risk reduction. Most women thought that the cosmetic results were better than expected. 'Unexpected' findings included the emotional consideration of loss of breasts and the need to 'mourn'; how breasts would be changed by surgery; and the importance of support from, and for, partners and family. The authors conclude that risk reducing mastectomy and IBR are well-accepted interventions with good cosmetic results. However, in this respect multidisciplinary team support, including psychological input, is mandatory for women undergoing risk reducing mastectomy.

Lloyd et al (2000)

Ten UK women with a family history of breast cancer who had undergone risk reducing mastectomy, and their partners, took part in a qualitative research study (semi-structured interviews) between 6 weeks and 3 years post-surgery. Of the 10 women, two were confirmed as gene carriers (BRCA1/BRCA2), with 4 having living 1st-degree female relatives with breast cancer; 9 women had undergone breast reconstruction, although type of surgical technique (subcutaneous or total mastectomy) was not reported. Data analysis revealed past suffering and multiple loss due to the family history of breast cancer as being central to women's decision making. Their partners' key experience was one of 'riding it through'. The authors found that attitudes towards risk reducing mastectomy were largely favourable, probably due to the pre-surgical psychological consultations. They suggest that: discussion/preparation with a multidisciplinary team of health professionals may be a prerequisite; support groups should be available; and that risk reducing mastectomy is best offered by specialist services.

Borgen et al (1998)

In this questionnaire survey, 370 US women who had undergone bilateral risk reducing mastectomy with a mean follow-up of 15 years were asked to report their satisfaction with their surgery. A family history of breast cancer (defined as at least one 1st-degree relative diagnosed with breast cancer) was reported by 59% of women. 75% of women had undergone reconstructive surgery, although type of surgery (subcutaneous or total) was not reported by the authors. 95% of women reported no regrets with their decision to have risk reducing surgery. Twenty one women (5%), however, reported regrets, 10 of whom had major regrets. Regrets were reported in 7.5% (19/255) women where the risk reducing mastectomy decision was initiated by their physician, compared with 2% (2/108) women where the decision was initiated by themselves ($P<0.05$). No significant differences were found in the level of regret between women who had preoperative psychological counselling, or who had a family history of breast cancer, and those who did not. The majority of women (84%) reported cosmetic results of their risk reducing mastectomy, regardless of reconstructive status, as excellent or acceptable, although 16% of women found their cosmetic results to be unacceptable. Three women were diagnosed with breast cancer post-bilateral risk reducing mastectomy (surgical technique not reported). The authors conclude that overall satisfaction with risk reducing mastectomy is high; that the most important factor that predicts an unfavourable outcome following risk reducing mastectomy is a physician-initiated discussion; and that bilateral risk reducing mastectomy does not provide 100% guarantee against development of breast cancer.

Stefanek et al (1995)

One objective of this study was to examine satisfaction with bilateral risk reducing mastectomy (surgical technique not specified), with or without breast reconstruction, among 14 US women with at least one 1st-degree relative diagnosed with breast cancer who underwent risk reducing surgery after counselling. Data from a questionnaire which was mailed to women a mean of 9 months post-surgery found that satisfaction with risk reducing mastectomy was very acceptable, with all 14 women reporting being 'quite a bit' or 'very much' satisfied with the decision to undergo surgery. The majority of women who underwent reconstruction (n=11) also reported similar satisfaction levels, although 3 women who had silicone implants reported cosmetic results as 'worse than expected'. The authors note, however, that the sample was small; and that women reported strong family and friend support, and had undergone risk counselling pre-surgery, without which the high degree of satisfaction with risk reducing mastectomy may not have been found.

Effectiveness of surgical techniques in risk reducing mastectomy

No evidence has been identified which compares the effectiveness of total versus subcutaneous risk reducing mastectomy in terms of reducing the incidence of breast cancer.

Case reports in the literature show that neither total nor subcutaneous risk reducing mastectomy are 100% effective in preventing breast cancer (Goodnight et al, 1984; Eldar et al, 1984; Ziegler et al, 1991; Willemsen et al, 1998).

In a case series of women with a family history of breast cancer or a BRCA1/BRCA2 mutation who underwent total risk reducing mastectomy (including nipple/areolar complex), there was no evidence of disease after a median follow-up of 2.5 years (range 1-5.9 years) in 79 women with no previous history of breast cancer, ovarian cancer or ductal carcinoma in situ, (Contant et al, 2002).

7.14.4 Evidence Tables

Table 7.10

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participan	Inclusion criteria/ Exclusion	Characteristics of participants	Follow-up period	Main outcome measures

Hartmann et al (1999)	Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer Retrospective cohort study (with some modelling)	**Subjects (C1)**: bilateral prophylactic mastectomy **Controls (C2)**: no bilateral prophylactic mastectomy	Mayo Clinic, Rochester, USA	**Total C1**: 639 (**C1** (high risk): 214; **C1** (moderate risk): 425) **C2**: 403 (controls for **C1** (high risk) group only) (**Risk definitions: C1 high risk:** 1 or more relatives with breast cancer; early age of breast cancer diagnosis; family history of ovarian/bilateral breast cancer or breast cancer in males; **C1 moderate risk:** all others who did not meet CI high risk criteria.)	**Included (C1):** all women with a family history of breast cancer who had bilateral subcutaneous, or bilateral total, mastectomy between Jan 1, 1960 and Dec 31, 1993. **Included (C2):** all biological sisters of **C1** (high risk) subjects who had not undergone bilateral prophylactic mastectomy.	**Median age at mastectomy (yr): C1** (high risk): 42; **C1** (moderate risk): 42 **Median age at menarche (yr): C1** (high risk): 13; **C1** (moderate risk): 13 **Nulliparous (%): C1** (high risk): 13; **C1** (moderate risk): 12 **Age at 1st live birth (yr): C1** (high risk): 21; **C1** (moderate risk): 21 **Subcutaneous mastectomy (%): C1** (high risk): 89; **C1** (moderate risk): 90 **Total mastectomy (%): C1** (high risk): 11; **C1** (moderate risk): 10 Characteristics of **C2** women not reported.	**Median follow- up**: 14 years, with a minimum of 2 years follow-up for 99% of the cohort Complete questionnaire and chart information available for 93% of women. Medical record information available for all women.	**Primary outcomes:** incidence of breast cancer; risk of death from breast cancer Gail model to predict expected incidence of breast cancer in **C1** (moderate risk) women. Weinberg's method (segregation analysis) to correct for multiple ascertainment in **C1** (high-risk) women.
Results								

Primary outcome: incidence of breast cancer

C1 (moderate risk) women: Predicted incidence (Gail model) among the 425 **C1** (moderate risk) women, with a median follow-up of 14 years, was 37.4. Actual incidence was 4. Reduction in risk of breast cancer was
89.5% (P<0.001) after bilateral prophylactic mastectomy in women with a moderate risk of breast cancer.

C1 (high risk) women: Numbers of breast cancers among the 214 **C1** (high risk) women were compared with the numbers among their 403 sisters who had not undergone prophylactic mastectomy. 156 (38.7%) of **C2** women had breast cancer at the end of follow-up: 115 cases were diagnosed before the respective **C1** (high risk) woman's prophylactic mastectomy, 38 were diagnosed afterwards, and the time of the diagnosis was unknown in 3 cases. Breast cancer was diagnosed in 1.4% (3 of 214) of the **C1** (high risk) women. Prophylactic mastectomy was associated with a reduction in risk of breast cancer of 90-94% (depending on method used to calculate expected rates).

All 7 breast cancers from C1 moderate/high risk groups developed in women who had undergone bilateral subcutaneous mastectomy. However the study was not sufficiently powered to detect a difference between this technique and total mastectomy. Postoperative complications are not reported.

Primary outcome: deaths from breast cancer

C1 (moderate risk) women: Predicted incidence of death was 10.4. The actual number was 0. Reduction in risk of death was 100% (95% confidence interval, 70-100).

C1 (high risk) women: Actual number of deaths was 2. Reduction in risk of death from breast cancer (depending on method used to calculate expected rates) was 81-94%.

Events in sisters used to calculate rate	**Person-years of follow-up**		**Breast cancer**		**Reduction in Risk (95% CI)**
	Sisters	Probands	No. Expected	No. Observed	
					percent
All breast cancers (before and after prophylactic mastectomy) from age 18 to end of follow-up					
Unadjusted	13,336	2964	52.9	3	94.3 (83.5-98.8)
Adjusted	12,710	2964	30.0	3	90.0 (70.8-97.9)
Breast cancer after prophylactic mastectomy to end of follow-up	3,109	2964	37.4	3	92.0 (76.6-98.3)

*The expected incidence of breast cancer was calculated on the basis of a number of factors analyzed in the control group consisting of sisters of the probands. CI denotes confidence interval.
=The method of adjustment for ascertainment bias is described in the Methods section

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Meijers-Heijboer et al (2001)	Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation Prospective cohort study	**Subjects (C1):** Prophylactic bilateral mastectomy (simple total, including nipple) **Controls (C2):** Surveillance (monthly breast self-examination; clinical breast examination every 6 months; yearly mammography; optional MRI; ultrasonography with/without fine-needle aspiration when indicated.	Daniel den Hoed Cancer Center, Rotterdam, The Netherlands	**Total**: 139 (**C1**: 76; **C2**: 63)	**Included**: all women given a molecular diagnosis of BRCA1 or BRCA2 mutation between Jan 1, 1992 and Jan 1, 2000, with no history of breast cancer.	**Mean age at entry**: **C1**: 37.7 ±7.7; **C2**: 39.5 ±11.5 (P=0.42) **Premenopausal oophorectomy**: **C1**: 58%; **C2**: 38% (P=0.03) **BRCA1 mutation**: **C1**: 84%; **C2**: 89%. **BRCA2 mutation**: **C1**: 16%; **C2**: 11% (P=0.42) Groups comparable except for numbers who had undergone premenopausal oophorectomy.	**Mean follow- up**: **C1**: 2.9 +1.4 years; **C2**: 3.0 +1.5 years No **C1** women were lost to follow-up. Of **C2** women, 3 died of ovarian cancer and 2 were monitored at another hospital.	**Primary outcome**: incidence of breast cancer Cox proportional-hazards model
Results								

Primary outcome:

There were no cases of invasive breast cancer observed in women who had undergone mastectomy (**C1)**; in the surveillance group (**C2)**, 8 invasive breast cancers were detected.

The actuarial mean 5-year incidence of breast cancer among all women in the surveillance group (**C2**) was 17±7%. On the basis of an exponential model, the yearly incidence of breast cancer in this group was 2.5%. The observed number of breast cancers in **C2** women was consistent with the expected number (ratio of observed to expected cases, 1.2; 95% confidence interval, 0.4-3.7, P=0.80). All affected women were from different families.

Cox proportional-hazards analysis showed that mastectomy significantly (P=0.003) reduced the incidence of breast cancer (hazard ratio, 0; 95% confidence interval, 0-0.36). After adjustment for the change in menopausal status, the protective effect of mastectomy remained statistically significant (P=0.01).

Further information:

The authors note that the results should be interpreted cautiously due to the length of follow-up. Postoperative complications are not reported.

Author (s)	Study Design	Objectives	Setting and location	Number of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Survey methods	Main outcome measures
Stefanek et al (1995)	Predictors of and satisfaction with bilateral prophylactic mastectomy Questionnaire survey	1.To examine satisfaction with PM and breast reconstruction among women who chose prophylactic mastectomy (PM) (2.To examine factors related to decision-making about PM among women attending high-risk breast cancer clinic who chose PM compared with women who chose surveillance without surgery **[findings not reported here]**)	Breast Surveillance Services, Johns Hopkins Oncology Centre, Baltimore, Maryland, US	14	**Included:** women with at least 1 first-degree relative diagnosed with breast cancer who underwent bilateral PM following counselling between Jan 1988 and Nov 1992.	**Mean age, years (SD, range):** 37.1 (8.1, 23-47) **Mean no. affected 1st-degree relatives (SD, range):** 1.4 (0.8, 1-3) **History of biopsies:** 7 women **Time to surgery following clinic visit:** mean 5.7 months (range 1-14 months) **Type of reconstruction (no.):** silicone: 6; saline: 3; abdominal flap: 2; none: 3 **Type of surgical technique (subcutaneous/total):** not reported	**Data collection:** Mailed questionnaire (x1) min. 6 months post-surgery (mean 9.4 months; SD=6.8 months; range 6-30 months) **Sampling:** Method not reported. Eligible women: 14 (100% response rate) **Analysis:** statistical analyses applied to study objective 1. only	Breast cancer worry Satisfaction with time needed to recover from surgery emotionally and physically Degree of discomfort after surgery, including expectation of discomfort Satisfaction with support given relating to PM decision Overall satisfaction with PM decision Whether women would recommend PM Satisfaction with reconstruction
Results								

Breast cancer worry: 12 of 14 women reported worry to be at least a 'moderate' problem.

Satisfaction with time needed to recover from PM: *Physically:* overall satisfaction was high (n=11 'quite a bit' or 'very much'; n=3 'somewhat' or 'a little'). *Emotionally:* satisfaction also quite high (n=13 'quite a bit' or 'very much'; n=1 'somewhat').

Discomfort after surgery: reported as high (n=7 'quite a bit' or 'very much'); 2 women reported discomfort as 'more than expected'.

Satisfaction with support given relating to PM decision: satisfaction reported as high ('quite a bit satisfied' or 'very much satisfied') from husband/partner (13 of 13), family (13 of 14) and friends (12 of 14).

Overall satisfaction with PM decision: 100% (n=14) reported satisfaction ('quite a bit' or 'very much').

Whether women would recommend PM: 12 of 14 women would recommend PM to other women at comparable risk.

Satisfaction with reconstruction: 7 of 11 women reported being 'quite a bit' or 'very much' satisfied; 3 were dissatisfied, reporting cosmetic results 'worse than expected' (all 3 had silicone implants).

Authors' conclusions: Satisfaction with PM was very acceptable in sample of women who reported strong family and friend support, and following formal risk counselling. Satisfaction with breast reconstruction was generally favourable, but less consistent than satisfaction with PM itself. Authors note that the sample was small; that the high degree of satisfaction may/may not be found without same degree of support and the counselling intervention.

Author (s)	Study Design	Objectives	Setting and location	Number of participants	Inclusionxclusion criteria	Characteristics of participants	Survey methods	Main outcome measures
Borgen et al (1998)	Patient regrets after bilateral prophylactic mastectomy Questionnaire survey	To evaluate the effects of bilateral prophylactic mastectomy (PM) on health outcomes (including satisfaction with surgery)	Recruitment from 43 US states via the media for entry to National Prophylactic Mastectomy Registry	370 women	**Included:** women who had undergone bilateral PM. **Excluded:** women as above who reported a previous biopsy with diagnosis of lobular carcinoma in situ.	**Mean age at PM, years (median; range):** 45.5 (46; 25-73) **Mean no. years follow-up (median; range):** 14.8 (14.6; 0.2-51.5) **Ethnicity:** 96% Caucasian **Previous breast biopsy:** 83% had at least 1 benign breast biopsy prior to PM **Breast reconstruction:** 75% of women **Type of surgery (subcutaneous/total):** not reported **Family history of breast cancer (%):** at least one 1st-degree relative: 59%; BRCA1 testing: 3% (none were positive)	**Data collection:** mailed questionnaire (x1) **Sampling:** convenience via volunteer participation **Analysis:** chi-square statistics	Specific outcome measures used on questionnaire not reported. Validation of questionnaire items or piloting not reported.

Results

Satisfaction after bilateral PM: 21 (5%) of women (mean age 45 years, range 29-59) reported that they regretted their decision to undergo PM, with 349 (95%) (mean age 45 years, range 25-73) reporting no regrets. Of women with regrets, 10 had major regrets (would not be likely to undergo PM today if faced with the choice); and 7 had minor regrets (4 did not report level of regret). Regrets reported in 7.5% (19/255) women where PM decision was initiated by physician, compared with 2% (2/108) women where PM decision initiated by themselves (P<0.05). No significant difference found in level of regret between women who had preoperative psychological counselling, or a family history of breast cancer, and those who did not (P values not reported). Of those women with regrets, 3% (3/88) were 40 years or younger at time of surgery, compared with 7% (18/227) who were over 40 (no significant difference; P value not given).

Satisfaction with cosmetic results (regardless of reconstruction status): Of 331 women who responded, cosmetic results reported as excellent in 116 (35%), acceptable in 163 (49%) and

unacceptable in 52 (16%) of women.

Follow-up: 3 women were diagnosed with breast cancer at 5, 20 and 23 years post-bilateral PM (surgical technique not reported).

Authors' conclusions: Overall satisfaction with bilateral PM was 95%, although this may have been explained by the voluntary nature of the registry. The most important factor that predicts an unfavourable outcome following bilateral PM is a physician-initiated discussion. Bilateral PM does not provide 100% guarantee against development of breast cancer.

Further information: Outcomes in terms of surgical technique and reconstructive status are not reported

Author (s)	Study Design	Objectives	Setting and location	Number of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Survey methods	Main outcome measures
Frost et al (2000)	Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy Questionnaire survey	To evaluate patients' long-term satisfaction and psychological and social function following prophylactic mastectomy (PM)	Tertiary health care clinic (Mayo Clinic, Rochester, US)	572	**Included:** all cancer-free women with a family history of breast cancer who had bilateral PM between 1960 and 1993. (Further details of inclusion/exclusion criteria previously reported in Hartmann et al (1999))	**Mean age (yrs)**: 57 **Mean age (yrs) at PM**: 42 **Married:** 81% **Family risk:** moderate: 65%; high: 35% **Follow-up after PM** (mean yrs): 14.5 **Type of PM:** subcutaneous with reconstruction: 89%; subcutaneous without reconstruction: 2%; simple with reconstruction: 6%; simple without reconstruction: 3% **Reconstruction – implants:** 100%	**Data collection:** Mailed questionnaire x1 **Sampling:** 572/609 women (94% response rate). Eligible women initially invited to participate: 639 **Analysis:** Descriptive statistics; multiple linear regression	Reasons for choosing PM Psychological and social consequences of PM Satisfaction with PM Choice to have PM again (Study-specific questionnaire used. Question clarity/face validity assessed by pane of experts. Questionnair pilot tested favourably w sample of women who ha had PM)

Results

Relationships identified as Those Most Strongly Associated With Increased Satisfaction			
Variable	r	ß	P
Increased satisfaction with appearance	0.49	.56	<.001
Lower level of stress in life	0.27	.18	<.001
Fewer problems with implants	0.16	.13	.003
No reconstruction	0.13	.16	.001
No change or improved sexual relationships	0.32	.14	.004
Family history of cancer as a reason for electing procedure	0.08	.12	.02
Decreased emotional concern about developing breast cancer	0.22	.09	.05

Reasons for choosing PM: Family history was most common reason cited for PM. Reasons for PM were comparable between moderate risk women and high risk women, except for: 1. more high risk women than moderate risk women cited family history of breast cancer as major reason (93% vs 60%, respectively; P=0.001); and 2. more moderate risk women than high risk women reported nodular breasts as a reason (88% vs 78%, respectively; P=0.002).

Psychological and social consequences of PM: 74% of women reported a reduction in emotional concern about developing breast cancer. Majority of women reported no change/favourable effects in level of emotional stability (68%/23%), level of stress (58%/28%), self-esteem (69%/13%), sexual relationships (73%/4%), feelings of femininity (67%/8%), and satisfaction with appearance (48%/16%). Responses to psychological/social variables not significantly associated with age at PM, length of follow-up, family history of moderate vs high risk for breast cancer, or whether mastectomy was simple or subcutaneous.

For some women, PM was associated with adverse psychological/social effects: 36% of women reported diminished/greatly diminished satisfaction with their body appearance after PM. Also adverse effects reported in level of emotional stability (9%), level of stress (14%), self- esteem (18%), sexual relationships (23%) and feelings of femininity (25%). 3 women reported adverse effects on every psychological/social variable.

Satisfaction with PM: 70% of women were either satisfied or very satisfied with their PM, with 19% being dissatisfied or very dissatisfied. **Choice to have PM again:** 67% of women reported that they definitely or probably would have PM again, with 18% reporting that they definitely or probably would not. Level of satisfaction not influenced by age, length of time since procedure, whether in high or moderate risk group, or whether the woman had a simple or subcutaneous mastectomy (after controlling for whether woman had had reconstruction).

Authors' conclusions: The majority of women reported satisfaction, reduction in level of emotional concern about developing breast cancer, and that they would be likely to choose PM again. Also, the majority of women reported favourable effects or no change in self-esteem, satisfaction with body appearance, feelings of femininity, sexual relationships, level of stress in life and overall emotional stability. The authors note, however, that some women were dissatisfied or gave a neutral response in terms of satisfaction with PM.

Appendix 9 (contd): Risk reducing mastectomy

Author (s)	Study Design	Objectives	Setting and location	Number of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Survey methods	Main outcome measures

Hopwood et al (2000)	Clinical follow-up after bilateral risk reducing (prophylactic') mastectomy: mental health and body image outcomes Questionnaire survey/qualitative interviews	To evaluate post-operative mental health and body image concerns in a cohort of patients who had had risk-reducing mastectomy (RRM)	Breast cancer Family History Clinic (FHC), Manchester, UK	Questionnaire data available for total of 52 women Interviews: 45 women	**Included (questionnaires)**: women with ≥1:4 lifetime risk of breast cancer who had RRM* between 1995 and 1999, following counselling. **Included (interviews):** women as above who scored above 10 on General Health Questionnaire or above 10 on the Body Image Scale, or any other women wanting to discuss psychological concerns. * Bilateral subcutaneous mastectomy with immediate implants or tissue expansion; bilateral simple mastectomy with or without reconstruction (flaps/ implants); contralateral RRM and bilateral reconstruction (for patients with prior breast cancer surgery)	**Mean age range:** Total women (n=52); 40.8 years (27-58 years. **Mean/median time from surgery to 1st follow-up:** 10.58/10 months **Type of surgery:** RRM with no breast reconstruction: 4 women; majority of other women had tissue expansion/implant procedure; 6% of women had more extensive flap reconstruction. **Marital status:** Majority of women reported as married/cohabiting	**Data collection:** Questionnaires (x1-3). 49 completed 1 questionnaire; 19 completed 2; and 9 completed 3. Compliance with questionnaire return was 69-90% over 6 clinics. Qualitative interviews. **Sampling:** Consecutive sampling. Eligible women = 76 when completed surgery **Analysis:** Descriptive statistics (means, medians, range of scores, standard deviations). No formal statistical testing due to small numbers.	**Questionnaires:** **Mental health** (28-item General Health Questionnaire (GHQ)). Summary score range from 0-28; scores above 9 suggest probable 'case' levels of distress) **Body image** (Body Image Scale (BIS)). Summary score range 0-30; higher scores denote increased negative change/ dissatisfaction with body image) **Interviews:** Experience of surgery; postoperative/current mental, physical, sexual and emotional functions; relationship with partner
Results								

Self-reported body image changes and mental health at year 1									
Subgroup	BIS					GHQ			
(n)	mean	S.D.	med	min	max	mean	S.D.	med	min
All patients (*n* = 49)	5.1	5.5	4.0	0	26	3.8	6.7	0.0	0
26									
Reconstructed (*n* = 45)	5.1	5.1	4.0	0	26	3.9	6.9	0.0	0
25									
Not reconstructed (*n* = 4)	5.3	9.8	0.5	0	20	2.0*	4.0*	0.0*	0
8*									

* Data missing for two women.

Questionnaires:

Mental health: 8 (17%) of women scored in the probably 'caseness' range (ie above 9 = probably distress). Comparison of mental health for the reconstructed vs non-reconstructed groups showed similar mean scores (3.9 vs 2.0).
Change over time: Of 19 women who had 1 and 2 year assessments, there was no significant change over time in scores: proportion of probably 'cases' was 11.1% and 15.5% respectively. Of 9 women who completed assessments for 1, 2 and 3 years, scores show little change over time and all mean scores are low.

Body image: Overall BIS mean (SD) and median scores for 1st assessment were 5.1 (5.5) and 4.0, range 0-26. At 1st assessment, 21% women reported no change (0 summary score) since their operation and two-thirds of women reported changes of minor degree (item scores 0 or 1 only). Comparison of scores for reconstructed group vs non-reconstructed group showed slightly higher scores (ie more negative body image changes) in women who did not undergo breast reconstruction. Body image items reported most frequently: decreased sexual attractiveness (55.1%); reduced physical attractiveness (53.1%); self-consciousness about appearance (53.1%); decreased satisfaction with body (46.9%); feeling less feminine (34.7%).

Interviews:

Reasons for high scores on BIS and/or GHQ included: surgical complications; difficulty accepting breast loss; psychosomatic symptoms relating to implants; avoidance behaviour relating to reconstructed breasts. 7/45 women interviewed required further psychiatric support; 3 of these required antidepressants.

Authors' conclusions: The majority of women experience only minor changes in body image and low levels of psychological distress from RRM, and both appear stable over time. Some

women who experience complications, however, need additional psychological support. Authors note the following limitations of the study: not a systematic research evaluation; information missing for some women; baseline questionnaire data not routinely collected; not all patients attended annual review; not all women were interviewed.

Author (s)	Objectives Design	Setting and location	Number of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Research methods	Findings/themes
Lloyd et al (2000)	To provide understanding of personal experiences of women who had undergone prophylactic mastectomy (PM) and their partners in terms of psychological adjustment Qualitative research design (semi-structured interviews)	Recruitment via a cancer hospital, UK. Most interviews took place in participants' homes. 2 preferred different location (at hospital and researcher's home)	10 women 8 husbands/ partners	**Included:** women who had had PM due to family history of breast cancer; were between 6 weeks-3 years post-surgery; had no previous diagnosis of cancer or ductal/lobular carcinoma in situ; were 18 years or over; had no mental illness; English speaking. Also included: women's husbands/partners	**Women: Mean age, years (range):** 40 (31-51) **Family history:** 2 were gene carriers (BRCA1/BRCA2); 4 had living 1st-degree female relative with breast cancer **Reconstructive surgery (no.):** 9; **Surgical technique:** not reported **Married/cohabiting (no.)**: 10 **Husbands/partners: Mean age, years (range):** 43 (33-56)	**Data collection:** Taped semi-structured interviews **Sampling:** Purposive/ theoretical **Analysis:** Grounded theory. Verbatim transcriptions; open/axial coding; constant comparison; triangulation	**Women's key experiences:** Deciding; telling; experiencing surgery and recovering; maintaining womanliness; processing the loss; moving on; isolation and being supported. Core category integrating themes was 'of suffering and countering multiple loss'. **Partners' key experience:** 'Riding it through'
Authors' interpretation: Attitudes towards prophylactic surgery were largely favourable, probably due to pre-surgical psychological consultations; discussion/preparation with multidisciplinary health professionals may thus be a prerequisite. Service provision should include formal/informal support groups. In view of small numbers of women undergoing PM, this type of surgery is best offered by specialist services.							

Author (s)	Objectives Design	Setting and location	Number of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Research methods	Findings/themes
Josephson et al (2000)	Women's satisfaction with bilateral PM and immediate breast reconstruction (IBR). (Women's experience with decision-making process prior to PM and IBR **[findings not reported here]**) Qualitative research design (semi-structured interviews)	Recruitment via Departments of General Surgery and Reconstructive Plastic Surgery, Karolinska Hospital, Stockholm, Sweden. Interviews took place in hospital.	15 women	**Included:** women with expected average lifetime risk of developing breast/ ovarian cancer of more than 20% referred between 1993-1997 who underwent bilateral PM (simple, including nipple)/IBR. **Excluded:** women as above who had breast cancer diagnosed at time of surgery; who had PM but not IBR.	**Mean age, years (range):** 39.8 (29-50) **Previous psychotherapy (no.):** 8; **Current psychotherapy (no.):** 1 **Marital status (no.):** Married/in permanent relationship: 13; Divorced: 2 **Employment status (no.):** In employment: 14; Student: 1 **Counselling:** all had received genetic/surgical, but not psychological, counselling	Data collection: **Taped semi-structured interviews, most at least 1 year post-surgery. Iterative approach.** **Sampling:** not described. **Analysis:** Interviews were transcribed. No description of analytic methods.	**Opinions of PM/IBR:** No women regretted having prophylactic surgery. Major benefit was perceived as risk reduction. Most thought cosmetic result was better than expected. **'Unexpected' findings:** Importance of how to emotionally consider/ anticipate the loss of breasts; how breasts would be changed post-surgery; 'taking good-bye'/mourning them; importance of partner support; recognition of partners'/ relatives' support needs.
Authors' interpretation: In the women's opinions, PM and IBR are well-accepted interventions with good cosmetic results. However, a multidisciplinary team approach, including a psychologist, seems mandatory, facilitating overall management of this group of women and family members.							

Author (s)	Study Design	Comparisons	Setting and location	Number of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Bebbington Hatcher et al (2001)	The psychosocial impact of bilateral prophylactic mastectomy:	**Cohort 1 (C1):** psychological and sexual morbidity in women who chose	Participants' homes throughout the UK.	**Total:** 154 **C1**: 79; **C2**: 64;	**Included:** women with a family history of	**Median age, years (range): C1**: 38 (26-57); **C2**: 40 (22-56)	**All women:** questionnaires administere	1. Psychiatric morbidity (General Health Questionnaire 30)

	prospective study using questionnaires and semistructured interviews Prospective cohort study (results of questionnaires reported only)	bilateral prophylactic mastectomy ('accepters') **Cohort 2 (C2):** psychological and sexual morbidity in women who declined bilateral prophylactic mastectomy ('decliners') and chose regular surveillance (mammography and clinical examination)	Women were referred by 20 surgeons, 4 geneticists, 4 medical oncologists and 1 psychiatrist via 20 UK participating centres.	11 women deferred decision (not included in analysis)	breast cancer or with sufficiently high risk factors for bilateral prophylactic mastectomy to be offered (genetic status determined by referring clinicians)	**Parous (%): C1**: 81; **C2**: 75 **In paid occupation (%): C1**: 73; **C2**: 83 **Type of surgery (C1 only), number: Implants:** 64; **TRAM:** 2; **Other:** 1; **No reconstruction:** 10 (details of surgical type for 2 further CI women not supplied) **Place of origin:** most women (54%) were from the North West health region. **Counselling status:** Most women were referred by surgeons, with few having received psychological counselling (numbers not reported).	d at interviews asap after referral to study, and at 6 and 18 months after 1st interview.	2. Anxiety and proneness to anxiety (Spielberger State-Trait Anxiety Inventory) 3. Sexual functioning (Sexual Activity Questionnaire) 4. Coping strategies (Ways of coping questionnaire) 5. Knowledge of risk (Risk perception questionnaire) 6. Perception of body image (Body image scale) All women completed all questionnaires at 1st interview. C2 at 6/18 months: questionnaires 1, 2 and 3. C1 at 6/18 months: questionnaires 1, 2, 3 and 6. **Analysis:** non-parametric tests; chi-square/McNemar; Wilcoxon; Mann-Whitney U. Analysis included all women at 1st assessment; only those women who completed assessments at subsequent time

								points.

Results

Psychiatric morbidity: **Proportion of C1 women who scored ≥4 (threshold for psychological morbidity) reduced over time, both between preoperative (baseline) and 6 month postoperative assessment (P=0.04), and between preoperative and 18 month assessment (P<0.001). Psychological morbidity decreased significantly over time among C1 women and the longer the time from surgery, the greater the decrease.**
Proportion of C2 women scoring ≥4 did not differ significantly between the 1st (baseline) and the 6 month assessment (P=0.08). Over 50% of C2 women had psychological morbidity at 1st assessment and this did not decrease significantly over an 18 month period (P=0.11). No significant differences between C1 and C2 women at any of the 3 assessments.

Anxiety/proneness to anxiety: **A significantly higher proportion of C2 women compared to C1 women were prone to anxiety (P=0.006). Proportion of C1 women with anxiety above normative score decreased between preoperative and 6-month assessment (P<0.001) and between preoperative and 18 month assessment (P=0.001). The proportion of C2 women scoring above the normative value did not differ significantly between baseline and the 6-month assessment (P=1.00) and baseline and the 18-month assessment (P=1.00). No significant differences between groups at any of the 3 assessments.**

Sexual functioning: **sexual discomfort changed little over time within or between groups, with median scores very close to max of 6 (indicating no discomfort). No significant differences in sexual pleasure found between or within groups.**

Coping strategies: **Median score for using problem focused coping was significantly higher among C1 women than C2 women (P=0.03); median score for using detachment as a coping mechanism was significantly higher among C2 women than C1 women (P<0.001).**

Perception of body image: **(C1 women only; most had immediate reconstruction): No differences in median score of 4 (range 0-30) were detected (P=0.84).**

Risk perceptions: **Overall, C1 women reported higher lifetime risks of developing breast cancer than C2 women (P=0.001). C2 women were more likely than C1 women to believe that screening could help (P=0.007).**

Postoperative complications (C1 women only): **Not yet known until qualitative analysis is complete.**

Authors' conclusions: **Bilateral prophylactic mastectomy reduces psychological morbidity and anxiety and does not have a detrimental impact on women's body image or sexual functioning. Women who choose surgery, however, have a higher perception of their risk of developing breast cancer and the authors suggest that if women are making decisions based on inaccurate perceptions, they might regret these decisions later.**

Further information: **The influence of presurgical counselling on psychological morbidity was not measured.**

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Contant et al (2002)	Review of medical records		Daniel den Hoed Cancer Centre, Netherlands	112 women who chose prophylactic mastectomy, either BRCA1 or BRCA2 gene mutation carriers or 50% risk carriers (defined as daughter of an affected woman from a hereditary breast [and ovarian] cancer family – HB(o)C)	Medical records of 112 consecutive women who underwent prophylactic mastectomy, Dec 1993- Dec 1999.	Median age at time of prophylactic mastectomy 38.8 years (range 23.4-63.9 years) Germ line mutations present in 76 women (63 BRCA1, 13 BRCA2) 36 women belonged to a HB(o)C family 207 prophylactic mastectomies performed (95 bilateral, 17 unilateral) Contralateral following unilateral prophylactic mastectomy in 14 patients Immediate breast reconstruction – 103 women. No reconstruction – 9 women. Laprascopic bilateral oophorectomy – 59 women (36 simultaneously, 23 consecutively)	Median follow up after prophylactic mastectomy 2-8 years (range 1.0-7.0 years)	Data collected: age, medical history, indication for prophylactic mastectomy, pathological results, post-op complication (short and long term oncological follow-up

Results

Of 103 patients (193 prophylactic mastectomies) who underwent phrophylactic mastectomy with immediate reconstruction, 73 (71%) had no complication during follow-up.

Complications after prophylactic mastectomy followed by immediate breast reconstruction with a subpectoral placed silicone prosthesis				
Complication	Early complication<6 weeks after operation		Late complication >6 weeks after operation	
	n (%)	Surgery	n (%)	Surgery
Bleeding	10 (5.2)	10		
Infection	5 (2.5)	3	4 (2)	4
Wound necrosis	2 (1)	2	1 (0.5)	1
Pneumothorax	2 (1)			
Luxation	2 (1)	2	4 (2.5)	4
Capsular contracture			14 (7.2)	8
Total	21 (11)	17 (9)	23 (12)	17 (9)

Values are number of patients (percentage)

Radiotherapy	n	Early complication		Late complication		Loss of prosthesis	
Total Yes No	193 14 179	21 6 15	 43% 8.4%	23 6 17	 43% 9.5%	10 4 6	 29% 3.4%
p		0.001		0.002		0.002	

Author's conclusions:

Complications after immediate breast reconstruction with a subpectoral prosthesis occur significantly more often in previously irradiated patients. Prophylactic mastectomy followed immediate breast reconstruction in non-irradiated patients has an acceptable complication rate.

7.15 Risk Reducing Oophorectomy for Women with no Personal History of Breast Cancer

7.15.1 Evidence statement

- Risk reducing oophorectomy before menopause is effective in reducing breast cancer risk. (III)
- In the general female population, undergoing a risk reducing oophorectomy at or below 40 years of age reduces the risk of breast cancer by between 50-75%. (III)
- For women with a family history (including BRCA1, BRCA2 carriers) the relative risk reduction (50-75%) is similar but absolute risk reduction will be greater. (III)
- The use of HRT following oophorectomy may have an impact (negative) on the level of risk reduction, but there is no good evidence. (IV)
- There is a lack of prospective studies of psychosexual outcomes in women with a family history of breast cancer.
- Anxiety may be a significant motivating factor for surgery in women seeking risk reducing oophorectomy. (IV)
- The evidence with respect to the reduction of cancer worry and of increased general psychological distress following surgery is conflicting (from retrospective studies). (IV)
- Negative impacts of surgery on sexual functioning and menopausal symptoms have been reported in small, qualitative, retrospective studies. (IV)
- Unmet needs for information about expected menopausal symptoms and safety in using HRT have been reported. (IV)

7.15.2 Summary: risk reducing oophorectomy research

The findings from 3 observational and 3 decision analysis studies suggest that risk reducing oophorectomy has a beneficial effect in terms of significantly reducing the risk of breast and/or various gynaecological cancers in women with BRCA1 and/or BRCA2 mutations. Postoperative complications were reported in a minority of women in one of the observational studies, and in a review of hospital records in Canada, 14% of women who underwent risk reducing oophorectomy experienced adverse effects from the surgery.

In terms of psychosocial outcomes the impact of risk reducing oophorectomy reported in a small number of smallish studies gave inconsistent findings. Findings about issues such as cancer worry and general satisfaction with the procedure were varied in different studies. These tended to depend upon factors such as age, menopausal status and so on.

7.15.3 Studies

Risk reducing oophorectomy may be considered as a risk reducing strategy in pre-menopausal women at high risk of developing breast cancer. BRCA1 gene carriers may also consider this option to specifically reduce their ovarian cancer risk.

Women considering risk reducing oophorectomy should be fully informed of the risks and potential complications of surgery and in particular the effects of an early menopause. The subsequent use of HRT post-oophorectomy should also be discussed and its effect on the level of risk reduction.

Risk reducing oophorectomy studies (effectiveness)

Kauff et al (2002)
In a prospective cohort study, the incidence of, and time to, breast cancer or BRCA-related gynaecological cancers after a mean follow-up of 24 months was studied in 98 women who underwent salpingo-oophorectomy at a mean age of 47.5 years and 72 women who underwent surveillance. Eligibility criteria were women with a BRCA1 or BRCA2 mutation aged 35 years or older.
The incidence of cancers was less in the oophorectomy group (3 breast and 1 peritoneal cancers) than in the surveillance group (8 breast, 4 ovarian, and 1 peritoneal cancers). The estimated proportion free from breast or BRCA-related gynaecological cancer at 5 years was significantly greater in the oophorectomy group than in the surveillance group (P=0.006). Postoperative complications were reported in 4 out of 80 women who underwent risk reducing oophorectomy without hysterectomy.

Rebbeck et al (2002)
This retrospective cohort study compared the incidence of coelomic epithelial and breast cancers in two separate groups of women with BRCA1 or BRCA2 mutations who had, or had not, undergone bilateral risk reducing oophorectomy.
In the first sample of women (coelomic epithelial cancer risk), coelomic epithelial cancer developed in 8 of 259 women who had undergone oophorectomy at a mean age of 42.0 years (mean follow-up of 8 years), compared to 58 of 292 controls (mean follow-up of 9 years). Of the 8 cancers in the oophorectomy group, 6 women received a diagnosis of ovarian cancer at the time of surgery. With the exclusion of these 6 women, bilateral risk reducing oophorectomy was associated with a statistically significant reduction in the risk of coelomic epithelial cancer (hazard ratio, 0.04 (95% CI, 0.01-0.16)).
In the second sample of women (breast cancer risk), breast cancer developed in 21 of 99 women who had undergone oophorectomy at a mean age of 40.1 years (mean follow-up of 11 years) compared to 60 of 142 controls (mean follow-up of 12 years). Bilateral risk reducing oophorectomy was found to significantly reduce the risk of breast cancer (hazard ratio, 0.47 (95% CI, 0.29-0.77)). Postoperative complications are not reported in either sample of women.

Rebbeck et al (1999)
The occurrence of primary invasive breast cancer was compared retrospectively in 43 women with BRCA1 mutations who underwent bilateral risk reducing oophorectomy at a mean age of 39.4 years (mean follow-up of 10 years), and a control group of 79 women with BRCA1 mutations who did not undergo surgery (mean follow-up of 8 years).
Ten breast cancers developed in the oophorectomy group compared to 30 breast cancers in the control group, indicating that, in women with BRCA1 mutations, bilateral risk reducing

oophorectomy was associated with a statistically significant reduction in absolute risk of developing breast cancer (adjusted hazard ratio = 0.53; 95% confidence interval = 0.33-0.84). This risk reduction was even greater in women who were followed up 5-10 years, or at least 10 years, after surgery. Use of HRT did not negate the reduction in breast cancer risk after surgery. Postoperative complications were not reported.

Other identified studies of relevance

Three studies were identified which used decision analysis to estimate: the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 or BRCA2 mutations (Schrag et al (1997); the effect of risk reducing oophorectomy and mastectomy in terms of survival, quality of life and cost-effectiveness in women with BRCA1 and BRCA2 women (Grann et al (1998); and the effect of risk reducing oophorectomy and mastectomy on life expectancy in women with BRCA1 mutations (van Roosmalen et al (2002). All 3 studies estimate life expectancy gains as a result of both types of risk reducing surgery in BRCA1 and/or BRCA2 women. However, as the findings of these studies are based on modelling techniques, the cohort studies summarised above will take precedence in terms of providing more robust evidence.

Preliminary analysis of a prospective cohort study by Struewing et al (1995) on the incidence of ovarian and breast cancers after risk reducing oophorectomy found a statistically non-significant reduction in both cancers among women who had undergone surgery compared to those who had not. However, data on the subjects and controls are not provided so the baseline comparability of populations can not be determined.

Data from hospital records on 263 women who underwent risk reducing oophorectomy in 41 hospitals in Ontario, Canada, between 1992-1998 were reviewed to determine indications, patterns of practice and complication rates (Elit et al, 2001). Family history of ovarian cancer was the reason for surgery in 127 of these women, with the remaining 136 having a coexisting gynaecological complaint. Sixteen of the women were recorded as having a BRCA1 or BRCA2 mutation. Overall, 36 (13.7%) of these women experienced complications from surgery, including intra-operative problems, reoperation, haematoma, infection and wound problems, and conversion from laparoscopy to laparotomy was required in 17 women during the operation. The frequency of complications by type of surgery were 17% (7/41) for laparoscopic-assisted vaginal hysterectomy, 23% (36/155) for laparotomy and 12% (5/38) for laparoscopy.

Risk reducing oophorectomy studies (psychosocial outcomes)

Tiller 2002

Tiller et al (2002) reported a small prospective study in 22 women having oophorectomy. Age was a significant predictor of surgery uptake in 95 women who originally expressed an intention to undergo surgery. 86.4% women were highly satisfied: the majority (12:15) of premenopausal women were taking HRT. Those not using replacement therapy consistently reported a negative impact on sexual functioning. There was a significantly greater reduction in cancer anxiety in women electing to have surgery compared to those who did not. The findings suggested that anxiety reduction potentially compensated for other adverse effects, but the small sample limits generalisation.

Elit 2002

Elit et al (2001) reported a negative impact on quality of life following risk reducing oophorectomy in 40 women with a family history of ovarian cancer (Women had all completed surgery since 1992: 53% underwent a preventive intervention alone whilst 47% had other gynaecological reasons. A comprehensive assessment of psychosocial functioning was completed which showed that

menopause quality of life scores were reduced (poorer QoL) compared to women of similar age, despite the fact that 65.7% reported current use of HRT. Only 8% reported menopausal symptoms as leading them to feel regret. Satisfaction with sexual functioning was moderately to extremely compromised in 42%-54% of women. Scores on measures of mental health was comparable to the general population. Further interpretation of Elit et al's results is difficult without data from a control group and the sample was too small to explore possible predictive factors of adjustment, such as age, type of surgery, use of HRT.

Fry 2001

A retrospective comparison study of 29 women who had had surgery and 28 in a screening control group (30) was carried out using self-report measures. Scores for social and emotional functioning were worse in the surgery group, using the Short-form 36 item Health Status questionnaire (SF-36). Scores for general psychological distress measured with the General Health Questionnaire, were also significantly higher, although there was only a trend to report more menopausal symptoms in the surgical group. It was concerning that there was no apparent benefit in terms of improved cancer worry scores in the women who had oophorectomy, but methodological limitations mean that results must be considered cautiously.

Meiser 2000

In a small qualitative study of 6 premenopausal women (and 8 women who had post-menopausal surgery), all bar one had used HRT, which had mitigated most of their menopausal symptoms and the sexual impact. Most women were satisfied with the procedure and emphasised reduced anxiety about cancer. Premenopausal women reported unmet information needs including the effects of surgical menopause and the link between HRT and breast cancer.

7.15.4 Evidence Tables

Table 7.10 Risk reducing oophorectomy

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Rebbeck et al (1999)	Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers Retrospective cohort study	**Subjects (C1)**: Bilateral prophylactic oophorectomy **Controls (C2)**: no history of oophorectomy	Participants identified from registry databases of 5 US institutions (Omaha, Boston, Philadelphia (x2), Salt Lake City)	**C1**: 43 **C2**: 79	**C1 included**: women with BRCA1 mutations who underwent bilateral prophylactic oophorectomy, with no history of breast or ovarian cancer and who had not had a prophylactic mastectomy **C2 included**: women with BRCA1 mutations who had no history of oophorectomy/breast or ovarian cancer **C2** women were matched to **C1** women according to collaborative institution and year of birth (±5 years)	**Mean year of birth (range)**: **C1**: 1945.4 (1910-1965); **C2**: 1948.3 (1910-1970) **Mean age in years at time of C1 women's surgery (range)**: **C1**: 39.4 (22-63); **C2**: 35.3 (17-65) **Mean parity (range)**: **C1**: 2.5 (0-7); **C2**: 2.0 (0-8) **Mean age at 1st live birth (range)**: **C1**: 25.1 (17-40); **C2**: 27.1 (17-40) **Mean age in at menarche (range)**: **C1**: 12.6 (9-16); **C2**: 12.6 (10-15) No statistically significant differences reported	Mean length in years of follow-up (range): **C1**: 9.6 (<1-36) **C2**: 8.1 (<1-43) No statistically significant difference in length of follow- up was reported between groups (P=0.384)	**Primary outcome**: occurrence of 1st diagnosis of primary invasive breast cancer Cox proportional hazards models
Results								

Primary outcome: Number of breast cancers (%): **C1**: 10 (23.3); **C2**: 30 (38.0). Cumulative incidence of breast cancer at ages 45, 60 and 75 years: **C1**: 11.6%, 14.0% and 18.6%; **C2**: 15.2%, 25.3% and 31.6% respectively. Bilateral prophylactic oophorectomy was associated with a statistically significant reduced risk of developing breast cancer in the total sample (adjusted hazard ratio (HR) = 0.53; 95% confidence interval 0.33-0.84). This risk reduction was even greater in women who were followed up 5-10 years, or at least 10 years, after surgery. Use of HRT did not negate the reduction in breast cancer risk after surgery.

Hazard ratio (95% confidence interval)

Group	Total Sample	Parous women	Surgery before age 50
Total sample	**0.53 (0.33-0.84) [n=122]**	**0.49 (0.30-0.79) [n=104]**	**0.57 (0.36-0.92) [n=90]**
Women without hormone replacement therapy exposure	**0.42 (0.22-0.81) [n=73]**	**0.35 (0.17-0.71) [N=61]**	**0.46 (0.23-0.90) [n=63]**
Duration of follow-up after surgery:			
<5 years	**0.55 (0.36-0.85) [n=53]**	**0.51 (0.32-0.81) [n=46]**	**0.60 (0.39-0.93) [n=51]**
Between 5 and 10 years	**0.28 (0.08-0.94) [n=38]**	**0.27 (0.08-0.91) [n=29]**	**0.32 (0.10-1.06) [n=26]**
>10 years	**0.33 (0.12-0.91) [n=31]**	**0.35 (0.13-0.95) [n=29]**	**0.34 (0.12-0.96) [n=13]**

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period (mean years)	Main outcome measures

Rebbeck et al (2002)	Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations Retrospectiv e cohort study	**Study 1 (coelomic epithelium cancer risk)** Subjects who had undergone bilateral prophylactic oophorectomy (PO) compared to matched controls who had not undergone the procedure **Study 2 (breast cancer risk)** Subjects who had undergone bilateral PO compared to matched controls who had not undergone the procedure	Participants identified from 11 N.American and European registries	**Study 1**: 259 subjects; 292 controls **Study 2**: 99 subjects; 142 controls	**Included (subjects & controls, both studies)**: women with BRCA1 or BRCA2 mutations **Study 1**: **Subjects:** included - bilateral PO; excluded - unilateral oophorectomy or history of ovarian cancer prior to PO. **Controls**: included if alive with both ovaries/no history of ovarian cancer when matched subject had PO. Also matched according to type of mutation, treatment centre and yr of birth (within 5 yrs) **Study 2**: **Subjects**: included – bilateral PO; excluded - unilateral oophorectomy or history of ovarian cancer prior	**Study 1** Subjects/controls comparable at baseline (eg BRCA1/2 status; age at PO; yrs of follow-up) except for use of HRT (47.9% vs 19.9%, P<0.001). 325 (59%) of women were related to at least one other person in the sample. The relatedness of 49 (9%) of women was unknown. Mean age of subjects at PO: 42.0 years **Study 2** Subjects/controls comparable at baseline (eg BRCA1/2 status; age at PO; yrs of follow-up)	**Study 1** Subjects: 8.2 Controls: 8.8 **Study 2** Subjects: 10.7; Controls: 11.9	**Primary outcomes** **Study 1**: diagnosis of cancer derived from the coelomic epithelium (in the ovary or peritoneum) **Study 2**: diagnosis of invasive breast cancer or a ductual carcinoma in situ Cox proportional hazards models
Results								

Study 1: Of 259 subjects who underwent PO, 8 (3.1%) received a diagnosis of ovarian cancer or papillary serous peritoneal cancer at or after oophorectomy, as compared with 58 of 292 controls (19.9%). Of the 8 cancers in the subjects, 6 women received a diagnosis of stage I ovarian cancer at the time of PO. With the exclusion of these 6 women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of
coelomic epithelial cancer (hazard ratio, 0.04 [95% CI, 0.01-0.16]). Neither breast nor ovarian cancer developed in 185/259 subjects who underwent PO (71.4%) during follow-up, compared with 153/292 controls (52.4%, P<0.001).

Study 2: PO was found to significantly reduce to risk of breast cancer: breast cancer developed in 21 (21.2%) women in the PO group, as compared with 60 (42.3%) in the control group (hazard ratio, 0.47 [95% CI, 0.29-0.77]). The subjects who underwent PO were significantly older than the controls at the time of diagnosis (52.5 years vs 46.7 years, P=0.03). The mean time to diagnosis of breast cancer after PO was 11.4 years for subjects who underwent PO and 8.0 years for controls (P=0.09).

Effect of Prophylactic Oophorectomy on the Risk of Ovarian and Breast Cancer, According to Selected Variables*

Variable		**Ovarian or Papillary Serous Peritoneal Cancer**		**Breast Cancer**
	NO.	HAZARD RATIO (95% CI)	NO.	HAZARD RATIO (95% CI)
All subjects	551	0.04 (0.01-0.16)	241	0.47 (0.29-0.77)
Age at oophorectomy=				
<35 yr	124	No events	76	0.39 (0.15-1.04)
35-50 yr	348	0.03 (<0.01-0.20)	146	0.49 (0.26-0.90)
≥50 yr	79	0.11 (0.02-0.76)	19	0.52 (0.10-2.70)
Personal history of breast cancer				
Yes	200	-≅	NA	-
	351	0.06 (0.01-0.25)	NA	-
Length of follow-up				
<5 yr	304	0.05 (0.01-0.34)	120	0.45 (0.21-0.95)
5-10 yr	103	0.13 (0.02-0.93) No	52	0.68 (0.22-2.11)
>10 yr	144	events	69	0.51 (0.24-1.07)
Parity				
≥1	461	0.04 (0.01-0.18)	204	0.45 (0.27-0.76)
0	90	-≅	35	0.58 (0.12-2.77)
Age at menarcheO				
≤12 yr	230	0.05 (0.01-0.37)	95	0.61 (0.29-1.30)
>12 yr	264	0.03 (<0.01-0.23)	122	0.40 (0.21-0.75)
Age at first live birthσ				
<30 yr	376	0.04 (0.01-0.17)	172	0.49 (0.30-0.82)
≥30 yr	70	-≅	27	0.62 (0.08-4.69)

*CI denotes confidence interval, and NA not applicable.
=For controls, the age at oophorectomy was the age at the time of prophylactic oophorectomy in the subjects with whom they were matched.
≅No cases of coelomic epithelial cancer occurred in this group.
OData were missing for 57 subjects in the ovarian-cancer study and 24 subjects in the breast-cancer study.
σData were missing for 15 subjects in the ovarian-cancer study and 5 subjects in the breast-cancer study.

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures
Kauff et al (2002)	Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation Prospective cohort study	**Cohort 1** (**C2**): risk-reducing salpingo-oophorectomy (with or without concomitant hysterectomy after receipt of genetic test results) **Cohort 2** (**C2**): ovarian cancer surveillance (annual or twice-yearly gynaecological examinations; twice-yearly transvaginal US examinations; and twice- yearly determinations of serum CA-125 concentration)	Memorial Sloan-Kettering Cancer Centre, New York, USA	**At start**: 177 **Included in analysis**: 170 (**C1**: 98; **C2**: 72) 4 patients were lost to follow-up and excluded from the analysis. 3 women from **C1** were found to have gynaecological cancer at time of surgery and were excluded from the analysis.	**Included**: women with a BRCA1 or BRCA2 mutation aged 35 years or older **Excluded**: women with BRCA1 or BRCA2 mutation who had undergone bilateral salpingo-oophorectomy before genetic testing or who were aged <35 years.	**Mean age at genetic test (PO carried out median of 3.6 months later)**: **C1**: 47.5 yrs; **C2**: 45.5 yrs (P=0.17) **BRCA1 (%)**: **C1**: 57; **C2**: 67. **BRCA2 (%)**: **C1**: 43; **C2**: 33 (P=0.27) **Mean no. of 1st/2nd degree relatives with breast, ovarian, fallopian-tube or primary peritoneal cancer (mean)**: **C1**: 1.64; **C2**: 1.86 (P=0.20) **Previous breast cancer (%)**: **C1**: 70; **C2**: 62 (P=0.32) **Previous chemotherapy (%)**: **C1**: 61; **C2**: 54 (P=0.43)	Mean duration of follow-up after risk-reducing salpingo-oophorectomy or start of surveillance: **C1**: 23.4 months; **C2**: 25.4 months	**Primary outcomes:** Occurrence of breast cancer or BRCA-related gynaecological cancers. Time to development of breast cancer or BRCA- related gynaecological cancers. Kaplan-Meier analysis. Cox proportional hazards model.
Results								

Primary outcomes: In the **C1** group, breast cancer was diagnosed in 3 women, and peritoneal cancer was diagnosed in 1 woman. In the **C2** group, breast cancer was diagnosed in 8 women, ovarian cancer in 4 and peritoneal cancer in 1. The estimated proportion free from breast cancer or BRCA-related gynaecological cancer at 5 years was significantly greater in **C1** women than in **C2** women (P=0.006).

The hazard ratio for the development of breast cancer or BRCA-related gynaecological cancer in **C1** women was 0.25 (95% confidence interval, 0.08-0.74). For new ovarian, fallopian-tube, and primary peritoneal cancers, the time to diagnosis of cancer was longer in the **C1** group than in the **C2** group (P=0.04).

There was no significant effect of the type of mutation (BRCA1 vs BRCA2) on the time to breast or gynaecological cancer (P=0.31).

Complications of risk-reducing salpingo-oophorectomy: complications were noted in 4/80 women who underwent salpingo-oophorectomy without hysterectomy. No complications were noted in 11 women who had a hysterectomy at the time of risk-reducing salpingo-oophorectomy or in 7 women whose uterine-surgery status was not specified at time of risk-reducing salpingo-oophorectomy.

Kaplan-Meier Estimates of Proportions Free from Cancer

Variable	**Salpingo Oophorectomy Group (n=98)**	**Surveillance Group (n=72)**	**P Value[1]**
Ovarian, fallopian-tube, or primary peritoneal cancer			0.04
No.	1	5	
Projected proportion free from cancer at 5 yr (%)	98	83	
Breast cancer[2]			0.07
No.	3	8	
Project proportion free from cancer at 5 yr (%)	94	79	
Breast cancer or BRCA-related gynecologic cancer			0.006
No.	4	12[3]	
Projected proportion free from cancer at 5 yr (%)	94	69	

[1]P values were determined by the log-rank test.

[2]Kaplan-Meier analysis was limited to the 131 women with breast tissue at the start of follow-up.

[3]Metachronous breast and ovarian cancers were diagnosed in one patient in this group during follow-up.

Hazard of Breast Cancer or BRCA-Related Gynecologic Cancer after Risk-Reducing Salpingo-oophorectomy*			
Variable	**Ovarian, Fallopian tube or primary peritoneal cancer**	**Breast Cancer**	**Breast cancer or BRCA related gynaecologic cancer**
No. Of patients included in the analysis	**170**	**131**	**170**
Mean no of months of follow-up	**23.3**	**22.6**	**22.7**

7.16 HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause

7.16.1 Review Question

What are the risks and benefits of HRT for women under the age of 50, with a *BRCA1* or *BRCA2* mutation who have undergone a bilateral salpingo-oophorectomy?

7.16.2 Background

Women found to be at risk for breast/ ovarian cancer because of an inherited BRCA1/2 mutation may undergo a bilateral salpingo oophorectomy (BSO) to reduce their chances of developing ovarian (and breast) cancer. Where this is done before the natural menopause, a surgical menopause will be precipitated and women may consider hormone replacement for symptom relief and/ or prevention of accelerated osteoporosis or heart disease. There has been much publicity regarding the increased risks of breast cancer associated with HRT but most of this data comes from studies where replacement is taken *after* the natural menopause. This question addresses the risks and benefits in the specific group of high risk women but before the natural menopause. Different types of HRT will be considered since women who have intact uteri will need progesterone in their replacement (combined HRT), whilst those with a hysterectomy can take oestrogen preparations only.

7.16.3 Question in PICO Format

Patients/population	Intervention	Comparison	Outcomes
Women without breast cancer who have BRCA1 or BRCA2 mutations or a family history of breast cancer and have a bilateral-salpingo oophorectomy before their natural menopause	HRT Treatment with: • Oestrogen only • Combined HRT	No HRT Treatment	• Incidence of cardiovascular disease • Incidence of osteoporosis • Health Related Quality of Life • Overall Survival • Breast Cancer • Primary peritoneal cancer

7.16.4 Relative importance of these outcomes?

All outcomes were given equal importance by the GDG.

7.16.5 How the information will be searched

What sources will be searched, e.g. will we look at Cinahl? (to be completed by reviewer/information specialist) Are there any study design filters to be used (RCT, systematic review, diagnostic test).

Date Limits	This is an update topic so the date limits would have been set from the end of the previous guideline 2003

	However, for this topic, a date limit of 1995 was applied by advice of the GDG, as before 1995 no large scale genetic testing was available.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	No filters to be applied for this topic as no randomised controlled trials are known to be available to address the topic
List useful search terms	HRT Oestrogen only Combination HRT BRCA1/2 CARRIERS Natural menopause Prophylactic surgery Oophorectomy Salpingo-oophorectomy etc etc Breast cancer risk

7.16.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	None

7.16.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1995-current	133	27	05/09/2011
Premedline	1995-current	3	1	05/09/2011
Embase	1995-current	247	25	06/09/2011
Cochrane Library	1995-current	11	1	06/09/2011
Web of Science (SCI & SSCI) and ISI Proceedings	1995-current	220	30	07/09/2011
PsycInfo	1995-current	5	2	06/09/2011

Total References retrieved (after de-duplication): 49

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. Ovariectomy/
25. (ovariectom$ or oophorectom$).tw.
26. (ovar$ removal or ovar$ surger$ or ovar$ ablat$).tw.
27. (prophylactic adj surger$).tw.
28. or/24-27
29. 23 and 28
30. exp Hormone Replacement Therapy/
31. ((hormon$ or oestrogen$ or estrogen$ or oestradiol or estradiol or progesterone$ or progestin) and replacement).tw.

32. hormone substitution.tw.
33. hrt.tw.
34. ((hormon$ or oestrogen$ or estrogen$ or oestradiol or estradiol or progesterone$ or progestin) adj2 (therap$ or treatment$)).tw.
35. or/30-34
36. 29 and 35
37. limit 36 to yr="1995 -Current"

Notes:
A date limit of 1995 was applied by advice of the GDG, as before 1995 no large scale genetic testing was available.
No search filters were applied.

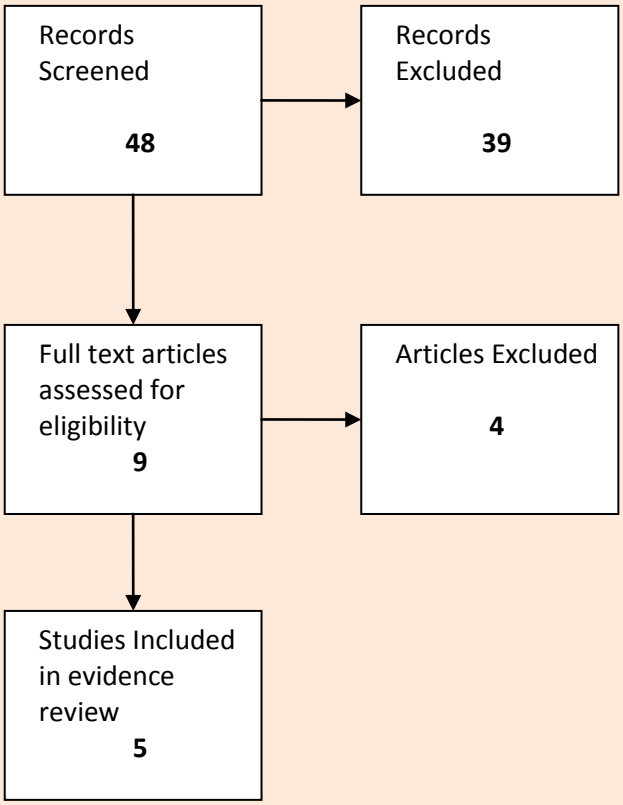
Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	05/09/2011-04/07/2012	10	3	04/07/2012
Premedline	05/09/2011-04/07/2012	5	0	04/07/2012
Embase	09/2011-07/2012	3	1	04/07/2012
Cochrane Library	09/2011-07/2012	1	0	04/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	09/2011-07/2012	5	2	04/07/2012
PsycInfo	09/2011-07/2012	0	0	04/07/2012

Premedline: 1 new reference added 05/09/2012

Total References retrieved (after de-duplication): 6

7.16.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=5)
Qualitative Study (n=0)

Table 7.11: Summary of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Challberg et al (2011)	Retrospective Questionnaire Survey	N=289	To investigate the uptake of HRT after bilateral risk reducing salpingo oophorectomy	Any HRT use following bilateral salpingo oophorectomy	No HRT use following bilateral salpingo oophorectomy	Menopausal Symptoms Changes in bone mineral density
Gabriel et al (2009)	Restrospective, descriptive data analysis	N=73	To examine the uptake of total abdominal hysterectomy and HRT and the relationship between TAH and HRT in unaffected female BRCA1/2 carriers who have undergone risk reducing salpingo oophorectomy			Type of surgery Patterns of HRT use Subsequent development of breast cancer
Eisen et al (2008)	Matched case control study	N=236 matched pairs	To examine whether or not the use of hormone therapy is associated with a subsequent risk of breast cancer	Hormone therapy	No hormone therapy	Risk of breast cancer
Madalinska et al (2006)	Retrospective observational study of a subgroup of patients from within a prospective cohort	N=1084	To assess the impact of HRT use on the levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone prophylactic bilateral salpingo oophorectomy	Hormone replacement therapy in premenopausal women who underwent oophorectomy	Gynaecological screening in high risk premenopausal women	Endocrine Symptoms Sexual Functioning
Rebbeck et al (2005)	Retropective analysis of a prospective cohort	N=462	To evaluate whether the breast cancer risk reduction conferred by bilateral prophylactic oophorectomy in	HRT		First diagnosis of in situ ductal carcinoma or invasive breast

			BRCA1/2 carriers is altered by the use of post BPO HRT			cancer

7.16.9 Evidence Statements

Risk of Breast Cancer
Three observational studies (Eisen et al, 2008; Rebbeck et al, 2005 and Gabriel et al 2009: GRADE Profile 1) of very low quality reported on the risk of breast cancer associated with HRT in this population. Their results , however, are conflicting possibly due to variations in study methodology, populations and outcome assessment.

Eisen et al (2008) reported that women who had used hormone therapy had a lower breast cancer risk than women who had never used hormone therapy (OR=0.58; 95% CI=0.35-0.96, p=0.03). Rebbeck et al (2005) reported 8% of bilateral prophylactic oophorectomy (BPO) patients and 21% of non-BPO patients were diagnosed with a first primary breast cancer during follow-up (HR=0.40, 95% CI, 0.18-0.91) irrespective of HRT use.

Gabriel et al (2009) reported that In 17 women using oestrogen only HRT, 3 subsequently developed breast cancer while none of the women taking combined or 'unknown' HRT preparations developed breast cancer. Among the 17 women who developed breast cancer, 9 had a BRCA1 mutation and 8 had a BRCA2 mutation.

Bone Protection
There is uncertainty about whether HRT provides bone protection in this population. One non comparative observational study (Challberg et al, 2011;GRADE Profile 4)reported on the role of HRT in bone protection: 38% of women scanned had abnormal results. 28% reported bone mass consistent with osteopenia and 10% indicated osteoporosis.

Endocrine Symptoms
There is uncertainty about whether HRT affects endocrine in this population. Two observational studies (Challberg et al, 2011 and Madalinska et al, 2006) of very low quality (GRADE Profile 2)reported endocrine symptoms as an outcome, both studies appear to use different methods for assessing symptoms in the study population and it is therefore not possible to make a definitive statement as to the effectiveness of HRT for endocrine symptoms.

Sexual Functioning
Very low quality evidence (Madalinksa et al, 2006; GRADE Profile 3) suggests no significant difference in sexual activity between women who are BRCA1/2 mutation carriers and have prophylactic bilateral salpingo oophorectomy (PBSO) and with those opting for gynaecological screening. This study did not report the relative or absolute rates of sexual activity so the relevance of its findings is unclear .

Overall survival, incidence of primary peritoneal cancer, cardiovascular disease or health related quality
There was no evidence about overall survival, incidence of primary peritoneal cancer, cardiovascular disease or health related quality of life related to HRT in this population.

7.16.10 Evidence Summaries

There was a lack of evidence with which to address this topic; no systematic reviews were available, nor were there any randomised trials comparing HRT with no treatment in pre-menopausal women undergoing prophylactic bilateral salpingo oophorectomy.

Five retrospective, observational, providing limited and low quality evidence were identified from the searches (GRADE profile 7.6-7.9).

Outcomes assessed in the included studies are varied and provide low quality, indirect evidence. No identified study assessed life expectancy or incidence of cardiovascular disease as outcomes. Breast cancer risk was the primary outcome in two studies (Eisen et al, 2008 and Rebbeck et al, 2005); endocrine symptoms were assessed in two studies (Challberg et al, 2011 and Madalinksa et al, 2006); Sexual functioning was assessed in a single study (Madalinska et al, 2006) and bone mineral density changes were assessed in a single study (Challberg et al, 2011)

Outcomes

Risk of Breast Cancer

Three studies reported breast cancer risk as an outcome although the quality of the studies was considered to be very low on assessment using GRADE (GRADE Profile 7.6).

Eisen et al (2008) reported that women who had used hormone therapy had a lower breast cancer risk than women who had never used hormone therapy (OR=0.58; 95% CI=0.35-0.96, p=0.03). When looking only at the subgroup of women with BRCA1 mutation carriers who had undergone surgical menopause the OR estimates were similar (OR=0.68, 95% CI=0.19-1.21) though the subgroup was quite small in number (n=62 pairs).

Rebbeck et al (2005) reported 8% of bilateral prophylactic oophorectomy (BPO) patients and 21% of non-BPO patients were diagnosed with a first primary breast cancer during follow-up (HR=0.40, 95% CI, 0.18-0.91) irrespective of HRT use. For women taking HRT, there was no difference in breast cancer risk associated with BPO (HR=0.37, 95% CI, 0.14-.96) suggesting that taking HRT following BPO does not alter the risk of breast cancer in women who are BRCA1 carriers.
Breast cancer risk reduction among BPO patients did not differ significantly when comparing patients taking progesterone with or without oestrogen versus oestrogen only **(**HR=2.56; 95% CI, 0.08-78.13 for combined therapy).

Gabriel et al (2009) reported that In the 17 women using oestrogen only HRT, 3 subsequently developed breast cancer while none of the women taking combined or 'unknown' HRT preparations developed breast cancer.
In the 29 women not taking HRT, 9 developed breast cancer; 3 were ER/PR negative, four unknown and two were ER^{+}/PR^{-}.
Of the 11 women with unknown HRT status, 5 developed breast cancer ER^{+}/PR^{+} in one women and ER/PR negative in the remaining four.
Among the 17 women who developed breast cancer, 9 had a BRCA1 mutation and 8 had a BRCA2 mutation.

Endocrine Symptoms

Two studies (Challberg et al, 2011 and Madalinska et al, 2006) reported endocrine symptoms as an outcome, both studies appear to use different methods for assessing symptoms in the study population and again the quality of the evidence for this outcome was considered to be very low on GRADE assessment (GRADE Profile 7.7).

Challberg et al (2011) compared HRT never users, previous users and current users and a significant difference in total mean endocrine scores was observed between all three groups (p=0.017) though it was thought that this was influenced but the difference observed between previous useds and current users (p=0.006).

The study noted a significant difference in endocrine scores between previous users and current users in the 40-49 year age group with a mean endocrine score of 58.7 for current users versus 53 for previous users indicating worse symptoms in previous users (p=0.001).
Madalinska et al (2006) also assessed endocrine symptoms; comparing premenopasusal women who were BRCA1/2 mutation carriers and had undergone PBSO with women who had opted for gynaecological screening. From the mean scores, women undergoing prophylactic bilateral salpingo oophorectomy and taking HRT reported significantly fewer symptoms overall when compared with women undergoing surgery but not taking HRT (p<0.05).
At an individual level, there were significant difference between users and non-users in relation to hot flushes (p=0.004), cold sweats (p=0.034) and night sweats (p=0.037) with HRT users reporting fewer symptoms.
When comparing the HRT users group with the screening group, significantly more endocrine symptoms were reported in the screening group (p<0.05).

Sexual Functioning
Sexual functioning was reported in a single study (Madalinska et al, 2006) and again the quality of the data for this outcome was considered to be very low on GRADE Assessment (GRADE Profile 7.8).

Madalinksa et al (2006) reported no significant differences in sexual activity between women who were BRCA1/2 mutation carriers and underwent prophylactic bilateral salpingo oophorectomy (PBSO) compared with those opting for gynaecological screening.
PBSO HRT users and PBSO non-users reported comparable levels of sexual functioning as measured by the pleasure, discomfort and habit scales of the Sexual Activity Questionnaire.
PBSO HRT users reported significantly more discomfort during sexual activity when compared with the screening group (p<0.01).

Bone Protection
One study reported on the role of HRT in bone protection as an outcome (Challberg et al, 2011). Bone protection was not listed as an outcome for the topic, the relevant outcome was incidence of osteoporosis however no study reported on incidence of osteoporosis though Challberg et al (2011) did report on indications of osteoporosis and therefore the data from the study are reported here (GRADE Profile 7.9).

GRADE Profile 7.6: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for reducing the risk of breast cancer?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Risk of Breast Cancer							
Eisen A et al (2008); Gabriel C et al (2009); Rebbeck T et al (2005)							
3	observational studies	very serious[1]	serious[2]	serious[4]	serious[3]	none	VERY LOW

[1] All studies were retrospective analysis of existing cohorts and the numbers involved in the individual studies were sufficiently small so to render the studies underpowered for the detection of any significant differences.

[2] Due to the small numbers, differing methods of assessing and reporting outcomes and a lack of studies reporting the same outcomes, it is not possible to comment with any confidence on the degree of consistency across the included studies.
[3] The numbers in the individual studies are too low to give precise results.
[4] The population included in Eisen et al (2008) included primarily women who had undergone natural menopause rather than surgical.

GRADE Profile 7.7: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for reducing endocrine symptoms?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Endocrine Symptoms							
Challberg et al (2011); Madalinska et al (2006)							
2	observational studies	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	VERY LOW

[1] All studies were retrospective analysis of existing cohorts and the numbers involved in the individual studies were sufficiently small so to render the studies underpowered for the detection of any significant differences.
[2] Due to the small numbers, differing methods of assessing and reporting outcomes and a lack of studies reporting the same outcomes, it is not possible to comment with any confidence on the degree of consistency across the included studies.
[3] The numbers in the individual studies are too low to give precise results.

GRADE Profile 7.8: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause on sexual functioning?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Sexual Functioning (Better indicated by lower values)							
Madalinska et al (2006)							
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	VERY LOW

[1] Retrospective case series
[2]Results included patients undergoing oophorectomy and patients choosing gynaecological screening.
[3] The numbers in the individual study are too low to give precise results despite the fact that more than 1000 patients were eligible, the results from this study include fewer than 500 patients total and only 164 patients had undergone prophylactic ophorectomy.

GRADE Profile 7.9: What is the effectiveness HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for bone protection?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**

Bone Protection (Better indicated by lower values)							
Challberg et al (2011)							
1	observational studies	serious[1]	no serious inconsistency	Serious[2]	serious[3]	none	VERY LOW

[1] All studies were retrospective analysis of existing cohorts and the numbers involved in the individual studies were sufficiently small so to render the studies underpowered for the detection of any significant differences.

,.

[3] The study does not specifically assess osteoporosis which was the outcome identified as being the important outcome for the topic, though it does report on indications of osteoporosis.

[4] Due to the small numbers being assessed

As part of this study (Challberg et al, 2011), bone scans were arranged for 119 women and 38% (45/119) were found to have abnormal results. 28% (33/119) reported bone reduced bone mass consistent with osteopenia while 10% (12/119) indicated osteoporosis.The prevalence of reduced bone mass was higher among women who had ≥24 months of oestrogen deprivation compared with those who had taken HRT to cover any period <50 years of age. X^2 analysis of HRT groups and DXA results showed a significant difference between those with ≥24 months oestrogen deprivation and those with no oestrogen deprivation <50 years (p=0.03)

7.16.11 Evidence Tables

Citation: Challberg, J et al (2011) Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT *British Journal of Cancer* 105;1:22-2

Design: Retrospective Questionnaire Survey

Country: UK

Setting:

Aim: To investigate the uptake of HRT after bilateral risk reducing salpingo oophorectomy (BRRSPO)

Inclusion criteria
Women at increased familial risk of ovarian cancer
Mutation (BRCA1/BRCA2) gene carriers
Women with at least a 10% lifetime risk of ovarian cancer due to family history of ovarian/breast cancer or Lynch Syndrome and who had undergone BRRSPO

Exclusion criteria
Women >48 who underwent BRRSPO due to the potentially short period of oestrogen deprivation before natural menopause.

Sample Size
N/A

Randomisation Method
N/A

Population
N=289 patients eligible to complete the questionnaire

N=212 patients returning completed questionnaire

Response Rate: 73%

Study Duration

No details provided

Interventions

Any HRT use following BRRSPO versus never users of HRT following BRRSPO

Outcomes

Menopausal Symptoms
Changes in bone mineral density

Note: the outcomes for the study were not clearly defined and the above are the outcomes as determined from reviewing the study.

Results

212/289 patients returned the questionnaire (73%)

For BRCA1/2 families 123/163 returned the questionnaire (75%) versus 89/126 non BRCA1/2 families (71%) Note: it appears from the study that the patients classed as being from non-BRCA families may not have been tested and therefore the non-BRCA group consists of negative for BRCA families and non-tested families.

HRT Use

- 37% of women had never taken HRT and 63% had taken HRT at some point.
- 87women used HRT immediately after BRRSPO and 47 women delayed HRT for up to 2 years following BRRSPO.
- 50% of women were current users of HRT at the time of completing the questionnaire.
- 79% used oestrogen only preparations while 7% used combined oestrogen and progesterone preparations.
- 14% used other preparations such as tiblone (n=12) and raloxifene (n=2).
- The mean time of HRT use was 3.4 years (range: 0.1-19 years)
- 58% (123/212) of women spent ≥24 months before the age of 50 not taking HRT which resulted in a significant amount of time without oestrogen protection
- 72% (153/212) of women reported that they remembered discussion the pros and cons of HRT with a heath professional.
- 60% of women that did not discuss HRT reported that they wished they had (22/37)
- 72% (56/78) of women reported that they refused HRT due to the breast cancer risk.

Menopausal Symptoms

- Women were divided into three groups for analysis: HRT never users (N), previous users (P) and current users (C)
- There were limitations to how these data could be interpreted due to the fact that the questionnaire was completed at different time points following oophorectomy (range was months to years) and by women of differing ages (24-48 years).
- For patients in group P, 66% (44/67) started HRT immediately after BRRSPO.
- Patients in group P had been off HRT for a median of 3.7 years (range 0.2-11 years).
- Never users were subject to oestrogen deprivation for a median of 5.2 years (range0.5-29 years)

- Results of covariate analysis were age when questionnaire completed (p=0.096), BRCA mutation (p=0.051) and HRT group (p=0.017). The study is not clear on what exactly these p values relate to, it is assumed by the reviewer that age and BRCA mutation were not significantly covariates affecting the outcome of the questionnaire scores for each group of patients (i.e. the degree of menopausal symptoms).
- Dividing age into ten year groups showed a greater percentage of patients in the 40-49year age group had a total score of <50, particularly in the past users group on completion of the questionnaire
- Comparison of means (t-test) showed significant difference in total scores between all three groups (p=0.017). This difference may be explained by the difference between the group (P) and group (C) where p=0.006.
- Splitting the groups into 10 year age groups showed a significant difference between groups P and C in the 40-49 year age group (p=0.001).
- Current users had a mean score of 58.7 versus 53 for previous users.
- Intergroup difference for mean score was not significant between group N and P (p=0.093), nor

between group N and C (p=0.093)

- Endocrine scores for women delaying the start of HRT versus women starting HRT immediately were compared and no significant difference was observed.

Bone Protection

- The mean period of non-HRT use among 139 women who were without oestrogen protection at some stage before age 50 was 5.2 years (range 1-19 years, median 5 years).
- 123 women had at least 2 years of oestrogen deprivation before age 50
- 36% (73/210) of women had a DEXA scan during an average period of risk
- 48/123 women with ≥24 months oestrogen deprivation had undergone a scan
- As part of the study, scans were arranged for 119 women and 38% (45/119) were found to have abnormal results.
- 28% (33/119) reported bone reduced bone mass consistent with osteopenia
- 10% (12/119) indicated osteoporosis
- The prevalence of reduced bone mass was higher among women who had ≥24 months of oestrogen deprivation compared with those who had taken HRT to cover any period <50 years of age
- X^2 analysis of HRT groups and DXA results showed a significant difference between those with ≥24 months oestrogen deprivation and those with no oestrogen deprivation <50 years (p=0.03)
- For patients not scanned prior to the study who had oestrogen deprivation ≥24 months, 95% (67/71) wanted to be scanned, although 24 women wanted the scans to be arranged by their GP and 8 women did not attend, resulting in data for the study from 35 women.

General comments

Limitations of the study include the fact that it is retrospective in nature and relies on the memories of the women taking part thus putting the study at risk of recall bias and the possibility that information reported on HRT use is not accurate.

A second source of bias is related to the response rate; a 73% response rate is good however there it is possible that the responders will disproportionally represent women who are more concerned about bone health.

The questionnaire asked about ever or previous HRT use, menopausal symptoms and whether DXA scans had been performed and what were the results.

Menopausal symptoms were assessed using an 18-item functional assessment of cancer therapy endocrine symptoms (FACT-ES) questionnaire. Questions related to occurrence of symptoms in the previous 7 days ranging from 'not at all' to 'very much'. Scores were then reversed and summed to obtain a total endocrine score ranging from 0-72 with lower values indicating worse symptoms.

Symptoms of oestrogen deprivation included hot and cold flushes, gastrointestinal problems, alterations in mood and sexual dysfunction.

DXA scanning was offered to all patients joining the study though was primarily aimed towards those with bone unprotected by oestrogen prior to 50 years of age.

Classification was undertaken using the WHO criteria based on age-matched controls. A T score in the lumbar vertebrae or left neck of the femur >-1.0 was considered normal while scores of -1.0 to -2.4 were considered osteopenic and ≤-2.5 was considered to be osteoporotic.

Citation: Gabriel C et al (2009) Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk reducing salpingo oophorectomy *Familial Cancer* 8;1:23-28

Design: Retrospective, descriptive data analysis

Country: USA

Setting:

Aim: to examine the uptake of total abdominal hysterectomy (TAH) and HRT and the relationship between TAH and HRT in unaffected female BRCA1/2 carriers who have undergone risk reducing salpingo oophorectomy (RRSO).

Inclusion criteria
Female
Positive BRCA1/2 status
Documented oophorectomy
Enrolment in a University of Pennsylvania approved protocol

Exclusion criteria
Oophorectomy for the treatment of gynaecological cancer
Diagnosis of breast cancer prior to oophorectomy
Documented use of HRT prior to oophorectomy
No documented BRCA1/2 mutation

Sample Size
N/A

Randomisation Method
N/A

Population
N=73 BRCA mutation carriers (47 BRCA1 and 26 BRCA2).

Study Duration

Interventions

Outcomes
Type of surgery
Patterns of HRT use
Subsequent development of breast cancer

Results
40 women (55%) underwent TAH in addition to RRSO and 17 of those (43%) used HRT
33 women (45%) underwent RRSO alone of whom 16 (48%) used HRT
No significant difference was observed in HRT use between women with or without TAH (p=0.06)

Predictors of TAH
BRCA1 versus BRCA2 status, use of prophylactic mastectomy and oophorectomy were not associated with TAH uptake.

Women undergoing RRSO under age 40 were more likely to have a TAH (76% versus 45%, p=0.02).
There was no increase in HRT use in women under 40 years of age compared with women over 40 years.

Predictors of HRT use
BRCA1 versus BRCA2 status, use of prophylactic mastectomy, age at RRSO and year of RRSO were not associated with HRT use.

HRT use
45% (33/73) women documents use of HRT, 40% did not use HRT and 11 women did not document HRT status.
In HRT users, 52% (17/33) used oestrogen only, 42% used combined HRT and 2 women used an unknown type of HRT.
In women using HRT following TAH/RRSO, 16 used oestrogen only HRT and one patient did not document HRT type.
6 women who used HRT also had a prophylactic mastectomy; 3 had TAH/RRSO and oestrogen only HRT and 3 had RRSO and combined HRT.
5 women who did not use HRT also had a prophylactic mastectomy
Prophylactic mastectomy did not appear to be associated with HRT use (p=0.75) however this was a small sample size.
Median age of HRT start was 40 years (29-52, SD 4.76) and median age of discontinuation (n=12 women with a discontinuation date) was 44 years (39-59, SD5.82).
Median length of HRT was 2.79 years (Range <1 month – 11 years, SD 3.22 years)
17 women with a known start age were still taking HRT at the point of last contact (no end date).
Median age of RRSO for HRT users was 40 years (29-52, SD 5.21) for the 31/33 HRT users with an exact date recorded.
Exact age at RRSO was known for 27/29 non-HRT users (median 42 years, range, 33-59, SD 6.21).
Median age for all women undergoing RRSO was 42 years (range 29.5-59.2, SD 5.82).
25 women underwent RRSO prior to age 40 of whom 15 took HRT and 40 women underwent RRSO on or after 40 years of whom 16 took HRT. There was no significant difference between the two age groups in relation to HRT use (p=0.13) though the numbers are too small to accurately detect any significant difference.

Women's Health Initiative Data
Secondary analysis aimed to examine whether the choice of TAH at the time of RRSO and the type of HRT that was chose had changed since the report of data from the WHI in 2002 which showed that the relative risk for breast cancer is higher in subjects using combined HRT compared with those using oestrogen only preparations.

65 women with an exact RRSO date were included in the analysis; 43 had RRSO prior to 31/07/2002 and 23 of these women underwent TAH and 23 elected to take HRT, 10 of whom were women who had undergone TAH.
22 women had RRSO after 31/07/2002 and 14 also had TAH. 8 women elected to use HRT of whom 6 had undergone TAH.
No significant difference was observed between RRSO before and after 31/07/2002 in either HRT use in women undergoing TAH (p=0.6) or in the overall use of HRT (p=0.12).
There was no significant difference between women with RRSO before and after 31/07/2002 in either combined HRT use (p=0.11) or oestrogen only HRT (p=0.53). Numbers in this analysis were again very small however and unlikely to be sufficient to detect a significant difference.

Prospective Cases of Breast Cancer

In the 17 women using oestrogen only HRT, 3 subsequently developed breast cancer while none of the women taking combined or 'unknown' HRT preparations developed breast cancer.
In the 29 women not taking HRT, 9 developed breast cancer; 3 were ER/PR negative, four unknown and two were ER^+/PR^-.
Of the 11 women with unknown HRT status, 5 developed breast cancer ER^+/PR^+ in one women and ER/PR negative in the remaining four.
Among the 17 women who developed breast cancer, 9 had a BRCA1 mutation and 8 had a BRCA2 mutation.

Time to oophorectomy from results disclosure
41 women had an exact date of disclosure available, 21 of whom had a disclosure date prior to 2002.
Median time from disclosure date to surgery was 124 days (range 32-807, SD 207).

General comments

Citation: Eisen A et al (2008) Hormone Therapy and the Risk of Breast Cancer in BRCA1 Mutation Carriers *Journal of the National Cancer Institute* 100;19:1361-1367

Design: Matched case control study

Country: North America

Setting:

Aim: To examine whether or not the use of hormone therapy (HT) is associated with a subsequent risk of breast cancer.

Inclusion criteria
Women in whom molecular analysis established were carriers of a deleterious mutation in BRCA1 or BRCA2.

Exclusion criteria

No a priori exclusion criteria were given for this study however the following women were excluded from the analysis:

- Women for whom menopausal status could not be determined
- Women with missing data for key variables relating to menopause
- Women with missing data relating to hormone therapy
- Women using hormone therapy prior to menopause
- Women diagnosed with ovarian, fallopian, peritoneal, omental cancer or other forms of cancer
- Women who underwent bilateral preventative mastectomy
- Women who took tamoxifen for prophylaxis

Sample Size
N/A

Randomisation Method
Method of randomisation was not relevant to this study as it was a matched case control study rather than a randomised trial.

Patients were case matched according to year of birth (within 2 years), age at menopause (within 2 years) and type of menopause (surgical versus natural).

Population
N=236 matched pairs
N=62 matched pairs of patients who underwent surgery (i.e. surgical menopause)

Study Duration

- The cohort, from which the study participants were drawn, was established in 1995 as part of a prospective study investigating non-genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers.
- No details were provided as to how long it took to recruit to the cohort, at what point recruitment ceased or in what year the current study commenced.

Interventions
Hormone therapy versus no hormone therapy

Outcomes
Risk of breast cancer – examined as the relationship between hormone therapy use and the risk of breast

cancer in BRCA1 mutation carriers and presented as an odds ratio.

Results

- Multivariate analysis, adjusted for parity, oral contraceptive use and country of origin, was conducted to compare women who had never used hormone therapy with women who had used hormone therapy.
- Most of the women in this study had undergone natural menopause
- There was a significant difference in the proportion of control women who had used hormone therapy at some stage compared with the case patients (29% versus 20%, p=0.02).
- The average duration of hormone therapy use was similar for case patients and control patients (4.0 years versus 3.7 years, p=0.7).
- Women who had used hormone therapy had a lower risk of breast cancer compared with women those who never used hormone therapy: **OR=0.58, 95% CI=0.35-0.96, p=0.03**
- The OR estimates were similar in the subgroup of BRCA1 mutation carriers who had undergone surgical menopause: **OR=0.68, 95% CI=0.19-1.21** though this group was small with only 62 pairs.
- For the whole cohort, the OR did not depend on age at diagnosis or age at menopause and there was no apparent modification of the OR with duration of use of hormone therapy.
- ER status information was available for 44% of patients (no details on what percentage underwent surgical menopause). Hormone therapy use was reported for 12% of patients with ER positive tumours and for 23% of ER negative tumours (p=0.29).

General comments

Citation: Madalinska, J et al (2006) The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy *Journal of Clinical Oncology* 24;22:3576-3582

Design: Retrospective observational study of a subgroup of patients from within a prospective cohort.

Country: The Netherlands

Setting:

Aim: to assess the impact of HRT use on the levels of endocrine symptoms and sexual functioning among premenopausal women who have undergone prophylactic bilateral salpingo oophorectomy.

Inclusion criteria
Women were eligible for the primary study if they were between 30-75 years of age, came from a hereditary breast/ovarian cancer family and had sought gynaecological advice on preventative measures at one of the clinics between 1996 and 2001.

Exclusion criteria
Women were excluded if they had undergone oophorectomy as treatment for a medical condition, or had metastatic cancer of any other severe co morbidities.

Sample Size
N/A

Randomisation Method
N/A

Population
N=1084 patients eligible for participation in this study

Study Duration
No information

Interventions
Hormone replacement therapy in premenopausal women who underwent PBSO compared with gynaecological screening in high-risk premenopausal women.

Outcomes
Endocrine Symptoms
Sexual Functioning

Results

- In total 450 premenopausal women were identified of whom, 36% (n=164) had undergone prophylactic oophorectomy with the remainder undergoing gynaecological screening.
- The PBSO group was significantly older, more likely to have been diagnosed with breast cancer, to be BRCA1/2 positive and to have undergone prophylactic mastectomy (all p<0.001).
- 47% of the PBSO group reported current use of HRT and the largest percentage were taking oestrogen/progesterone medications.
- HRT users were younger (45 vs. 47; p<0.05) and had undergone PBSO at a younger age (41 vs. 44; p<0.01), were less likely to have a history of breast cancer (17% vs. 47%; p<0.001) and were more likely to have undergone prophylactic mastectomy (62% vs. 41%; p<0.01) when compared with non-

users.
- 82% of current HRT users received a prescription at the time of PBSO and 72% reported having started HRT directly after surgery.
- 99% of HRT users reported being highly compliant with HRT.

Endocrine Symptoms
- Endocrine symptoms were assessed using the FACT-ES scale and calculating a mean FACT-ES scale score and the individual symptom frequencies.

- From the mean scores, PBSO HRT users reported significantly fewer symptoms overall when compared with the PBSO non-users group ($p<0.05$)
- At the individual level there were significant differences between users and non users in relation to hot flushes ($p=0.004$) cold sweats ($p=0.034$) and night sweats ($p=0.037$) in favour of HRT use.

- Significantly more endocrine symptoms were reported in the HRT users group overall compared with the screening group ($p<0.05$).
- Significant differences were found in the frequency of all vasomotor symptoms, vaginal dryness, pain/discomfort during intercourse and loss of interest in sex with the PBSO HRT users reporting more problems ($p<0.01$).

Sexual Functioning
- No significant difference in reported sexual activity was observed between the groups after controlling for age, history of breast cancer, tamoxifen use and prophylactic mastectomy.
- PBSO HRT users and PBSO non-users reported comparable levels of sexual functioning as measured by the pleasure, discomfort and habit scales of the Sexual Activity Questionnaire.
- PBSO HRT users reported significantly more discomfort during sexual activity when compared with the screening group ($p<0.01$).

General comments
Only the results that were relevant to the topic under investigation are reported here, this is particularly relevant when it comes to looking at the population data as the study appears to include many more women in the study; the study provides a detailed population flow chart outlining the patients and reasons for exclusions at each point.

Citation: Rebbeck T et al (2005) Effect of short term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: The PROSE study Group *Journal of Clinical Oncology* 23;31:7804-7810

Design: Retrospective analysis of a prospective cohort.

Country: USA

Setting:

Aim: to evaluate whether the breast cancer risk reduction conferred by bilateral prophylactic oophorectomy in BRCA1/2 carriers is altered by the use of post BPO HRT.

Inclusion criteria
In the original prospective cohort, women with germline, disease associated BRCA1/2 mutations that had BPO of any type were included. BRCA1/2 status confirmed by direct mutation testing with full informed consent.

BPO Cases
Women with disease associated BRCA1/2 mutation who underwent BPO

Non-BPO Controls
Women with disease associated BRCA1/2 mutation and were alive with at least one ovary intact and had no history of ovarian cancer at or before centre ascertainment.

Exclusion criteria
In the original prospective cohort, women with BRCA1/2 variants of unknown functional significance were excluded.

BPO Cases
BPO cases reported before assessment of BRCA status
BPO cases that reported a breast or ovarian cancer diagnosis before or within 6 months of centre ascertainment.
BPO cases if there was a history of ovarian cancer including borderline tumors and tumors of low malignant potential prior to BPO or if they had undergone unilateral or bilateral mastectomy before BPO or had a personal history of breast cancer (including DCIS) at or before the time of BPO.
Women in whom BPO was performed to treat ovarian cancer
Women whom had used HRT prior to BPO.

Non-BPO Controls
Women who had undergone bilateral or unilateral mastectomy or had a history of breast or ovarian cancer at, before or within 6 months of centre ascertainment.

Sample Size
A prospective sample was generated from a cohort of BRCA1/2 mutation carriers using recommendations which were made to specifically address potential sampling and information biases in the studies of prophylactic surgery from multicentre cohorts.

Randomisation Method
N/A

Population

Total sample with BRCA1/2 Mutation = 462
BPO patient cases = 155
Non-BPO patient controls = 307

Study Duration
No details provided

Interventions
HRT

Outcomes
Primary Endpoint: first diagnosis of *in situ* ductal carcinoma or invasive breast cancer (DCIS was included as it was thought to be a precursor to invasive breast cancer and therefore subject to the same risk exposures)

Follow-up
BPO patients were followed up from time of surgery and non-BPO patients were followed from the date of centre ascertainment or genetic testing (if testing preceded centre ascertainment) until first breast cancer diagnosis or other censoring event.

In a secondary analysis, non-BPO patients were followed from the time of centre ascertainment though this has the potential to induce bias due to the possibility that patients tested and subsequently diagnosed with ovarian cancer before centre ascertainment would not be included in the analysis. Follow-up time from the date of genetic testing in non-BPO patient controls was therefore selected to provide a more conservative estimate of risk reduction.

Censoring events included date of ovarian or primary peritoneal carcinoma diagnosis, prophylactic mastectomy, death or date of last contact if none of these events occurred.

Results

- BPO patients were significantly more likely to have taken HRT compared with non-BPO controls (60% vs. 7%; p<0.001) due to the need for menopausal symptoms management in women undergoing surgery.
- There was no significant difference between the groups in relation to contraceptive use or the probability of having a BRCA1/2 mutation.
- BPO patients were significantly older than non-BPO patients (42.7 years vs. 35 years; p<0.001)
- Analysis was therefore controlled for age, BRCA status, centre of ascertainment and parity.

- Mean follow-up for BPO patients was 2.6 years and for non-BPO patients was 4.1 years. 16% of BPO patients and 33% of non-BPO patients were followed for at least 5 years.

- Only first primary breast cancer was considered in the risk reduction analysis though a second primary cancer developed in 6 non-BPO patients.

- 8% (12/155) of BPO patients and 21% (65/307) of non-BPO patients were diagnosed with a first primary breast cancer during follow-up **(HR=0.40; 95% CI, 0.18-0.91)**
- Women who underwent BPO were diagnosed later with a mean age at diagnosis of 45.6 years versus 39.3 years in non-BPO patients.
- Median time to diagnosis was 2 years (range: 0.8-5.8) for BPO patients and 3.7 years (range 0.5-12.9 years) for non-BPO patients.

- 25% of women used HRT of some description; 93/155 (60%) of BPO patients and 21/307 (7%) of non-BPO patients used HRT.

- The reduction in breast cancer risk associated with BPO did not differ in women who had taken HRT **(HR=0.37, 95% CI, 0.14-0.96)** than in the overall cohort.

- 90% of BPO patients had their surgery before the age of 50 and 64% of those used some form of HRT. HRT use did not significantly alter the postsurgical breast risk **(HR=1.35, 95% CI, 0.16-11.58)**
- 54 patients (58%) of BPO patients taking HRT used an oestrogen only preparation and 34 patients (22%) took progesterone with or without oestrogen while 5 patients did not specify HRT type.
- Breast cancer risk reduction among BPO patients did not differ significantly when comparing patients taking progesterone with or without oestrogen versus oestrogen only **(HR=2.56; 95% CI, 0.08-78.13 for combined therapy)**. The number of women taking combined HRT was quite small however and therefore the study lacked the power to detect a meaningful effect.

General comments

7.17 The level of risk of future primary breast cancer at which, and the circumstances under which, the option of risk-reducing surgery should be discussed

7.17.1 Review Question

7.17.2 What level of risk indicates that risk reducing surgery is a viable option?**Background:**

For patients with an inherited risk of breast and ovarian cancer risk reducing surgery is often considered though the uptake is variable. Bilateral risk reducing mastectomy removes most of the breast tissue and consequently reduces the risk of developing breast cancer in the future. It is however not possible to remove all breast tissue and even with risk reducing surgery there will be a small risk of future breast cancer. Removal of both ovaries and fallopian tubes reduces the future risk of developing both ovarian cancer and breast cancer. Despite surgery there will remain a small risk of developing primary peritoneal carcinoma.

Surgical procedures are however associated with risks. For mastectomy these risks include immediate complications of surgery and in the longer term the need for cosmetic revision procedures in the future as well as the psychological implications of the surgery. Removal of the ovaries induces a surgical menopause which renders the women infertile as well as exposing the women to risks of premature oestrogen deficiency with loss of bone strength, higher risks of cardiovascular disease and menopausal symptoms.

The alternative to surgery is screening which would include mammography and MRI for women at high risk of breast cancer. The aim of screening is to allow early detection of a cancer and therefore more successful treatment of the cancer. Screening does not prevent the cancer developing, but, many breast cancers are not life threatening. Ovarian cancer screening is more difficult with more limited evidence of efficacy than breast cancer screening.

All women are at risk of breast cancer with the average lifetime risk of a British female being just over 10%; women with BRCA1/2 mutations have lifetime risks of 40-80%. Many women who are not BRCA1/2 carriers (for example women who have had 1 breast cancer) will have risks in excess of the UK average. The decision to recommend prophylactic surgery is complex and includes factors such as the remaining life time risk of cancer (and the risk of dying of that cancer compared to risk of dying of other diseases), risks (and costs) of surgery, effectiveness of any screening intervention and the patient's wishes.

7.17.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women who have had a diagnosis of breast cancer and who are at risk (sub group by low, moderate, high) of future primary breast cancer due to an inherited risk of breast/ovarian cancer	Risk reducing breast or ovarian surgery • Mastectomy • Bilateral Salpingo oophorectomy • Combination treatment • No risk reducing surgery (i.e. treat primary but no additional treatment)	Each Other	• Incidence of ovarian/breast cancer • Overall Survival • Health related quality of life

7.17.4 Relative Importance of these outcomes

The listed outcomes were the only outcomes considered to be of importance to the topic in question

7.17.5 How the information will be searched

Searches:	
Can we apply date limits to the search	None
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT's are not likely to be available for this topic so it is not appropriate to apply filters.
List useful search terms.	Breast cancer risk prophylactic surgery

7.17.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced. Comment from GDG: Effectiveness of surgery at reducing risk, effectiveness at saving lives, comparison with surveillance, health-related costs
List subgroups here and planned statistical analyses.	Re subgroups not sure. There are patients with very strong FH of cancer i.e. BRCA1/2 carriers and then others with a variable risk of breast cancer e.g. patients with a personnel history of cancer who may consider prophylactic surgery.

	Could use future lifetime risk as subgroup (similar to topic B) e.g. 10%, 10-20% etc.

7.17.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All dates	350	55	01/02/2012
Premedline	All dates	13	2	06/02/2012
Embase	All dates	562	51	08/02/2012
Cochrane Library	All dates	49	6	06/02/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All dates	636	46	07/02/2012

Total References retrieved (after duplicates removed): 99

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. ((high adj risk) or (increas$ adj risk)).tw.
20. or/9-19
21. 8 and 20
22. exp Mastectomy/
23. mastectom$.tw.
24. mammaplast$.tw.
25. mammoplast$.tw.
26. mammectom$.tw.
27. or/22-26
28. *Ovariectomy/
29. (oophorectom$ or ovariectom$ or salpingooophorectom$).tw.

30. 28 or 29
31. ((risk reduc$ or preventive or prophylactic) adj surg$).tw.
32. 27 or 30 or 31
33. 21 and 32
34. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis) adj3 (diagnos$ or confirm$ or past or histor$ or affect$)).tw.
35. 33 and 34
36. risk$.tw.
37. 35 and 36

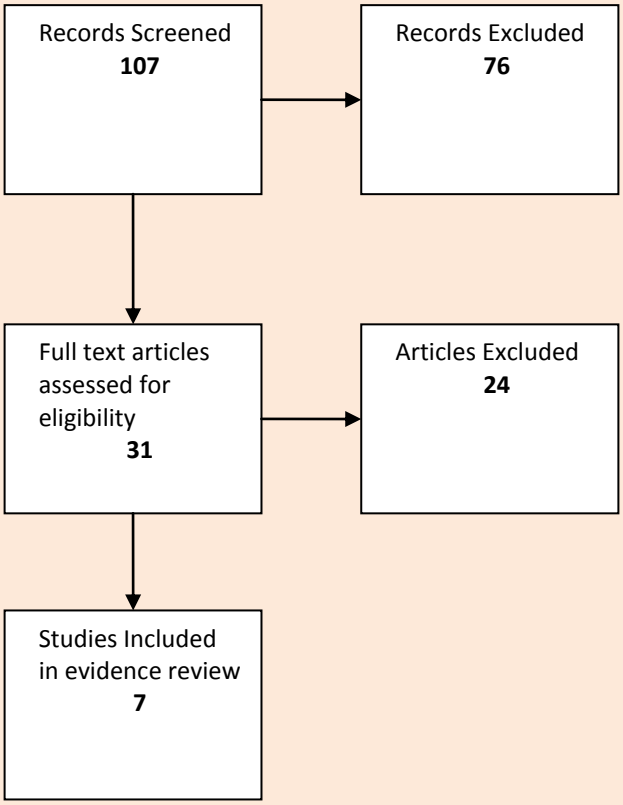
Notes:
No search filters were applied.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	01/02/2012-17/07/2012	11	3	17/07/2012
Premedline	01/02/2012-17/07/2012	13	2	17/07/2012
Embase	02/2012-07/2012	16	3	17/07/2012
Cochrane Library	02/2012-07/2012	10	0	23/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	02/2012-072012	12	2	23/07/2012

Premedline: 2 references added 10/09/2012
Embase: 1 reference added 01/10/2012

Total references retrieved after duplicates removed: 11

7.17.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews
No data/single case studies

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=2)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=5)
Qualitative Study (n=0)

Table 7.12: Summary of included studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcome
Boughey (2010)	Retrospective Case Series	385 (Cases) 385 (Controls)	Investigate whether contralateral prophylactic mastectomy in addition to therapeutic mastectomy is associated with a survival advantage in high-risk women with breast cancer	Therapeutic mastectomy + contralateral prophylactic mastectomy	Therapeutic mastectomy only	Overall Survival Disease Free survival Breast Cancer specific Survival
Domchek (2010)	Prospective multicentre cohort study	2482	To estimate the risk and mortality reduction following risk reducing salpingo oophorectomy and risk reducing mastectomy stratified by mutation status and prior cancer status	Risk Reducing Mastectomy Risk reducing salpingo oophorectomy		Ovarian cancer diagnosis Breast cancer diagnosis Second primary breast cancer diagnosis Mortality
Evans (2009)	Prospective Case Series	550	To assess the effectiveness of risk reducing surgery in high risk women including both BRCA carriers and non-carriers	Risk reducing mastectomy (bilateral or unilateral)		Observed and expected breast cancers
Kaas (2010)	Case Series Study	107	To examine the outcome of prophylactic mastectomy in a hospital based series of BRCA1/2 gene mutation carriers with and without a history of breast cancer	Contralateral prophylactic mastectomy		Occult breast cancer in symptomatic carriers Breast cancer incidence in symptomatic carriers
Lostumbo (2010)	Systematic Review of case series studies	7,384 women represented from 38 articles	To determine the effect of prophylactic mastectomy in women who have never had breast cancer and in women with a history of breast cancer	All types of prophylactic mastectomy		All cause mortality Breast cancer mortality Disease free

Study	Study Type	Population	Aim	Intervention	Comparison	Outcome
						survival Breast cancer incidence Physical morbidity Quality of life
Metcalfe (2011)	Retrospective Case Series	396	To estimate the risk of non-synchronous ipsilateral breast cancer after a diagnosis of breast cancer in BRCA carriers and evaluate the effects of various treatments on this risk	Breast conserving surgery plus Radiotherapy Chemotherapy Tamoxifen Bilateral oophorectomy	Each other	Incidence of ipsilateral breast cancer
Rebbeck (2009)	Summary of a systematic review and meta-analysis	8 studies	To present a summarised magnitude of risk reduction in women with BRCA1/2 mutations who have undergone bilateral risk reducing salpingo oophorectomy	Risk reducing bilateral salpingo oophorectomy	No risk reducing salpingo oophorectomy	Gynaecological Cancers Breast Cancers

7.17.9 Evidence Statements

Risk reducing Mastectomy

Overall Survival
Very low quality evidence suggests contralateral prophylactic mastectomy improves overall survival (Lostumbo et al 2010; Boughey et al; GRADE profile 7.10). In their systematic review of observational studies, Lostumbo et al (2010) estimated 15 year overall survival with prophylactic mastectomy as 64% versus 48% without (HR 0.6; 95% CI, 0.5-0.72).

Breast Cancer Incidence
Very low quality evidence consistently shows that contralateral prophylactic mastectomy reduces the incidence of breast cancer (Lostumbo et al, 2010; Domchek et al, 2010; Evans et al 2009 and Kaas et al, 2010; GRADE Profile 7.10). In Lostumbo et al (2010) the incidence of breast cancer was 0/64 in those treated with contralateral prophylactic mastectomy versus 36/82 in those who were not. Evans et al (2009) observed no incident breast cancers during 1178.58 person years follow-up after prophylactic mastectomy versus 13.15 expected.

Health Related Quality of Life
Very low quality evidence suggests most women are satisfied with their decision to undergo contralateral prophylactic mastectomy. In their systematic review Lostumbo et al (2010) found 83-94% of women were satisfied with their choice for prophylactic mastectomy and no significant difference was observed in satisfaction with their cosmetic outcome when compared with women who did not have contralateral prophylactic mastectomy (21.5% versus 15%).

Risk reducing Bilateral Salpingo Oophorectomy

Breast Cancer Incidence
Very low quality evidence (Rebbeck et al, 2009; Metcalfe et al, 2011; GRADE Profile 7.11) shows prophylactic bilateral salpingo oophorectomy (PBSO) is associated with a lower incidence of breast cancer when compared with women who did not undergo PBSO. The relative reduction in breast cancer risk with PBSO versus no PBSO was 51%; HR 0.49; 95% CI, 0.37-0.65 (Rebbeck et al, 2009)

Gynaecological Cancers
Very low quality evidence (Rebbeck et al, 2009; GRADE Profile 7.11) suggests the incidence of gynaecological cancers is lower in women who had PBSO compared with those who did not: Relative reduction in risk of 79%; HR, 0.21; 95% CI, 0.12-0.39 (Rebbeck et al, 2009).

7.17.10 Evidence Summaries

The overall body of evidence for this topic was comprised of case series and cohort studies with variable populations, interventions, outcomes and follow-up times and for this reason the quality of the evidence was considered to be very low for all outcomes (GRADE Profile 1&2).

The majority of the evidence for the topic was drawn from two systematic reviews of case series studies; one investigating the impact of risk reducing mastectomy (Lostumbo, 2010) and one investigating the impact of bilateral salpingo oophorectomy (Rebbeck, 2009).
None of the included studies reported subgroup analysis for low, medium and high risk patients

Outcomes

Risk Reducing Mastectomy

Overall Survival

- 15 year OS was 64% in the CPM group versus 48% in the comparison group (p=0.26) (Lostumbo, 2010).
- OS was improved in the CPM group versus the comparison group: HR=0.6, 95% CI, 0.5-0.72 (Lostumbo, 2010).
- All cause mortality was 5.8% after 7.8 years of follow-up after CPM (Lostumbo, 2010)
- BRCA1/2 carriers undergoing CPM showed improved survival compared with BRCA carriers not undergoing CPM (94% versus 77%, p=0.03) (Lostumbo, 2010)
- 10 year overall survival for patients undergoing CPM was 83% compared with 74% in the therapeutic mastectomy group: HR=0.77, 95% CI, 0.6-0.98, p=0.03) (Boughey, 2010).

Breast Cancer Incidence

- There was significantly lower breast cancer incidence in women undergoing CPM compared with controls (0/64 versus 36/182, p=0.005) (Lostumbo, 2010),
- BRCA1/2 carriers undergoing CPM had significantly lower incidence of breast cancer compared with patients not undergoing CPM (1.3% versus 14%, p<0.001) (Lostumbo, 2010),
- No cancers were observed following contralateral prophylactic mastectomy during 1178.58 person years follow up. The expected incidence rate was 13.15(Evans, 2009).

Ovarian Cancer Incidence

No studies reported on ovarian cancer incidence for women undergoing prophylactic mastectomy.

Health Related Quality of Life

- 83% -94% of women were satisfied with their decision to undergo contralateral prophylactic mastectomy (Lostumbo, 2010)
- There was a significant difference in the number of women undergoing CPM expressing concern about breast cancer compared with women who did not (50.3% versus 73.8%, p<0.001) (Lostumbo, 2010)
- There was no statistically significant difference in satisfaction in women undergoing CPM compared with those who did not in relation to cosmetic outcome (21.1% versus 15%.
- Women opting not have reconstruction following CPM reported significantly less regret compared with women opting for reconstruction (p=0.01) (Lostumbo, 2010).

Risk Reducing Bilateral Salpingo Oophorectomy

Overall Survival

No study reported overall survival following prophylactic bilateral salpingo oophorectomy (BSO).

Breast Cancer Incidence

- The relative reduction in risk of breast cancer following BSO was 51% for BRCA1 and BRCA2 carriers combined: HR=0.49, 95% CI, 0.37-0.65) (Rebbeck, 2009)
- The relative reduction in risk of breast cancer for BRCA1 carriers was alone was 53%: HR=0.47, 95% CI, 0.35-0.64 and for BRCA2 carriers was also 53%: HR=0.47, 95% CI, 0.26-0.84) (Rebbeck, 2009)
- In women undergoing breast conserving surgery and bilateral oophorectomy there was a significantly lower risk of ipsilateral breast cancer compared with women who did not undergo oophorectomy RR=0.33, 95% CI, 0.13-0.81, p=0.02 (Metcalfe, 2011).

- Oophorectomy was associated with a significant reduction in the risk of ipsilateral breast cancer in BRCA1 carriers (RR=0.25, 95% CI, 0.07-0.89, p=0.03) but not in BRCA2 carriers (RR=0.56, 95% CI, 0.16-2.02, p=0.38) (Metcalfe, 2011).

Gynaecological Cancers

- The relative reduction in risk of gynaecological cancers was 79% for women undergoing BSO: HR=0.21, 95% CI, 0.12-0.39 (Rebbeck, 2009)
- For BRCA1 carriers only the relative reduction in risk of gynaecological cancers was 85%: HR=0.15, 95% CI, 0.04-0.56 (Rebbeck, 2009).

Health Related Quality of Life

No studies reported on health related quality of life following prophylactic bilateral salpingo oophorectomy.

GRADE Profile 7.10: The level of risk of future primary breast cancer at which, and the circumstances under which, the option of risk-reducing surgery should be discussed

Quality assessment						
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Breast Cancer Incidence						
Lostumbo, 2010 (7 studies[1]); Domchek, 2010; Evans, 2009; Kaas, 2010						
10	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	VERY LOW
Overall Survival						
Lostumbo, 2010 (4 studies); Boughey, 2010						
5	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	VERY LOW
Health related Quality of Life						
Lostumbo et al, 2010						
17	observational studies	very serious[5]	Serious[6]	Serious[7]	very serious[8]	VERY LOW
Ovarian Cancer Incidence						
0	No Evidence Available					

[1]Lostumbo et al (2010) is a Cochrane Review including 39 studies of which only 7 were relevant to this outcome
[2] All case series studies with no standardised time points for assessing the incidence of breast cancer.

[3] All case series studies with different follow-up times and small numbers of patients
[4] Small numbers of patients in each studies (total n from 4 studies = 246)
[5]None of the included studies were designed with the specific aim of assessing quality of life outcomes
[6]There was heterogeneity across the individual studies in relation to methodologies used to assess health realted quality of life
[7]Not all studies reporting quality of life included relevant populations however due to the way in which the results were reported, it was not possible to separate the relevant studies only
[8]Due to the heterogeneity in methodologies of assessment of the quality of llife outcome it was felt that the results should be considered with caution and as such the decision was made to downgrade for imprecision.

GRADE Profile 7.11: The level of risk of future primary breast cancer at which, and the circumstances under which, the option of risk-reducing surgery should be discussed

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Risk reducing bilateral salpingo oophorectomy	control	Relative (95% CI)	Absolute	Quality
Overall Survival											
0	no evidence available										
Gynaecological Cancer Incidence Rebbeck et al 2009 (3 studies)											
3	observational studies	serious[1]	no serious inconsistency	serious[2,3]	serious[4]	none			HR 0.21 (0.12 to 00.39)		VERY LOW
Breast cancer incidence Rebbeck et al 2009 (3 studies); Metcalfe et al 2011											
4	observational studies	serious[1]	no serious inconsistency	serious[2,3]	serious[5]	none			HR 0.49 (0.37 to 0.65)		VERY LOW

[1] All studies were case series studies with variations in methodology including follow-up times and there were some questions around whether all the populations in each study overlapped.
[2] Some studies included BRCA carriers who did not have a diagnosis of breast cancer
[3] BRCA carriers do not constitute the whole 'at risk' population
[4] The total number of patients was large (n=2840) but there were questions around whether the statistical methods were applied as stated as the systematic review, labeled forest plots as relative risks and states in methodology section that relative risks were calculate yet reports hazards ratios

7.17.11 Evidence Tables

Citation: Boughey JC et al (2010) Contralateral prophylactic mastectomy is associated with a survival advantage in high risk women with a personal history of breast cancer *Annals of Surgical Oncology*

Design: Retrospective Case Series
Country: USA
Setting: Follow-up
Aim: to investigate whether contralateral prophylactic mastectomy in addition to therapeutic mastectomy is associated with a survival advantage in high-risk women with breast cancer

Inclusion criteria
Women with a family history of breast cancer and who underwent unilateral mastectomy for stage I/II breast cancer and prophylactic contralateral mastectomy

Exclusion criteria
Patients with both tumour stage and number of positive nodes were unknown
Contralateral prophylactic mastectomy occurred more than 2 years after breast cancer diagnosis
Cases with cancer found in the contralateral prophylactic mastectomy

Sample Size
None calculated

Randomisation Method
N/A

Population
N=385 patients undergoing contralateral prophylactic mastectomy
N=385 patients undergoing therapeutic mastectomy

Study Duration
Recruitment period: 1971-1993

Follow-up: <1 year to 38.8 years for the whole cohort

Interventions
Therapeutic Mastectomy + Contralateral Prophylactic Mastectomy (CPM)
Therapeutic Mastectomy Only (TM)

Outcomes
Overall Survival
Disease Free Survival
Breast Cancer Specific Survival

Results
Median Follow up was 18 years in the CPM group and 16.4 years in the TM only group

One TM patient was matched to one CPM patient according to age at breast cancer diagnosis, year of diagnosis, tumour stage (I or II) and nodal status (0, 1-2, or 3+ positive nodes)

A total of 33 contralateral breast events were observed with a median time to diagnosis of 7.2 years (range 94 days-26 years) - 2 patients in the CPM cohort and 31 patients in the TM cohort.
HR: 0.05, 95% CI 0.01-0.22, p<0.0001 (95% reduction in risk of CBC for patients undergoing CPM)
HR: 0.05, 95% CI 0.01-0.19, p<0.0001 (adjusted for age, stage, nodal status and first degree family history)

Overall Survival
10 year overall survival estimates were 83% for women in the CPM group and 74% for women in the TM group.
HR: 0.68, 95% CI 0.54-0.86, p=0.001
HR: 0.77, 95% CI 0.6-0.98, p=0.03 (following multivariate analysis to account for numerous factors including age, stage, nodal status and whether a patient underwent oophorectomy for a malignancy)

Disease Free Survival
Difference in disease free survival rates between the two groups was significant
HR: 0.66, 95% CI 0.53-0.82, p=0.0002 (favouring CPM)
HR: 0.67, 95% CI 0.54-0.84, p=0.0005 (following multivariate analysis

Breast Cancer Specific Survival
There were limited data on breast cancer specific survival and subject to ascertainment bias.
Analysis excluding patients for whom cause of death was unknown showed a non-significant survival advantage for patients in the CPM group:
HR: 0.75, 95% CI 0.55-1.02, p=0.07
HR: 0.82, 95% CI 0.59-1.14, p=0.24 (on multivariate analysis)

Impact of contralateral breast cancer on Survival
The TM only group recorded more recurrences overall, including more distant recurrences (82 distant recurrences versus 60 distant recurrences)
There were more deaths in the TM only group (162 versus 128)
The higher rate of recurrence and death was not accounted for solely by the higher rate of CBC
HR: 1.3, 95% CI 0.7-2.2, p=0.38 (TM group only, hazard ratio for risk of death in patients with and without CBC).

Subgroup Analysis
No statistically significant interaction between age group (<50 versus ≥50years) and CPM
Adjusted OS HR: 0.78 (CPM vs. TM only in patients aged <50)
Adjusted OS HR: 0.71 (CPM vs. TM only in patients aged ≥50)

No statistically significant interaction was between overall stage and CPM or between ER status and CPM.
Adjusted OS HR: 0.73 (CPM vs. TM only in patients with stage I disease)
Adjusted OS HR: 0.79 (CPM vs. TM only in patients with stage II disease)

Adjusted OS HR: 0.79 (CPM vs. TM only for ER negative patients)
Adjusted OS HR: 0.89 (CPM vs. TM only for ER positive patients)

General comments
Matching was performed by statistical personnel without knowledge of patient outcomes and by computerized programs to implement mathematically optimal matching algorithms.

Citation: Domchek S et al (2010) Association of risk reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality *JAMA* 304;9:967-975

Design: Prospective multicentre cohort study
Country: Multicentre (Europe and North America)
Setting: Follow-up
Aim: to estimate the risk and mortality reduction following risk reducing salpingo-oophorectomy and risk reducing mastectomy stratified by mutation status (BRCA1 or BRCA2) and prior cancer status

Inclusion criteria
Patients with no prior ovarian cancer diagnosis and no salpingo oophorectomy at the time of ascertainment
Minimum 6 months follow-up

Exclusion criteria
Patients receiving a cancer diagnosis within the first 6 months of follow-up
Women with both BRCA1 and BRCA2 mutations (n=12)
Salpingo oophorectomy before ascertainment date (n=525)
Ovarian cancer diagnosis prior to ascertainment date (n=363)
Follow up of less than 6 months (n=738)
Incident cases of cancer (n=135)

Sample Size
Not calculated

Randomisation Method
N/A

Population
N=2482

Study Duration
Patients mutation status ascertained between 1974 and 2008
Patients followed up to the end of 2009

In patients undergoing surgery:
Median follow-up was 3.65 years
Minimum Follow-up was 0.52 years
Maximum follow-up was 27.4 years

In patients not undergoing surgery:
Median follow-up was 4.29 years
Minimum follow-up was 0.5 years
Maximum follow-up was 27.9 years

Interventions
Risk reducing mastectomy
Risk reducing salpingo oophorectomy

Outcomes
Ovarian cancer diagnosis
Breast cancer diagnosis
Second primary breast cancer diagnosis
Mortality

Results

Breast Cancer

Risk reducing mastectomy was associated with a decreased risk of breast cancer in BRCA1 and BRCA2 mutation carriers. There were no breast cancer events during 3 years of follow-up compared with 98 events for women not undergoing risk reducing mastectomy.

Salpingo oophorectomy was associated with a reduction in risk for breast cancer in both BRCA1 and BRCA2 mutation carriers.

HR=0.63, 95% CI, 0.41-0.96 (BRCA1)

HR=0.36, 95% CI, 0.16-0.82 (BRCA2)

IN BRCA1 carriers with no prior breast cancer there was evidence of an age related breast cancer risk reduction, with women younger than 50 years showing a 49% reduction in risk for breast cancer if they underwent salpingo oophorectomy compared with women who did not. There was no significant difference in breast cancer risk for women undergoing salpingo oophorectomy over the age of 50 years compared to women who did not.

HR=0.51, 95% CI, 0.32-0.82 (Women aged <50 years who underwent salpingo oophorectomy)

HR=1.36, 95% CI, 0.26-7.05 (Women aged >50 years who underwent salpingo oophorectomy)

BRCA1 and BRCA2 carriers who had a previous diagnosis of breast cancer showed no reduction in risk of a second diagnosis of primary breast cancer if they underwent salpingo oophorectomy.

Ovarian/Primary Peritoneal Cancer

Risk reducing salpingo oophorectomy was associated with a decreased risk of ovarian/primary peritoneal cancer.

In patients with no prior breast cancer the **HR=0.31 (95% CI, 0.12-0.82)** for all BRCA1 mutation carriers.

There were no ovarian cancer events recorded in BRCA2 carriers without prior breast cancer who underwent salpingo-oophorectomy (6 years prospective follow-up) compared with 8 patients with BRCA2 mutation who did not undergo salpingo oophorectomy

In patients with prior breast cancer the **HR=0.15 (95% CI, 0.04-0.63)** for BRCA1 mutation carriers.

No cases of ovarian/primary peritoneal cancer were diagnosed in BRCA2 mutation carriers.

All Cause Mortality

Salpingo oophorectomy was associated with lower all cause mortality both in patients with no prior breast cancer and in patients with prior breast cancer.

HR: 0.45, 95% CI, 0.21-0.95 (women with no prior breast cancer)

HR: 0.30, 95% CI, 0.17-0.52 (women with prior breast cancer)

There was no significant difference in all cause mortality among BRCA2 patients though this may reflect the smaller population and fewer events occurring.

HR: 0.52, 95% CI 0.22-1.23

Overall survival was associated with salpingo oophorectomy in younger women (<50 years) and also in women over 50 years but the test for interaction was not significant which suggests no difference in overall mortality between the two groups:

HR: 0.41, 95% CI, 0.25-0.67 (<50 years)

HR: 0.37, 95% CI, 0.15-0.94 (≥50 years)

Breast Cancer Specific Mortality

Salpingo oophorectomy was associated with lower breast cancer specific and ovarian/primary peritoneal cancer specific mortality in all eligible women (not split by BRCA mutation status or prior breast cancer diagnosis).

HR: 0.44, 95% CI, 0.26-0.76 (breast cancer)
HR: 0.21, 95% CI, 0.06-0.80 (ovarian cancer/primary peritoneal cancer)

Women with BRCA1 mutations who underwent salpingo oophorectomy showed reduced breast cancer specific and ovarian cancer mortality (all BRCA1 women not split by breast cancer diagnosis).
HR: 0.38, 95% CI, 0.20-.072 (breast cancer)
HR: 0.22, 95% CI, 0.06-0.83 (ovarian cancer/primary peritoneal cancer)

There were no deaths from ovarian cancer or from breast cancer in the BRCA2 population

General comments
The study is not clear whether any patients had a bilateral salpingo oophorectomy or whether all patients had a unilateral salpingo oophorectomy.

The study compares the risk of primary peritoneal cancer with ovarian cancer risk in patients undergoing risk reducing salpingo oophorectomy which suggest that some patients underwent bilateral salpingo oophorectomy. It is not clear however whether all ovarian cancer outcomes include primary peritoneal cancer diagnoses.

Citation: Evans DG et al (2009) Risk reducing mastectomy: outcomes in 10 European centres *Journal of Medical Genetics* 46;4:254-258

Design: Prospective case series
Country: Europe wide study
Setting: Follow-up
Aim: to ass the effectiveness of risk reducing surgery in high risk women, both BRCA carriers and non-carriers

Inclusion criteria
No inclusion criteria for the study listed.

Women were considered eligible for bilateral risk reducing mastectomy if their lifetime risk of breast cancer was in excess of 25%
Women were considered eligible for unilateral risk reducing mastectomy if they already had a diagnosis of in-situ or invasive breast cancer in the contralateral breast.

It is assumed that women eligible for risk reducing surgery comprise the eligible population for the current study.

Exclusion criteria
No details are provided

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=550 women undergoing risk reducing surgery in total

Study Duration
1995 until October 2008 (when all centres were last contacted).

Interventions
Risk reducing mastectomy (bilateral or unilateral)

Outcomes
No clear outcomes listed for the study – appear to be the observed number of breast cancers compared with the expected number in women undergoing risk reducing surgery.

Results
There were 314 bilateral mastectomies in unaffected women and 236 contralateral mastectomies.
Follow-up was available for 539 women
16 women who had tumour in the at risk breast at the time of surgery were censored for further follow-up.
Life tables calculated and expected number of breast cancers of 21.30.
No breast cancers were recorded post-surgery in 2155.15 person/years follow-up

In 236 women undergoing contralateral mastectomy there were 1178.58 person/years follow-up with 13.15 cancers expected.
No cancers were recorded in the at-risk unaffected breast during follow-up.

In total there were 3334 person/years follow-up during which time no events were recorded following risk

reducing mastectomy (95% CI 0-3.7).

Median combined follow-up was 7.5 years (mean was 6.1 years).

The point estimate observed for annual incidence rate was 0/3334 person/years of follow-up (95% CI 0-3.7/3334) or 0.001 cases annually which is equivalent to at least a 90% reduction in breast cancer risk.

Total expected cancers at the date of last follow-up (October 2008) was 49 and at the time of publishing no cancers had been reported.

Subgroup analysis (by centre)
In Manchester 245 risk reducing mastectomies were performed with 1672.87 person/years follow-up.
From life table analysis, 16.82 cancers were expected but none were observed.
There were a total of 367 controls with 2438.44 person/years follow-up.
20.8 cancers were expected following life table analysis and a total of 21 cancers were diagnosed during follow-up.

A total of 58 women underwent risk reducing mastectomy: 28 women prior to risk reducing mastectomy and 30 after.
Oophorectomy reduced the expected cancers from 16.82 to 14.63.

Data on oophorectomy were not available for other centres however if a similar proportion of patients in other centres had undergone risk reducing oophorectomy, the expected cancers in at risk breast tissue would have been reduced from 34.44 to 29.87

General comments

Citation: Lostumbo L et al (2010) Prophylactic mastectomy for the prevention of breast cancer *Cochrane Database of Systematic Reviews*

Design: Systematic Review
Country: Multi-national
Setting:
Aim: to determine the effect of prophylactic mastectomy in women who have never had breast cancer and in women with a history of breast cancer.

Inclusion criteria
Women at risk of breast cancer including women with:

- a positive family history
- BRCA1/BRCA2 mutation carriers
- Previous cancer in one breast
- Previous multiple breast biopsies
- Previous diagnosis of lobular carcinoma in situ, atypical hyperplasia or proliferative breast disease

Exclusion criteria
Non specified

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=38 articles (involving 39 studies)

N=7,384 women represented

N=3,727 participants with prophylactic bilateral mastectomy

Study Duration

Interventions
All types of prophylactic mastectomy including:

- Subcutaneous mastectomy
- Total or simple mastectomy
- Modified radical mastectomy
- Radical mastectomy

Outcomes
All Cause Mortality (n=4 studies)

Breast cancer mortality (n=10 studies)
Disease free survival (n=5)
Breast cancer incidence (n=18 studies)
Physical morbidity (n=10 studies)
Quality of Life (including satisfaction with decision, psychological well being, impact on body image and impact on primary relationships and sexuality) (n=17 studies)

Risk of Bias/Methodological Quality

- Methodological quality varied across the individual studies.

- Selection bias represented the most likely potential source of bias as most studies did not adjust for potential confounding factors or failed to adjust for all major variables associated with a given outcome.
- Performance bias was not considered to be a problem for the included studies
- Potential for detection bias varied across the individual studies and common sources were recall bias in quality of life assessments and assessment of disease free survival due to the fact that regular intervals of follow-up were not generally specified.
- Studies did not generally report masking/blinding the study outcomes assessor or medical records extractor when determining cause of death from medical record which may be another source of detection bias.
- Attrition bias was of concern in a few studies as most studies accounted for all participants in the initial sample specified.
- Many studies lacked a comparison group
- Older studies will have included women who would no longer be considered high risk under current guidelines.
- Many of the studies did not allow subset identification by genetic testing

Results

Bilateral Prophylactic Mastectomy

All Cause Mortality
No study reported on all cause mortality

Breast Cancer specific mortality
A total of 4 studies reported on breast cancer specific mortality. No meta-analysis was conducted.

BRCA1 and BRCA2 mutations (1 study)
No deaths due to breast cancer were reported in women undergoing BPM (n=76) versus one death in the surveillance group (n=63) (follow-up was 3 years)

High Risk (strong family history but not necessarily BRCA mutation carriers)
From one study (Hartmann 1999b) 214 high risk participants underwent BPM and 403 controls (participants sisters) were followed up for a median of 14 years.
There were two deaths from breast cancer in the BPM group compared with 90 deaths in the control group. Depending on which model was used the risk reduction ranged from 81% to 94%

Moderate Risk
One study (Hartmann 1999b) reported no deaths among the 425 participants in the moderate risk group compared with the expected 10.4 deaths (GAIL model) giving a 100% risk reduction.
A second study (Geiger, 2005) reported no deaths in 276 women who underwent BPM compared with a calculated death rate of 1600/666,800 (0.2%) in matched controls (after 10 years of follow-up). This was despite the fact that 65% of the cases had multiple risk factors as compared with 12% of controls.

Breast Cancer Incidence
10 studies reported on breast cancer incidence and BPM (Borgen, 1998; Contant, 2002; Evans, 1999; Geiger, 2005; Hartmann 1999b (2 studies, one paper); Hartmann, 2001; Meijers-Heijober, 2001; Mulvihill, 1982; Rebbeck, 2004).

BRCA1 and BRCA2 mutations

3 studies (Hartmann, 2001; Meijers-Heijober, 2001; Rebbeck, 2004)
Hartmann, 2001 reported 0/26 breast cancers following BPM versus an expected incidence of 6-9 cancers. Relative risk reduction varied from 85% (95% CI, 15.6-99.6) to 100% (95% CI, 54.1-100.0).
Follow up time ranged from 5.8-28.5 years (median=13.4 years).

Meijers-heijober, 2001observed a significant difference in the incidence of breast cancer in the BPM group at three years follow-up (0/76 versus 8/63, p=0.003).

Rebbeck, 2004 reported a significant difference in breast cancers in BRCA1/2 carriers who underwent BPM compared with those who did not over a 5 year period of follow-up (2/102 versus 184/378, p<0.0001).
On exclusion of women who had a bilateral salpingo oophorectomy (BPO) the incidence of breast cancer in the BPM group versus controls remained significant (2/59 versus 149/305, p<0.001).
The reduction in breast cancer incidence also remained significant when analyzing subjects who opted for BPM after BRCA status was determined (0/24 versus 24/107, p<0.0001) and also remained significant on exclusion of those with BPO (0/19 versus 19/69, p<0.0001).

High Risk (Strong family history but not necessarily BRCA mutation carriers)
Hartmann, 1999b reported 3 participants developed breast cancer after surgery compared with and expected incidence of 30-52.9 cancers for a 90-94% reduction in incidence for this group.

Contant, 2002 reported no breast cancer in the 79 women who underwent BPM and who were BRCA mutation carriers or had a greater than 50% risk for breast cancer (2.8 years follow up).

Moderate Risk
Hartmann, 1999b observed significantly reduced incidence of breast cancer compared with expected incidence (GAIL model) for moderate risk women who underwent BPM.
4 participants developed breast cancer versus 37.4 as estimated based on the GAIL model for a reduction of 89.5% (median follow up was 14 years).

Geiger, 2005 reported a significant reduction in breast cancer in women who underwent BPM versus controls (1/276 versus 26,800/666,8000; HR=0.05, 95% CI, 0.001-0.044).

The remaining three studies (Evans, 1999 and Mulvihill, 1982) did not report detailed risk assessments.

Disease Free Survival
None of the included studies reported disease free survival as an outcome.

Physical Morbidity
A total of 5 studies reported on physical morbidity following BPM or CPM with breast reconstruction (Barton, 2005, Gabriel 1997, Metcalfe 2004b, Zion 2000; Zion 2003).
From Zion (2003) physical morbidity was defined as unanticipated reoperation. A total of 311/593 participants had unanticipated operations following initial surgery for reasons including; immediate post-operative complications, implant related issues and aesthetic concerns. (This was updated data in Zion 2000after longer follow-up (10.3 years).
In the initial study (Zion, 2000) it was reported that 432/1182 original implants were removed with 90% replaced and the percentage of reoperations without reconstruction following BPM was 21% (8/39).

Gabriel (1997) reported that 34% (95% CI 27.2-41.3) of cancer patients had complications following breast implant compared with 30.4% (95% CI 23.1-38.4) of women having prophylactic surgery and 12% (95% CI, 9.1-15.2) of women having implants for cosmetic reasons.

Metcalfe (2004) reported post-surgical symptoms in 38/60 women completing a questionnaire. Symptoms included numbness (45%), pain (12%), tingling (12%), infection (12%), swelling (3%) and breast hardness (3%).

Barton (2005) reported 64% of women with one or more complications with pain being the primary complication reported.

Quality of Life

There were 12 studies reporting on outcomes relating to Quality of Life 9(Borgen, 1998; Frost, 2000; Hatcher, 2001; Hopwood, 2000; Josephon, ,2000; Lloyds, 2000; Lodder, 2002; Metcalfe 2004b; Metcalfe, 2005; Mulvihill, 1982; Stefanek, 1995; van Oostrum, 2003) including satisfaction with decision, satisfaction with cosmetic outcome, satisfaction with medical process, psychological well-being/cancer related anxiety and body image and sexuality.

Satisfaction with decision

None of the studies compared the satisfaction with decisions between women who underwent PM versus surveillance.

Women reported a high degree of satisfaction with their decision and would recommend the surgery to other women with the same risk (Metcalfe 2004b, Stefanek, 1995), would chose BPM again (Borgen 1998, Frost 2000) and had no regrets with their decision (Borgen 1998, Josephson 2000) or were satisfied with their decision (Metcalfe 2004b).

Borgen (1998) reported 5% (21/370) of women being dissatisfied with their decision to have BPM

van Oostrum reported 79%(15/19) women felt that BPM was worth the adverse consequences.

Regrets were more common in women who reported that physicians initiated the discussion of BPM, a finding also observed by Frost (2000) with a correlation between dissatisfaction and listing physicians advice as the reason for BPM.

Satisfaction with cosmetic outcome

Stefanek 1995 reported 7/11 women opting for reconstruction were ‘quite a bit’ or ‘very much’ satisfied with the cosmetic results, 1/11 was ‘somewhat satisfied and 3/11 were ‘dissatisfied’ reporting that they felt the results to be ‘worse than expected’.

Frost (2000) reported similar findings with 70% (393/562) of women reporting that they were either ‘satisfied’ or ‘very satisfied’ with BPM, 11% (69/562) were neutral and 19% (107/562) were ‘dissatisfied’ or ‘very dissatisfied’ with the results.

Josephson (2000) found that 87% (13/15) women reported the outcome of their cosmetic surgery to be ‘better than expected’ though 53% (8/15) reported that they did not feel their new breast were part of their own body.

Hopwood (2000) reported 16% (7/45) patients required further psychiatric help following BPM and the psychiatric distress was associated with surgical morbidity.

Borgen (1998) reported 16% (52/331) felt the cosmetic results of their BPM were unacceptable.

Satisfaction in women who did not undergo reconstruction following BPM was also considered; from one study 3/14 women reported high satisfaction (Stefanek, 1998) and from a second study there was a high degree of correlation between the decision not to undergo reconstruction and satisfaction (p=0.001) (Frost, 2000).

Satisfaction with the medical process
A single study investigated patient satisfaction with regards the medical process (Josephson, 2000). The aim of the study was to investigate the degree to which counselling procedures helped women prepare for BPM with immediate reconstruction. It was reported that 66% of women felt dissatisfied with the support they received during information sessions and found it difficult to translate the genetic information they received and indicated that the felt 'blocked' from receiving the information.

Physchological well being/cancer related anxiety
From one study (Hatcher, 2001) psychological morbidity in women undergoing BPM decreased significantly at six months postoperatively (p=0.04) but decreased less for women opting not to undergo BPM (no data). Frost (2000) reported a diminished level of emotional concern about developing breast cancer in 74% (423/572) of women having BPM and neutral or favourable effects on emotional stability in 91% (520/572). 86% of women reported no change or favourable effects on stress.

Metcalfe (2004b) measured current psychological stress and reported 32.2% (19/59) women undergoing BPM had psychological distress symptoms consistent with the need for psychological counselling after a mean follow-up of 52.2 months (no pre-surgical baseline to compare against).

BRCA1 and BRCA2 mutations
BRCA1/2 mutation carriers opting for BPM reported a great reduction in anxiety and cancer-related distress from pre-test to one year after disclosure when compared with BRCA1/2 carriers who opted for surveillance and non-carriers ($p<0.05$) (Lodder, 2002).

In a study of BRCA1/2 carriers, van Oostrum (2003) reported a decrease in fear of developing breast or ovarian cancer in all women opting for BPM and/or BSO after 5 years.
Both BRCA1/2 carriers and non-carriers reported increased levels of anxiety and depression five years after disclosure as compared with one year after disclosure (p=0.009 and p=0.005 repsectively).

Body image and sexuality
Lodder (2002) reported significant negative differences for intimate relationships between women opting for BPM compared with those not opting for BPM (p=0.05).
From Metcalf (2004b) the impact of surgery on body image varied with 28.3% (17/60) reporting improved self image and 23.3% (14/60) reporting diminished image.
Responses about sexuality ranged from:

- no-one reporting a change in sexual activity or pleasure after surgery (Hatcher, 2001; Mulvihill, 1982)
- 23% reporting adverse effects Frost, 2000)
- 31.7% reporting worsened sexual lives (Metcalfe, 2004b)
- 55.1% reporting feeling less sexually attractive (Hopwood, 2000)
- 70% reporting changes in sexual relations (van Oostrum, 2003)
- 23% of participants reported adverse effects relating to feelings of femininity (Frost, 2000)
- 12% of participants reported moderate to negative change in body image (Hopwood, 2000)

Impact on interpersonal relationship
38% (5/13) respondents indicated that their relationship with their partner had changed following surgery but did not specify how (Josephson, 2000).

Predictors of Quality of Life
From Metcalfe (2005) two significant predictors of quality of life were identified; psychological distress and vulnerability (one sub scale of body image). Every one unit of increase in these two scores was correlated to

a decrease in quality of life scores by 74% and 13% respectively.

Contralateral Prophylactic Mastectomy

A total of 12 studies involved patients with a previous diagnosis of breast cancer who chose to undergo a contralateral prophylactic mastectomy in the other breast.

All cause mortality

All cause mortality was reported in 4 studies (Goldflam, 2004; Herrinton, 2005; Peralta, 2000; van Sprundel, 2005).

In a group of 246 patients, overall survival at 15 years was 64% for patients having SPM versus 48% for patients in the comparison group (p=0.26) (Peralta, 2000).

Survival in the CPM group was improved compared with survival in the comparison group, HR=0.6; 95% CI, 0.5-0.72 (Herrinton, 2005).

Survival was improved for BRCA1/2 carriers undergoing CPM versus those choosing not to undergo CPM (94% versus 77%, p=0.03) though this was primarily due to a higher mortality related to breast cancer and ovarian cancer and following adjustment for BSO, the difference was no longer significant (van Sprundel, 2005).

After mean follow-up of 7.8 years, all cause mortality was 5.8%following CPM (Goldflam, 2004).

Breast Cancer specific (disease specific) survival

A total of six studies reported on breast cancer specific survival with inconsistent results (Babiera, 1997; Goldflam 2004; Herrinton, 2005; Lee, 1995; Peralta, 2000; van Sprundel, 2005).

- A significant difference in breast cancer specific survival was observed: HR=0.57, 95% CI; 0.45-0.72 when comparing women undergoing CPM and no CPM at 5 years (Herrinton, 2005).
- There was no significant difference in disease specific survival in women with an initial stage 0-2 breast cancer diagnosis who underwent CPM; 71% (95% CI, 52-84) versus 53% (95% CI 42-62), p=0.06 (Peralta 2000)
- No disease specific survival advantage was observed at 5 years (Babiera, 1997)
- A significant disease specific survival advantage was observed for those who had CPM or biopsy in the contralateral breast at 15 year follow-up (Lee, 1995).
- Breast cancer mortality was 2.5% (8/239) after a mean follow-up of 7.8 years (Goldflam, 2004).

Incidence of breast cancer

Seven studies reported on breast cancer incidence (Contant, 2002; Gladflam, 2004; Herrinton, 2005; McDonnell, 2001; Metcalfe, 2004a; Peralta, 2000; van Sprundel, 2005).

- There was significantly lower breast cancer incidence in women undergoing prophylactic surgery compared with controls (0/64 versus 36/182, p=0.005) (Peralta, 2000).
- There was a reduced risk of breast cancer in the CPM treatment groups: HR=0.03 (Herrinton, 2005 and Metcalfe, 2004a)
- In BRCA1/2 carriers undergoing CPM there was a significant difference in breast cancer incidence compared with patients choosing not to undergo CPM (1.3% versus 14%, p<0.001) (van Sprundel, 2005).
- After a median follow-up of 10 years, 8/745 women undergoing prophylactic surgery later developed breast cancer of whom 6 were premenopausal. The expected contralateral incidence in premenopausal women, adjusted for Tamoxifen use was 106.2/388 for an adjusted reduction in breast cancer incidence of 94,4% (p<0.05). The expected contralateral incidence in postmenopausal women, adjusted for tamoxifen use and adjuvant therapy, was 50.3/357for an adjusted reduction in breast cancer incidence of 96% (p<0.05) (McDonnell, 2001).
- There was a 59% reduction in contralateral breast cancer associated with patients who had BPO

(Metcalfe, 2004a).

Disease free survival/recurrence

There were 4 studies which reported on disease free survival/recurrence (Babiera, 1997; Leis, 1981; Peralta 2000, van Sprundel, 2005).

- 5 year disease free survival was 89% in patients receiving CPM versus 90% in the control group (p=0.98) (Babiera, 1997).
- 15 year disease free survival was 55% (95% CI, 38%-69%) in patients receiving CPM compared with 28% (95% CI, 19%-36%) for the control group (p=0.01) (Peralta, 2000).
- Disease free survival was 93.1% (54/58) after 10 years of follow-up (Lei, 1981)
- In BRCA1/2 carriers, there was no improvement in disease free survival in the CPM group (p=0.11). In women who underwent both CPM and BPO there was a significant improvement in disease free survival when compared with women who did not also undergo BPO, HR=0.16, 95% CI, 0.04-0.61 (van Sprundel, 2005).

Physical Morbidity

There were 3 studies reporting on physical morbidity (Frost, 2005; Goldflam, 2004; Zion, 2003).

- 37% (189/506) of patients who had reconstruction underwent reoperation (Zion, 2003).
- 27% (157/583) of patients had unanticipated reoperation following CPM with or without reconstruction. 72% of these were related to implants (Frost, 2005).
- 16.3% (39/239) of patients had complications following CPM including reoperation, bleeding, necrosis and infection (Goldflam, 2004).

Quality of Life/Psychological Morbidity

Three studies reported on quality of life, satisfaction with mastectomy and other aspects of emotional or social functioning (Frost, 2005; Geiger, 2006; Montgomery, 1999).

Satisfaction with decision

All three studies reported on satisfaction with decision to undergo mastectomy:

- After a mean follow up of 10.3 years, 83% of women were satisfied with their decision to undergo CPM (Frost, 2005)
- 86.4% (371/429) of women were satisfied with their decision to undergo CPM (Geiger, 2006)
- Only 6% of women (18/296) women regretted their decision to undergo CPM with cosmetic results the primary reason for dissatisfaction and regrets were more common in women with whom the decision to undergo CPM was initiated by their physician (Montgomery, 1999).
- 75% of women undergoing subcutaneous mastectomy would chose to undergo CPM again versus 89% of women undergoing total mastectomy.

Satisfaction with cosmetic outcome

There were 3 studies reporting on satisfaction with cosmetic outcome (Frost, 2005; Geiger, 2006; Montgomery 1999).

- There was no statistically significant difference in satisfaction in women undergoing CPM compared with those who did not: 21.1% (108/510) versus 15% (9/60) respectively (Frost, 2005).
- 16% (18/111) of women who had reconstruction reported to be dissatisfied with the results (Montgomery, 1999)
- There was a correlation between having regrets and reconstruction with the 185 women opting not to have reconstruction after CPM expressing significantly less regret than those opting for reconstruction (p=0.01)

Psychological well being and cancer related anxiety
Two studies reported on psychological well-being and anxiety (Frost, 2005 and Geiger, 2006).

- 50.3% (257/511) of CPM acceptors expressed concern about breast cancer compared with 73.8% (45/61) of CPM decliners (p<0.001) (Geiger, 2006)
- There were no reported differences in between CPM acceptors and CPM decliners in relation to contentment with quality of life 76.3% versus 75.4% (Geiger, 2006).
- 74% of women undergoing CPM reported a diminished level of emotional concern about developing breast cancer (Frost, 2005).

Body Image/Sexuality
Two studies reported on body image and sexuality related outcomes (Frost, 2005; Geiger, 2006).

- No difference was observed between CPM acceptors and CPM decliners in relation to their satisfaction with their sexual lives (40.9% versus 40.3% respectively) (Geiger, 2006).
- 33% of women reported that their body image was negatively affected following CPM, 26% reported feeling less feminine, 23% had an adverse effect on their sexual lives and 12% reported adverse effects on their emotional stability (Frost, 2005).

Combined Bilateral and contralateral prophylactic mastectomy
There were a total of five studies reporting combined data on patients receiving either BPM or CPM (Bresser, 2006; Contant, 2002; Evans, 1999; Horton, 1978; Pennisi 1989) and collectively involved 2.008 participants, 88% of whom received BPM and 12% received CPM.

All cause Mortality
70% of patients (n=1500) were followed for 9 years and 0.3% were reported to have died of 'other causes' (Pennisi, 1989)

Breast Cancer/Disease specific mortality
3/1500 patients receiving prophylactic surgery subsequently died from breast cancer though 30% of patients were lost to follow-up (Pennisi, 1989).

Incidence of Breast Cancer
A total of three studies reported on breast cancer incidence (Horton, 1978; Pennisi, 1989; Evans, 1999)

- No breast cancer developed in any participant following prophylactic surgery (Horton, 1978)
- 6/1500 participants developed breast disease following surgery but 30% of participants were lost to follow-up (Pennisi, 1989)
- No breast cancers developed after surgery in patients who underwent prophylactic surgery despite and expected incidence of 4 (follow up was less than 5 years) (Evans, 1999)

Disease free survival
There were no data reported on disease free survival

Physical Morbidity
Two studies reported on outcomes related to physical morbidity (Contant, 2002; Pennisi, 1989)

- 29% (30/103 women who underwent PM with reconstruction had post-operative complications of which 77% required re-operation (Contant, 2002)
- 22% (2/9) patients who did not undergo reconstruction required re-operation (Contant, 2002)
- 5% of patients receiving prophylactic surgery developed skin necrosis (Pennisi, 1989)

Quality of Life/Psychological Morbidity

One study report outcomes related to quality of life (Bresser, 2006)

- 60% (68/113) of women who had reconstruction were satisfied with the result
- Significantly more women felt dissatisfied with the information provided (p=0.02)
- Significantly more women who reported complication were dissatisfied as compared with women not reporting complications (p=0.01)
- 15.5% (n=7) women would not opt for CPM again (p=0.01).

Satisfaction with medical process
14% (16/112) of patients reported not feeling sufficiently informed about prophylactic mastectomy (Bresser, 2006)

Body image/Sexuality
44% (40/90) women reported PM as having a negative effect on sexual relationship and this finding was significantly correlated with feeling insufficiently informed (p=0.01) and also with reporting that surgery did not meet their expectation (p=0.01).

General comments
All information on psychological outcomes may not be included as PsychINFO was not included in the search plan and was not searched.

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Citation: Kaas R et al (2010) Prophylactic Mastectomy in BRCA1 and BRCA2 mutation carriers: very low risk for subsequent breast cancer *Annals of Surgery* 251;3:488-492

Design: Case Series study
Country: Netherlands
Setting: Surgical follow-up
Aim: to examine the outcome of prophylactic mastectomy in a hospital based series of BRCA1/2 gene mutation carriers with and without a history of breast cancer.

Inclusion criteria
Symptomatic carriers should be free of distant disease
Prophylactic surgery to be carried out at the centre where the study was taking place
DNA analysis to be done before risk reducing surgery but not always prior to breast cancer diagnosis
At least 1 round of surveillance to be completed, consisting of clinical breast exam, annual mammography, and from 1998 onward MRI.
At prophylactic mastectomy the date of last MG/MRI should not exceed 6 months

Exclusion criteria
None given

Sample Size
No details

Randomisation Method
Not applicable

Population
N=107 symptomatic women included

Study Duration
1995-2008
Follow-up was until July 2008

Interventions
Contralateral prophylactic mastectomy

Outcomes
Not clearly stated, appear to be:

- Occult breast cancer in symptomatic carriers
- Breast cancer incidence in symptomatic carriers

Results
Occult Breast Cancer in symptomatic Carriers
107 women underwent contralateral prophylactic mastectomy (n=79 BRCA1 carriers and n=28 BRCA2 carriers).
No invasive cancer was diagnosed and occult DCIS was found in 2/79 BRCA1 and 3/28 BRCA2 carriers at prophylactic mastectomy following 313 woman years of post breast cancer treatment follow-up.
Significantly more favourable stages pTis + pT1N0 were found in BRCA1 carriers compared with BRCA2 carriers (p=0.027)

Follow-up after unilateral mastectomy in symptomatic carriers
Mean follow up was 5.8 years (SE=3.1) for BRCA1 carriers versus 4.2 (SE=3.0) for BRCA2 carriers
1/107 women was diagnosed with an incident breast cancer in the incompletely removed axillary tail of the

breast after an interval of almost two years. 7.8% (n=6) of BRCA1 carriers and 3.6% (n=1) of BRCA2 carriers were diagnosed with systemic disease of their first breast cancer. 3 BRCA1 and 1 BRCA2 carriers died with disease.
General comments The study included both asymptomatic and symptomatic BRCA carriers however only those patients with a breast cancer diagnosis (symptomatic) are of relevance to the topic and so only data relating to these patients are included in the evidence table.

Citation: Metcalfe KA et al (2011) Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers *Breast Cancer Research and Treatment* 127;1:287-296

Design: Retrospective Case Series

Country: USA

Setting: Follow-up

Aim: to estimate the risk of non-synchronous ipsilateral breast cancer after a diagnosis of breast cancer in BRCA carriers and evaluate the effects of various treatments on this risk.

Inclusion criteria
Women from families with a documented BRCA1/2 mutation were eligible if they:

- Diagnosed with stage I or II breast cancer at age 65 or younger and between 1975 and 2008
- Living and deceased women were eligible

Exclusion criteria
Women with a prior diagnosis of cancer, including breast cancer
Women who resided outside North America
Affected women who were known to be non-carriers

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=396 patients included in the analysis (methods section appears to suggest that there should be 422 patients so it would appear that 24 patients are unaccounted for in the analysis).

Study Duration
Recruitment phase was between 1975 and 2008
Mean follow-up was 10.5 years

Interventions
Breast conserving surgery and

- Radiotherapy
- Chemotherapy
- Tamoxifen
- Bilateral oophorectomy

Outcomes
Incidence of ipsilateral breast cancer

Results
A total of 396 with stage I or II breast cancer and intact ipsilateral breast were included in the analysis.

N=254 from BRCA1 mutation families
N=137 from BRCA 2 mutation families
N=5 from BRCA1 and 2 mutation families

Mean follow-up was 10.5 years and 81.1% of participants were alive at time of last follow up (81.1% of

participants were alive at study entry suggesting there were no additional deaths during the course of the study follow up)

All patients
There were 48 (12.1%) ipsilateral breast cancers diagnosed during the course of follow up.
Mean time from first breast cancer to ipsilateral cancer was 7.46 years (range 0.02-19.99 years)
No difference in time to diagnosis between BRCA1 (6.5 years, range 0.02-19.99)and BRCA2 carriers (8.7 years, range 1.02-19.0 years) p=0.18.

5 year actuarial risk of ipsilateral breast cancer was 5.8% (95% CI, 3.2-8.4%)
10 year actuarial risk of ipsilateral breast cancer was 12.9% (95% CI, 8.7-17.1%)
15 year actuarial risk of ipsilateral breast cancer was 15.8% (95% CI 10.6-21%)
Annual ipsilateral breast cancer risk was 1.2%

Cumulative risks of ipsilateral breast cancer for BRCA1 patients were 5.7% at 5 years, 11.2% at 10 years and 14% at 15 years
Cumulative risks of ipsilateral breast cancer for BRCA2 patients were 6.3% at 5 years, 17.5% at 10 years and 20.6% at 15 years.

Bilateral oophorectomy
64.4% (255/396) women underwent bilateral oophorectomy (20 prior to breast cancer diagnosis, 5 within the year following breast surgery, 224 at a later date and 6 dates are missing)
Patients with oophorectomy had a significantly lower risk of ipsilateral breast cancer compared with women who did not undergo oophorectomy**: RR=0.33, 95% CI 0.13-0.81, p=0.02**

In BRCA1 carriers, oophorectomy was associated with a significant reduction in the risk of ipsilateral breast cancer: **RR=0.25, 95% CI, 0.07-0.89, p=0.03**
There was no statistically significant difference for women with a BRCA2 mutation: **RR=0.56, 95% CI, 0.16-2.02, p=0.38**

Radiotherapy
87.4% (n=346) of women had radiotherapy following breast conserving surgery.
There was a 72% reduction in risk of ipsilateral breast cancer for women undergoing radiotherapy: **RR=0.28, 95% CI, 0.12-0.63, p=0.002**
In the whole cohort, the 10 year risk of ipsilateral breast cancer was 34% for women who did not receive radiotherapy versus 9% for women who did.
There was a significant protective effect of radiotherapy in BRCA1 carriers: **RR=0.26, 95% CI,0.10-0.70, p=0.008**
No significant effect was observed in BRCA2 carriers: **RR=0.59, 95% CI 0.06-5.40; p=0.64**

Chemotherapy
There was a significantly lower risk of ipsilateral breast cancer in women who had chemotherapy compared with women who did not: **RR=0.45, 95% CI, 0.24-0.84, p=0.001)**
The effect was similar in BRCA1 and BRCA2 carriers
There was no observed effect of tamoxifen on the risk of ipsilateral breast cancer.

General comments

Citation: Rebbeck TR et al (2009) Meta-analysis of risk reduction estimates associated with risk reducing salpingo oophorectomy in BRCA1 and BRCA2 mutation carriers (Provisional Abstract) *Journal of the National Cancer Institute* 101;2:80-87

Design: Systematic Review and Meta-analysis
Country: Multiple
Setting: Surgical Follow-up
Aim: to aid women and their clinicians in the making of cancer risk reducing treatment decisions by presenting a summarised magnitude of risk reduction in women with BRCA1/2 mutations who have undergone risk reducing bilateral salpingo oophorectomy

Inclusion criteria
Full details not provided as this study is a summary version
Information indicates that all studies which report risk reduction estimates due to RRSO in BRCA1/2 carriers published January 1999 and December 2007.

Exclusion criteria
None given apart from studies not reporting an estimate of risk reduction

Sample Size
No details

Randomisation Method
Not Applicable

Population
N= 8 studies estimating the risk of breast cancer in BRCA1/2 mutation carriers who were treated with RRSO

Study Duration
8 years

Interventions
Risk reducing bilateral salpingo oophorectomy

Outcomes
Gynaecological cancers
Breast Cancers

Results
Limitations of currently available data include variability in study design small sample sizes in individual studies, retrospective studies, and short follow-up times in prospective studies.
Breast cancer risk in BRCA1/2 mutation carriers treated with RRSO compared with BRCA1/2 carriers who did not receive RRSO was estimated in 8 studies
From 3 non-overlapping studies with a total of 5703 patients, the estimated relative reduction in risk of breast cancer in BRCA1/2 carriers who received RRSO relative with those who did not was 51% **HR=0.49 (95% CI, 0.37-0.65).**
From four non-overlapping studies the relative reduction in risk for BRCA1 carriers only was 53% **HR=0.47 (95% CI, 0.35-0.64)**
From three non-overlapping studies the relative reduction in risk for BRCA2 carriers only was also 53% **HR=0.47 (95% CI, 0.26-0.84)**
From three non-overlapping studies (n=2840), the relative reduction in risk of gynaecological cancer was 79% **HR=0.21 (95% CI, 0.12-0.39)**
From one study, the relative reduction in risk of gynaecological cancers in BRCA1 mutation carriers was 85%

HR=0.15 (95% CI, 0.04-0.56)

General comments

10 studies investigated breast or gynaecological cancer outcomes in BRCA1/2 mutation carriers who had undergone RRSO

8 studies estimated the risk of breast cancer in BRCA1/2 mutation carriers receiving RRSO compared to patients who did not receive RRSO.

When two or more studies had overlapping study samples, only one published report from each group was included.

No evidence of publication bias was observed

The methodology section of the study states that relative risks were calculated however the data presented was hazards ratios and the forest plots were labeled as being relative risks despite being hazard ratios therefore there are some questions over the methodological quality of the study.

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Kauff ND et al (2008) Risk reducing salpingo oophorectomy for the prevention of BRCA1 and BRCA2 associated breast and gynaecological cancer: A multicentre prospective study *Journal of Clinical Oncology* 26;8:1331-1337

Kramer et al (2005) Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers *Journal of Clinical Oncology* 23;34:8629-8635

Rebbeck et al (2002) Prophylactic oophorectomy in carriers of BRCA1 and BRCA2 mutations *New England Journal of Medicine* 346;21:1616-1622

Rebbeck et al (1999) Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers *Journal of the National Cancer Institute*91;17:1475-1479

7.18 The factors which indicate that offering risk reducing surgery is not appropriate

7.18.1 Review Question

What are the factors that indicate that offering risk reducing surgery is not appropriate?

7.18.2 Background

Bilateral mastectomy and/or removal of ovaries and fallopian tubes can reduce the risk of breast cancer, ovarian and fallopian tube cancers in women at high risk of such cancers. The aim of surgery is to prevent a potentially life threatening cancer. There are however risks associated with surgery and there are circumstances when surgery would be inadvisable. Such circumstances include patients with co-morbidities that either significantly increase the risk of surgery or significantly increase the risk of dying before any potentially preventable cancer would become life threatening. Other circumstances may be relevant to patient choice, for example women keen to have children would advised to avoid removal of ovaries until they have completed their family.

7.18.3 Question in PICO format

Patients/population	Intervention	Factors	Outcomes
Women who have had a diagnosis of breast cancer and who are at risk of future primary breast cancer due to an inherited risk of breast/ovarian cancer	Risk reducing breast or ovarian surgery • Mastectomy • Bilateral salpingo oophorectomy • Combination treatment	• Parity • Age • Menopausal Status • Co morbidities • Patient Choice • Life Expectancy • Metastatic Disease	• Health related quality of life • Patient Satisfaction (Concentrate on qualitative/patient reported data to inform this topic.)

7.18.4 Relative importance of these outcomes

There were limited outcomes of interest to this topic and all were considered to be of equal importance.

7.18.5 How the information will be searched

Searches	
Can we apply date limits to the search	None given
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT's are not likely to be available to address this topic and therefore filters are not appropriate
List useful search terms.	

If our original search finds nothing are we going to adjust the PICO and re-run the search? (*Note:* Due to time constraints, this is a situation we would make every effort to avoid and would only occur in exceptional circumstances)

7.18.6 The review strategy

The GDG subgroup were unsure how much value there was in doing a literature review for this topic. Assuming those who should be considered for prophylactic surgery in H1 were defined, then this group is really people for whom surgery would normally be considered but for whom it may be inappropriate because they have co-morbidities, they want children etc. Such decisions tend to be pragmatic and the GDG subgroup were not sure what, if any, data there will be out there. It was considered that the topic could include patients who are too low risk for it to be worthwhile but that has been included by default in H1 anyway.

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	No details

7.18.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All dates	466	73	23/01/2012
Premedline	All dates	21	2	23/01/2012
Embase	All dates	733	75	24/01/2012
Cochrane Library	All dates	51	5	25/01/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All dates	723	48	25/01/2012

Total References retrieved (after duplicates removed): 127

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.

7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. ((high adj risk) or (increas$ adj risk)).tw.
20. or/9-19
21. 8 and 20
22. exp Mastectomy/
23. mastectom$.tw.
24. mammaplast$.tw.
25. mammoplast$.tw.
26. mammectom$.tw.
27. or/22-26
28. *Ovariectomy/
29. (oophorectom$ or ovariectom$ or salpingooophorectom$).tw.
30. 28 or 29
31. ((risk reduc$ or preventive or prophylactic) adj surg$).tw.
32. 27 or 30 or 31
33. 21 and 32
34. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis) adj3 (diagnos$ or confirm$ or past or histor$ or affect$)).tw.
35. 33 and 34

Notes:

No search filters were applied

Update Searches

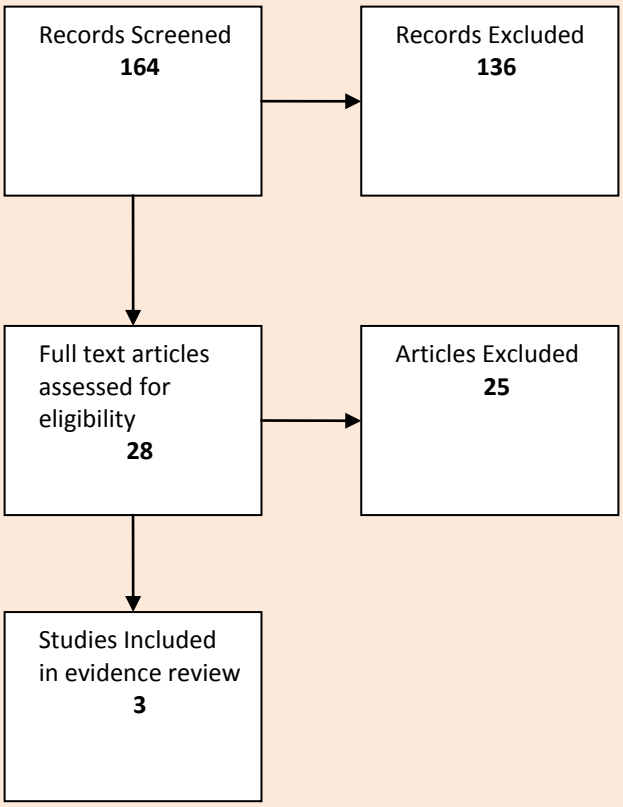
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	01/02/2012-17/07/2012	92	14	17/07/2012
Premedline	01/02/2012-17/07/2012	50	14	17/07/2012
Embase	02/2012-07/2012	20	2	17/07/2012
Cochrane Library	02/2012-07/2012	10	0	23/07/2012
Web of Science (SCI & SSCI) and ISI	02/2012-07/2012	64	7	23/07/2012

Proceedings				

Premedline: 2 references added 05/09/2012
Premedline: 1 reference added 10/09/2012
Embase: 2 new references added 01/10/2012

Total references retrieved after duplicates removed: 37

7.18.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=3)
Qualitative Study (n=0)

Table 7.13: Summary of Included Studies

Study	Study Type	Population	Aim	Intervention	Comparison	Outcome
Graves et al (2007)	Prospective Case Series	N=435	To prospectively evaluate the psychosocial outcomes of contralateral prophylactic mastectomy (CPM) among previously diagnosed breast cancer patients following the receipt of genetic test results	Contralateral prophylactic mastectomy	None	Cancer specific distress General distress
Montgomery et al (1999)	Retrospective Case Series	N=296	To understand the factors which may cause a woman to regret her decision to undergo prophylactic surgery in order to help counsel patients facing the decision and minimise future regret	CPM	None	No clear outcome listed, appears to be assessing the level of regret among women who underwent contralateral prophylactic mastectomy and the factors associated with regret.
Tercyal et al (2007)	Prospective Case Series with a Qualitative Assessment of a subset of patients who agreed to baseline interview and genetic testing	N=167	To compare the impact of BRCA1/2 genetic test result and contralateral prophylactic mastectomy on quality of life and psychosocial functioning among newly diagnosed breast cancer patients who opted for CPM at the time of their definitive surgical treatment versus patients who did not	CPM	None	The impact of CPM in the short and long term in relation to sociodemographics, disease and treatment characteristics, surgical recommendations, genetic test result, definitive surgery, breast reconstruction, oophorectomy, quality of life,

						psychological distress.

7.18.9 Evidence Statements

This is conflicting low quality evidence about the relationship between age and outcome following contralateral prophylactic mastectomy in women diagnosed with breast cancer (Tercyak et al, 2007; Montgomery et al, 1999 and Graves et al, 2007; GRADE Profile 1). Two studies did not find a difference in the quality of life of younger and older patients following contralateral prophylactic mastectomy (Tercyak et al, 2007; Montgomery et al, 1999) whereas younger age was associated with general distress in Graves et al (2007).

Literature searches identified no evidence about the relationship between parity, menopausal status, comobidity, patient choice, co-mobidities, patient choice, life expectancy, metastatic and quality of life following contralateral prophylactic mastectomy.

GRADE Profile 7.12: The factors which indicate that offering risk reducing surgery is not appropriate

Quality assessment							
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Quality of Life							
3	observational studies	serious[1]	very serious[2]	serious[3]	serious[4]	none	VERY LOW

[1] All studies were case series studies and were not primarily designed to assess quality of life in the patients participating.
[2] Three studies provide conflicting evidence that age is related to quality of life outcomes. The conflict in the results may be due to the fact that the three studies compared different age groups and used different assessments of quality of life/distress.
[3] None of the studies were designed to assess the impact of the various factors listed in the PICO on quality of life or on patient satisfaction.
[4] All included studies had small numbers of patients and in at least one case there was a high risk of selection bias due to the method of recruitment used, all of which will have and impact on the precision of the results presented.

7.18.10 Evidence Tables

Citation: Graves KD et al (2007) Predictors of contralateral prophylactic mastectomy among breast cancer survivors *Breast cancer Research and Treatment* 104;3:329
Design: Prospective case series study **Country**: USA **Setting:** Follow-up **Aim**: to prospectively evaluate the psychosocial outcomes of contralateral prophylactic mastectomy among previously diagnosed breast cancer patients following the receipt of genetic test results
Inclusion criteria Women affected with unilateral breast cancer who received BRCA1/2 test results between 1995 and 2000
Exclusion criteria Patients unaffected with breast cancer Patients with bilateral breast cancer or ovarian cancer Male patients Any individual who had taken part in the intervention arm of a clinical trial to evaluate psychosocial telephone counseling following genetic testing for BRCA1 and BRCA2 mutations Women who received a true negative genetic test result
Sample Size No details
Randomisation Method Not Applicable
Population N=488 eligible women 11% (n=53) were dropped due to missing baseline data giving a final sample of 435 women
Study Duration Patients were diagnosed and tested between 1995 and 2000 No final cut-off date for follow-up data collection was recorded however 99 patients did not complete 12 month follow up and so were not included in the 12 month analysis
Interventions Contralateral prophylactic mastectomy
Outcomes Cancer specific distress using the 15 item Impact of Event Scale (IES) General distress using the validated Hopkins symptom checklist (HSCL-25)
Results Internal consistency for cancer specific distress was 0.87 Internal consistency for general distress was 0.91 Mean age of participants was 50.1 years (range: 26.7-80.4 years, SD=10.4) Mean time from initial diagnosis for the population was 5.7 years (range: 0.03-35.2 years, SD=6.2)

Rates of CPM
At baseline, 16% of patients had undergone contralateral prophylactic mastectomy prior to referral for genetic counselling and testing.

In the remaining 365 women there were 51 positive test results
9/51 (17.6%) of women opted to undergo contralateral prophylactic mastectomy in the 12 months following testing
8/314 women with uninformative test results underwent contralateral prophylactic mastectomy

By 1 year post genetic testing. 20% of the total population (87/435) had opted for contralateral prophylactic mastectomy.

Predictors of contralateral prophylactic mastectomy prior to genetic counselling
Logistic regression analysis indicated that having CPM prior to genetic counselling was independently associated with:
Younger age at breast cancer diagnosis – OR=0.95, 95% CI, 0.92-0.98,
More time since breast cancer diagnosis – OR=1.07, 95% CI, 1.02-1.11
Having at least one affected first degree relative – OR=3.63, 95% CI. 1.78-7.44
Not being in full time employment – OR=0.57, 95% CI 0.33-0.99

Predictors of contralateral prophylactic mastectomy following genetic counselling
Logistic regression analysis indicated that having CPM in the 12 months following genetic counselling and testing was independently associated with:
Genetic test result (patients with positive result were more likely to undergo CPM): OR=0.23, 95% CI, 0.08-0.66
Age at time of breast cancer diagnosis (patients younger at time of breast cancer diagnosis were more likely to undergo CPM): OR=0.94, 95% CI, 0.88-1.0
Baseline cancer specific distress (women more distressed prior to genetic counselling were more likely to undergo CPM): OR=3.28, 95% CI, 1.29-8.34

Impact of CPM on psychological distress
The impact of CPM was assessed at the 12 month follow-up

Cancer specific distress
Baseline variables associated with cancer-specific distress outcomes included:
Baseline cancer specific distress ($p<0.001$)
Age ($p=0.001$)
When controlling for baseline cancer specific distress and age, genetic test result (positive versus uninformative) was not significantly associated with cancer specific distress at 12 months
CPM status (no CPM versus CPM prior to genetic counselling versus CPM following genetic counselling) was not significantly associated with cancer specific distress at 12 months.

General distress
Baseline variables associated with general distress outcomes included:
Baseline general distress ($p<0.001$)
Age ($p=0.001$)
Time since breast cancer diagnosis ($p<0.001$)

Genetic test result and CPM status were not significant predictors of general distress at 12 months General distress at baseline ($p<0.001$) and less time since diagnosis ($p=0.039$) were independent predictors of general distress at 12 months.
General comments The study was only investigating BRCA1 and BRCA2 mutation carriers and so represents only a subset of the population of interest for this topic. Patients did not differ in relation to baseline data on any psychosocial or sociodemographic variables

Citation: Tercyak KP et al (2007) Quality of life after contralateral prophylactic mastectomy in newly diagnosed high risk breast cancer patients who underwent BRCA1/2 gene testing *Journal of Clinical Oncology* 25;3:285-291

Design: Prospective case series with a Qualitative Assessment of a subset of patients who agreed to baseline interview and genetic testing.

Country: USA

Setting:

Aim: to compare the impact of BRCA1/2 genetic test result and contralateral prophylactic mastectomy on quality of life and psychosocial functioning among newly diagnosed breast cancer patients who opted for CPM at the time of their definitive surgical treatment versus patients who did not

Inclusion criteria
Newly diagnosed patients (DCIS to grade III breast cancer) who had not received definitive local breast cancer treatment and who had a 10% probability of carrying a BRCA1/2 mutation

Exclusion criteria
No details

Sample Size
No details

Randomisation Method
Not Applicable

Population
N=167 women who completed baseline interview and underwent genetic counseling and testing

Study Duration
1997-2003

Interventions
Structured telephone interview assessing sociodemographics, family history, disease characteristics, quality of life/distress and surgical recommendations

Genetic counselling session with an oncology nurse educator or a genetic counsellor.

Follow up interviews were completed at 1, 6 and 12 months after disclosure of test results.

Outcomes
The impact of CPM in the short and long term by analyzing the 1 and 12 month assessments only in relation to:
Sociodemographics
Disease and treatment characteristics
Surgical recommendations
Genetic test result
Definitive surgery
Breast reconstruction
Oophorectomy
Quality of life

Psychological distress

Results

There was no significant difference in short or long term quality of life and distress according to age (<40 years compared with ≥40 years).

Multivariate predictors of short term quality of life and distress

Quality of Life

After controlling for baseline FACT-B, stage and receipt of adjuvant chemotherapy, neither test result nor receipt of CPM predicted cancer specific distress.

Family history of breast cancer was associated with cancer specific distress at 1 month (β=0.17, p=0.02). Patients with 2 or more affected relatives reported more distress compare with those with a weaker family history.

Genetic testing specific distress

Genetic test result was significantly associated with genetic testing distress (ΔR^2=0.17, p<0.001).

Carriers reported significantly more genetic testing specific distress compared with patients with uninformative results (β=0.41, p<0.001).

Receipt of CPM was unrelated to short term genetic testing distress (ΔR^2=0.01, p=0.11)

Multivariate Predictors of Long term quality of life and distress

Quality of Life

After controlling for baseline Fact-B score, stage and receipt of oophorectomy neither genetic test result nor CPM predicted quality of life.

Only receipt of oophorectomy was associated with quality of life in the final model (β= -0.15, p=0.04) with women undergoing oophorectomy reporting a poorer quality of life.

Cancer specific distress

After controlling for stage and receipt of adjuvant chemotherapy, BRCA1/2 test result significantly predicted long-term distress (ΔR^2=0.06, p=0.001).

Mutation carriers (β=0.23, p=0.001) and those who received chemotherapy (β=0.17, p=0.01) reported higher genetic testing distress.

No interaction between test result and surgery decision was observed in any of the models.

General comments

Possible source of selection bias: Recruitment was by self referral either following physician recommendation or through signing up with a family history screening form which was distributed in the waiting rooms of participating surgeons.

Citation: Montgomery LLT et al (1999) Issues of regret in women with contralateral prophylactic mastectomies *Annals of Surgical Oncology* 6;6:546-552

Design: Retrospective Qualitative Case Series

Country: USA

Setting: Follow up

Aim: to understand the factors which may cause a woman to regret her decision to undergo prophylactic surgery in order to help counsel patients facing the decision and minimise regret in the future.

Inclusion criteria
Patients with breast cancer who had undergone prophylactic mastectomy
Patients with a family member with breast cancer who had undergone prophylactic mastectomy

Exclusion criteria
No details

Sample Size
No Details

Randomisation Method
Not Applicable

Population
N=296

Study Duration
Recruitment started in October 1996, no end date is given but study published in 1999.

Interventions
Questionnaire

Outcomes
No clear outcome given – appears to be assessing the level of regret among women who underwent contralateral prophylactic mastectomy and the factors associated with regret.

Results
Surgical procedures were carried out between 1954 and 1998
The mean number of years of follow up was 10.9 years (median 4.9, range 0.25-43.8)
Mean age at CPM was 53.8 years (median 53, range 27-80)

89 women (30%) reported at least one first degree relative with breast cancer and of these, 14 patients (16%) reported having more than one first degree relative with breast cancer.
9 women (3%) had undergone BRCA testing (2 BRCA carriers, 5 non-carriers and 2 women did not know their results).
58 women (20%) reported at least one second degree relative with breast cancer

Initiation of Discussion
Physician initiated discussion about CPM occurred in 72% of patients (n=212) and 28% of patients initiated the discussion themselves.
74% of women who themselves initiated the discussion about CPM had a first degree relative with breast

cancer.

Reason for CPM
Physician advice regarding high risk of developing contralateral breast cancer – 30% (n=88)
Fear of developing more breast cancer – 14% (n=43)
Desire for cosmetic symmetry – 10% (28)
Family history of breast cancer – 7% (n=21)
Fibrocystic breast disease – 4% (n=13)
A combination of the above – 32% (n=95(
Other Reasons – 2% (n=6)
Unknown reasons – 0.7% (n=2)

Timing of CPM and Reconstruction
36% of women (n=106) had simultaneous COM at the time of therapeutic mastectomy and 64% (n=190) had a delayed CPM.
63% (n=185) of women did not have breast reconstruction and of the remaining 111 patients undergoing reconstruction, 62% (n=69) had immediate reconstruction.
Cosmetic results were reported as excellent, acceptable or unacceptable:
Excellent = 32% (n=35)
Acceptable = 48% (n=53)
Unacceptable = 16% (n=18)

Pathology in CPM
Respondents reported and incidental finding of cancer in 8% (n=24/296) CPM specimens

Regrets
6% of women (n=18) expressed regrets about the decision to undergo CPM
Reasons for regret included:
Poor cosmetic result of the CPM or of the reconstruction – 39% (n=7)
Diminished sense of sexuality – 22% (n=4)
Lack of education regarding alternative surveillance methods or CPM efficacy – 22% (n=4)
Other reasons – 17% (n=3)

12/111 undergoing reconstruction had regrets compared with 5/185 women who did not undergo reconstruction (p=0.01)

Regrets tended to be less common in women whose physician initiated CPM discussion compared with women who themselves initiated the discussion though the difference was small and not statistically significant (11/212 versus 7/84, p=ns).

Age at surgery, family history of breast cancer, stage of index lesion and reason for CPM had no impact of regret status.

General comments
Recruitment to the study was via advert in several lay journals asking eligible patients to get in contact if they were interested in taking part. This represents a strong source for potential selection bias and as such the representativeness of the population taking part in the study in relation to the wider eligible population.

7.19 The effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ with a TP53 mutation or at high risk of TP53 mutation.

7.19.1 Review Question

What is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ (DCIS) with a TP53 mutation or at high risk of TP53 mutation?

7.19.2 Background

The main concern over use of radiation therapy as an adjunct to breast conserving surgery is that it may increase the risk of future new primary cancers compared to mastectomy without radiation treatment. The use of radiotherapy is important as it substantially reduces the risks of local recurrence after wide local excision (WLE) and large scale clinical trials have shown no survival advantage of mastectomy over WLE + radiotherapy for breast cancer in general. There is nonetheless an increased rate of local recurrence and possibly new primary cancer in the treated breast area in WLE + radiotherapy. As such women are in general offered a choice between the two options unless the breast involvement is very great (multiple primaries or multifocal disease). For many women the thought of a mastectomy is still awful and it can impact on future quality of life. A number of studies have shown that whilst the risk of breast cancer in the untreated (contralateral) breast is high in BRCA1 and BRCA2 carriers WLE + radiotherapy is still fairly effective on the treated side. Nonetheless some studies do show a higher rate of new primary cancers for these hereditary type cancers on the treated side. The evidence for an increase in new primaries outside the treated area from radiation scatter such as in the opposite breast needs further investigation but does not appear compelling in BRCA1/2 carriers. The main concern in TP53 carriers is the relative ineffectiveness of radiotherapy treatment and its potential to induce highly malignant sarcomas. Most of the human evidence for this is anecdotal.

7.19.3 Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with a newly diagnosed breast cancer including DCIS with a TP53 mutation or at high risk of TP53 mutation	Mastectomy	Breast conserving surgery + radiotherapy	• Overall Survival • Recurrence • Quality of Surgery • Health related quality of life • New primary cancer

7.19.4 Relative importance of these outcomes?

The number of outcomes for this topic was limited to five in total and all outcomes were considered to be of equal importance.

7.19.5 How the information will be searched

What sources will be searched, e.g. will we look at Cinahl? (to be completed by reviewer/information specialist)
Are there any study design filters to be used (RCT, systematic review, diagnostic test).

Searches: *All studies that compare mastectomy with* WLE + radiotherapy. All studies that report on cancer incidence or survival after radiotherapy treatment in BRCA1, BRCA2 or TP53 carriers. Laboratory studies of increased radiation sensitivity/resistance in BRCA1, BRCA2 or TP53 carriers.	
Can we apply date limits to the search	1990 onwards for BRCA1, BRCA2 or TP53 carriers. Most of the trials of *mastectomy versus* WLE + radiotherapy are from the 1970-80s.
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT best but may need other studies including case reports.
List useful search terms.	BRCA1, BRCA2, TP53, mastectomy, radiotherapy, breast conserving surgery, breast cancer, sarcoma, new primary, local recurrence. Radiation sensitivity/resistance.

7.19.6 The review strategy

What data will we extract and how will we analyse the results?	Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. Studies which are identified as relevant will be critically appraised and quality assessed using GRADE methodology and/or NICE checklists. Data relating to the identified outcomes will be extracted from relevant studies. If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence as it relates to the topic of interest will be produced.
List subgroups here and planned statistical analyses.	*Ccompare mastectomy with* WLE + radiotherapy for BRCA1, BRCA2 and TP53.

7.19.7 Search Results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1970-current	108	8	09/01/2012
Premedline	1970-current	0	0	09/01/2012
Embase	1970-current	356	9	09/01/2012
Cochrane Library	1970-current	44	1	09/01/2012
Web of Science (SCI & SSCI) and ISI Proceedings	1970-current	26	3	09/01/2012

Total References retrieved (after de-duplication): 15

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. Tumor Suppressor Protein p53/
10. Genes, p53/
11. (TP53 or P53 gene).tw.
12. Li-Fraumeni Syndrome/
13. or/9-12
14. 8 and 13
15. exp Mastectomy/
16. (mastectomy$ or mammaplast$ or mammoplast$ or mammectom$).tw.
17. 15 or 16
18. (risk reduc$ adj surg$).tw.
19. (breast conserv$ adj surg$).tw.
20. (breast sparing adj surg$).tw.
21. ((local excision or segmental or partial or limited) adj2 (surg$ or resection$ or mastectom$)).tw.
22. lumpectom$.tw.
23. segmentectom$.tw.
24. or/18-23
25. exp radiotherapy/
26. radiotherap$.tw.
27. (radiation adj (therap$ or treatment$)).tw.
28. irradiati$.tw.
29. 25 or 26 or 27 or 28
30. 24 and 29
31. 17 or 30
32. 14 and 31

Notes:

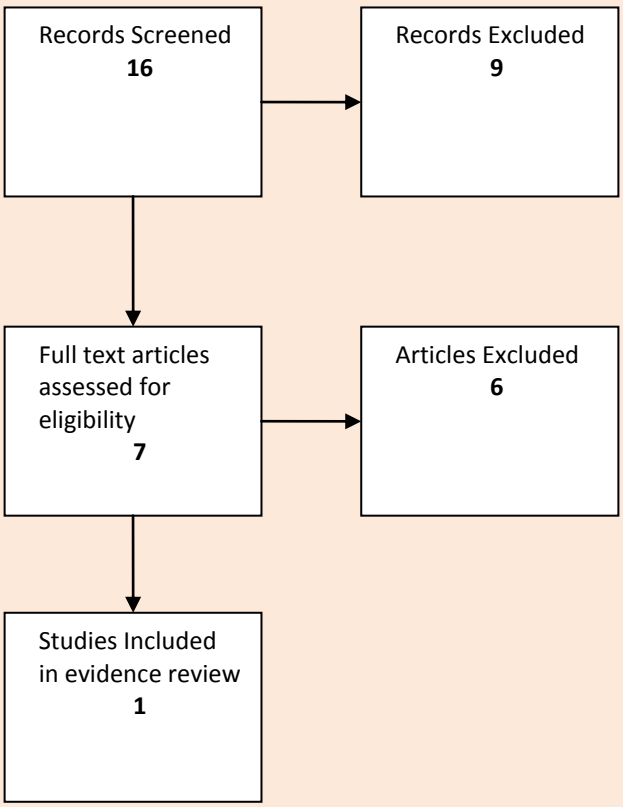
No search filters were applied.

Update Searches

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	09/01/2012-09/07/2012	1	0	17/07/2012
Premedline	09/01/2012-09/07/2012	0	0	17/07/2012
Embase	01/2012-07/2012	6	0	17/07/2012
Cochrane Library	01/2012-07/2012	6	0	09/07/2012
Web of Science (SCI & SSCI) and ISI Proceedings	01/2011-07/2012	5	0	23/07/2012

Total references retrieved after duplicates removed: 1

7.19.8 Screening Results



Reasons for Exclusion:
Studies not relevant to PICO (population, intervention or comparison not part of the PICO)
Foreign language studies with no translations
Expert Reviews/Opinion papers
Meeting Abstracts/Conference Proceedings
Relevant Studies included in systematic reviews

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=1)
Qualitative Study (n=0)

Table 3: Summary of included studies

Study	Study Type	Population	Aim	Intervention	Comapriso n	Outcomes
Heyman n et al, 2010	Retrospective Case Series	8	To assess the incidence of radio induced malignancies in women with P53 mutation treated with loco-regional radiotherapy	Loco-regional radiotherapy	No loco-regional radiotherap y	Radio induced malignancy

7.19.9 Evidence Statements

There was no evidence about the effectiveness of mastectomy compared to breast conserving surgery plus radiotherapy in patients with a newly diagnosed breast cancer and a TP53 mutation (or at high risk of TP53 mutation).
Radio Induced Malignancy

Very low quality evidence suggests a significant risk of radio induced malignancy following radiotherapy for breast cancer in women with a p53 mutation. In one retrospective case series study

(Heymann et al, 2010), 6 women with p53 mutation who received loco-regional radiotherapy for breast cancer were identified. There were 2 recorded cases of radio induced malignancy in this group

GRADE Profile 7.13: what is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ with a TP53 mutation or at high risk of TP53 mutation?

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Breast conserving surgery and adjuvant radiotherapy	Mastectomy	Relative (95% CI)	Absolute	Quality
Radio Induced Malignancy (follow-up median 6 years) (Heymann et al, 2010)										
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	2/6 (33.3%)	0/2 (0%)	not pooled	not pooled	VERY LOW
							0%		not pooled	

[1] Only 8 patients in the study, though this is possibly due to the fact that this topic is investigating an extremely rare event and therefore large randomised trials are unlikely to be possoble.
[2] There are not enough data or studies to comment on the consistency with any certainty
[3] There are only 8 patients included in the study and all 8 patients received different treatment plans, though only the effects of radiotherapy and incidence of radio-induced malignancies are of interest to this topic

7.19.10 Evidence Tables

Citation: Heymann et al (2010) Radio-induced malignancies after breast cancer post operative radiotherapy in patients with Li-Fraumeni syndrome *Radiation Oncology* 5;1
Design: Retrospective Case Series **Country**: France **Setting**: Follow-up **Aim**: to assess the outcome of patients with germ-line p53 mutations who were treated for breast cancer as first tumour event.
Inclusion criteria Female patients with breast cancer and TP53 mutation
Exclusion criteria None given
Sample Size None calculated
Randomisation Method Not applicable
Population N=8
Study Duration Recruitment Period: 1997-2007
Interventions Adjuvant Radiotherapy
Outcomes Radio induced malignancies
Results Median Follow-up = 6 years, range = 2-13 years. 6/8 patients received loco-regional radiotherapy 3 ipsilateral breast relapses were recorded 4 contralateral breast relapses were recorded 2 radio-induced cancers were recorded
General comments This study is very low quality in terms of the evidence base it provides for the topic, however as it represents the only available evidence for germ-line p53 mutations in women with breast cancer, it was decided, in discussion with GDG members , to include it in the evidence review.

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Reason: Outcomes not relevant to PICO

8 Literature Searches (CG14/41)

Evidence pathway: to help identify areas for research literature searching
(NB this is not a management/care algorithm – see Quick Reference Guide for management/care algorithms)

- Women present with concerns about family history of BC in either NHS or private setting, eg GP, NHS Direct, Occupational Health, etc
- Women identified with family history of BC via family member's use of genetics services

- ***Take family history***
- ***Assess & communicate level of risk (?low/medium/high)***
- ***Triage***

Spectrum of referral routes according to assigned level of risk

Mammography/Breast Unit/Cancer Genetics Clinic/Familial Breast Cancer Clinic

Spectrum of interventions according to assigned level of risk

No follow-up (except reassurance, etc)
or deferment

Education/self-care interventions
preventive
Information & education packages
Advice on changing lifestyle
management (eg pill, HRT, diet)
Breast self-examination/awareness
Support groups
Genetic register

Diagnostic interventions/screening
Clinical breast examination
Mammogram (not within NHS BSP)

Ultrasound
MRI
Other breast screening
?Genetic/diagnostic testing (affected women)
Breast biopsy

Clinical interventions
Tamoxifen & other SERMs)
Oophorectomy)

Mastectomy)
Participation in clinical trial
Psychiatric/psychological referral

APPROPRIATE REASSURANCE/COUNSELLING/PSYCHOLOGICAL SUPPORT

Search strategies

Comprehensive searches were conducted in the major (11 in total) electronic bibliographic databases covering biomedical, nursing, psychological, social science and health economic literature. The searches were conducted from March 2002 until February 2003. In addition, the Web sites of several HTA and guideline producing bodies were consulted. Finally, the references lists of included articles were checked for additional references and citation searches were performed on key authors and papers in the Science and Social Science Citation Indexes.

Sources searched

Electronic databases

1. CDSR (Cochrane Database of Systematic Reviews), The Cochrane Library, Issue 4, 2002
2. CENTRAL/CCTR (Cochrane Central Register of Controlled Trials), The Cochrane Library, Issue 4, 2002
3. Cinahl, 1982-2002
4. Embase, 1980-2002
5. Medline, 1966-2002
6. NHS DARE (Database of Abstracts of Reviews of Effects), The Cochrane Library, Issue 4, 2002
7. NHS HTA (Health Technology Assessment), The Cochrane Library, Issue 4, 2002
8. PreMedline, August 2002
9. PsycINFO, 1980-2002
10. Science Citation Index, 1981-2002
11. Social Science Citation Index, 1981-2002

Other sources

1. National Guideline Clearinghouse
2. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
3. NICE (National Institute for Clinical Excellence)
4. SIGN (Scottish Intercollegiate Guidelines Network)
5. TRIP (Turning Research into Practice Database)

Search terms used in Medline (Ovid)

Breast cancer

1. exp breast neoplasms/
2. ((breast$ or mammar$) and (cancer$ or tumor$ or tumour$ or neoplasm$ or metasta$)).ti
3. or/1-2

Familial breast cancer

1. exp breast neoplasms/
2. ((breast$ or mammar$) and (cancer$ or tumor$ or tumour$ or neoplasm$ or metasta$)).ti
3. or/1-2
4. exp genetics/
5. exp genetic predisposition to disease/
6. exp genetic techniques/
7. brca1.tw
8. brca2.tw
9. high risk.ti

10. familial.tw
11. family histor$.ti
12. hereditary.ti
13. inherit$.ti
14. genetic$.ti
15. (gene or genes).ti
16. exp breast neoplasms/ge
17. or/1-16

Surgical interventions

1. exp mastectomy/
2. mastectomy$.tw
3. mammectom$.ti
4. ovariectomy/
5. oophorectom$.tw
6. prophyl$ surg$.tw
7. *surgery/
8. exp breast neoplasm/su
9. or/1-8

Tamoxifen

1. tamoxifen.af
2. nolvadex.af
3. 10540-29-1.rn
4. or/1-3

Risk modification factors

1 exp diet/
2 exp diet therapy/
3 eating/
4 exp body weight/
5 diet$.ti
6 food.ti
7 weight.ti
8 eat$.ti
9 exercise/
10 exercise therapy/
11 exp exertion/
12 physical fitness/
13 exp sports/
14 exercise$.ti
15 fitness.ti
16 sport$.ti
17 menarche/
18 menarche.ti
19 alcohol drinking/
20 alcohol.ti
21 exp smoking/
22 smok$.ti
23 breast feeding/
24 breast feed$.ti

25 breastfeed$.ti
26 breastfed.ti
27 breast fed.ti
28 exp family planning/
29 exp contraception/
30 family planning.ti
31 contracept$.ti
32 pill.ti
33 birth control.ti
34 exp reproductive techniques, assisted/
35 in vitro fertil$.tw
36 ivf.tw
37 fertilization in vitro/
38 exp hormone replacement therapy/
39 hrt.tw
40 ((hormone or oestrogen$ or estrogen$ or oestradiol or estradiol or progesteron$ or progestin) and replacement).ti
41 exp self-examination/
42 self-examin$.tw
43 self-awar$.tw
44 or/1-44

Breast/genetic screening

exp mammography/
mammography$.tw
(breast$ and screen$).ti
exp ultrasonography/
ultraso$.ti
exp magnetic resonance imaging/
magnetic resonance.ti
((non-invasive$ or non-invasive$) and (imag$ or diagnos$)).ti
mri.ti
mass screening/
genetic screening/
genetic test$.ti
or/1-10

Genetic counselling/ information/ communication

1. genetic counselling/
2. (genetic$ and counsel$).ti
3. *patient education/
4. ((patient or health or genetic$) adj2 (educat$ or information)).ti
5. leaflet$.ti
6. video$.ti
7. pamphlets/
8. education$ material$.ti
9. (communicat$ and risk$).ti
10. or/1-9
11. exp communication/
12. exp risk
13. and 12
14. or 13

Risk classification

1. risk assessment/
2. (assess$ adj2 risk$).ti
3. ((classif$ or category$ or stratify$) adj2 risk$).tw
4. model$.ti
5. *models, theoretical/
6. exp * models, statistical/
7. *models, genetic/
8. risk$.ti
9. gail model$.tw
10. or/1-9

Family history taking

1 exp medical history taking/
2 (history$ adj2 tak$).tw
3 or/1-2

Epidemiology

1. exp epidemiology/
2. incidence.ti
3. prevalence.ti
4. epidemiol$.ti
5. or/1-4

Psychological impact/support & patient compliance

1. psycho$.ti
2. psychological support.tw
3. counseling/
4. exp *patient acceptance of health care/
5. adaptation, psychological/
6. patient compliance/
7. patient satisfaction/
8. *health status/
9. *quality of life/
10. or/1-9

a. Search approach

A staged approach to searching was undertaken. This involved initially searching specifically for the search concepts of interest (e.g. tamoxifen, surgical interventions, etc.) in conjunction with familial breast cancer search terms. Where this yielded, few or no relevant references, the search was expanded to cover high level evidence (i.e. guidelines, systematic reviews and randomised controlled trials) relating to breast cancer in general. Literature searches were also specifically undertaken in Medline, Embase, NHS EED and HEED, to specifically identify cost-effectiveness literature relating to familial breast cancer.

b. Search restrictions

No date restrictions were applied to the searches, other than those imposed by the sources searched. Searches were, however, restricted to English language. No study or publication

type restrictions were applied, with the exception of the more general breast cancer searches which were restricted to the highest levels of evidence (i.e. guidelines, systematic reviews and randomised controlled trials). The corresponding methodological search filters used in Medline (Ovid) are given below.

c. Methodological search filters used in Medline (Ovid)

Guidelines

1 guideline.pt
2 practice guideline.pt
3 exp guidelines/
4 health planning guidelines/
5 or/1-4

Systematic reviews

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta analysis.pt
5 review academic.pt
6 review literature.pt
7 (systematic$ adj3 (review$ or overview$)).tw
8 letter.pt
9 review of reported cases.pt
10 historical article.pt
11 review multicase.pt
12 or/1-7
13 or/8-11
14 12 not 13

Randomised controlled trials

1 clinical trial.pt

Economic evaluations

1 economics/
2 exp “costs and cost analysis”/
3 economic value of life/
4 exp economics, hospital/
5 exp economics, medical/
6 economics, nursing/

7 economics, pharmaceutical/
8 exp models, economic/
9 exp “fees and charges”/
10 exp budgets/
11 ec.fs
12 cost$.ti
13 economic$ or pharmacoeconomic$ or price$ or pricing.ti
14 or/1-13

Quality of life

1 exp quality of life/
2 quality of life.tw
3 life quality.tw

4 hql.tw
5 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
6 qol.tw
7 (euroqol or eq5d or eq 5d).tw
8 qaly$.tw
9 quality adjusted life year$.tw
10 hye$.tw
11 health$ year$ equivalent$.tw
12 health utilit$.tw
13 hui.tw
14 quality of wellbeing$.tw
15 quality of well being.tw
16 qwb.tw
17 (qald$ or qale$ or qtime$).tw
18 or/1-17