National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[L] Methods of surveillance

NICE guideline NG241

Evidence reviews underpinning the final 2 bullets of recommendation 1.8.18 and the first bullet of recommendation 1.8.20 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5832-0

Contents

Review question 6

Introduction 6

Summary of the protocol 6

Methods and process 7

Diagnostic evidence 8

Summary of included studies 8

Summary of the evidence 11

Economic evidence 12

Summary of included economic evidence 12

Economic model 12

Evidence statements 13

The committee's discussion and interpretation of the evidence 13

Recommendations supported by this evidence review 15

References – included studies 15

Appendices 18

Appendix A Review protocol 18

Review protocol for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 18

Appendix B Literature search strategies 29

Literature search strategies for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 29

Appendix C Diagnostic evidence study selection 39

Study selection for: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 39

Appendix D Evidence tables 40

Evidence tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 40

Appendix E Forest plots and SROC plots 78

Forest plots for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 78

Appendix F Modified GRADE tables 97

GRADE tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 97

Appendix G Economic evidence study selection 101

Study selection for: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 101

Appendix H Economic evidence tables 102

Economic evidence tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 102

Appendix I Economic model 103

Economic model for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 103

Appendix J Excluded studies 104

Excluded studies for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 104

Appendix K Research recommendations – full details 110

Research recommendations for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer? 110

Appendix L Outcome data tables 111

Methods of surveillance

Review question

How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

Introduction

Ovarian cancer is a disease that is difficult to diagnose early due to the vague nature of its symptoms. However, as the cancer develops it can lead to changes in the ovary that can be seen on scan or can raise levels of proteins, or other markers in the blood. Therefore, there are technologies that can be used either in isolation or in combination to help detect ovarian cancer early. In addition, these can be used once or repeated over time. However, to be able to recommend these technologies, first it has to be established that they are effective; that is their use finds ovarian cancer early in women with increased familial risk and by finding these cancers early clinical outcomes can be improved. Here we explore the different methods of ovarian cancer surveillance in women with an increased familial ovarian cancer risk and attempt to define their effectiveness.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) and Population, Index test, Reference standard and Target conditions (PIRT) characteristics of this review.

Table 1: Summary of the protocol (PICO and PIRT table)

Population	Women at increased risk of familial ovarian cancer

Intervention/ index test	Regular screening for ovarian cancer, for example a combination of:
	• CA125 test
	• MRI
	• CT
	• Transvaginal ultrasound
	• Prediction rules:
	  ○ Risk of Ovarian Cancer Algorithm test (the ROCA Test)
	  ○ multi-maker algorithms
	  ○ mathematical evaluation (other algorithms or techniques)

Comparison/ Reference standard	**Comparisons** • A different surveillance regime (different tests or screening frequency) • No surveillance **Reference standard** • Histopathological diagnosis in those having surgery • Clinical follow-up / continued screening tests in those not having surgery

Outcomes/ Target conditions	**Critical**
	• Quality of life
	• Survival:
	  ○ cancer specific survival
	  ○ overall survival
	  ○ recurrence free survival (surrogates: zero residual after definitive ovarian cancer treatment)
	• Performance characteristics (sensitivity, specificity, likelihood ratios) for detection of ovarian cancer
	Important
	• Treatment related adverse effects and test related morbidity such as:
	  ○ anxiety
	  ○ investigation of false positive results
	• Psychological outcomes and wellbeing including:
	  ○ patient satisfaction
	  ○ acceptability and attitudes
	• Healthcare use
	Target conditions
	• Ovarian cancer:
	  ○ incidence
	  ○ stage at diagnosis
	  ○ screen detected and interval related cancers
	  ○ histological type

CA125: cancer antigen 125; CT: computer tomography; MRI: magnetic resonance imaging; ROCA: risk of ovarian cancer algorithm;

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Diagnostic evidence

Included studies

Thirteen studies were included for this review, 12 cohort studies (Cortesi 2017, Evans 2009, Hemsen 2007, Lentz 2020, Nanez 2021, Oei 2006, Philpott 2023, Rosenthal 2013, Rosenthal 2017, Skates 2017, Stirling 2005, Woodward 2007) and 1 randomised controlled trial (Karlan 2014).

The included studies typically reported the performance characteristics of surveillance using a combination of serum CA125 measurement and transvaginal ultrasound (TVUS) for ovarian cancer. Four of the studies investigated the ROCA Test based screening (Philpott 2023, Rosenthal 2017, Skates 2017, Lentz 2020). Two of the studies also measured HE4 as part of their screening protocol (Lentz 2020, Karlan 2014).

The randomised trial (Karlan 2014) compared the order of HE4 and CA125 testing before transvaginal ultrasound (TVUS) during surveillance, but both arms were combined in the reporting of diagnostic results so it was treated as a prospective cohort study for the analysis.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Surveillance protocol	Reference standard	Outcomes
Cortesi 2017 Observational study Italy	N=620 women at increased risk n=101 *BRCA1/2* carriers[1] Age, median (range), years: 50 (25-85);	• 6 – 12 monthly CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Evans 2009 Observational study UK, the Netherlands, Norway	N=3532 women >=10% lifetime risk n=981 *BRCA1/2* carriers[1] Age, median (range), years: not reported	• Annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Stage at diagnosis • Histological type
Hermsen 2007 Observational study	N=459 women *BRCA1/2* carriers	• Annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued	• Performance characteristics ○ Sensitivity ○ Specificity

Study	Population	Surveillance protocol	Reference standard	Outcomes
The Netherlands	Age, median (range), years: not reported		screening for those not having surgery	• Stage at diagnosis • Histological type
Karlan 2014 Observational study (RCT arms combined) USA, Sweden	N=1172 women at increased risk n=208 *BRCA1/2* carriers[1] Age, mean (SD), years: 52 (11.5)	• 6 monthly CA125 and HE4; TVUS if either positive • 6 monthly CA125 followed by HE4; TVUS if either positive	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity
Lentz 2020 Observational study USA	N=149 women *BRCA1/2* carriers Age, mean (SD), years: 41.3 (12.1)	• The HE4 ROCAtest	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Histological type
Nanez 2021 Observational study USA	N=530 women (n=108 with regular surveillance) *BRCA1/2* carriers Age, median (range), years: 38 (37-40)	• 6 monthly CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity
Oei 2006 Observational study The Netherlands	N=512 women at high risk n=265 *BRCA1/2* carriers[1] Age, median (range), years: 42 (20-75)	• Annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Philpott 2023 Observational study UK	N=767 women who were *BRCA1/2* carriers' Age, median (range), years: 40 (34.5-85)	• The ROCA Test (repeat ROCA in 6 weeks if mildly elevated, TVUS within 6 weeks if moderately elevated, referral to gynaecologist	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type

Study	Population	Surveillance protocol	Reference standard	Outcomes
		if significantly elevated)		
Rosenthal 2017 Observational study UK	N=4348 women at >=10% lifetime risk n=734 *BRCA1/2* carriers[1] Age, median (range), years: 45.5 (34.2-84.8)	• The ROCA Test (TVUS annually if ROCA results normal or within 2 months of an abnormal ROCA result)	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Rosenthal 2013 Observational study UK	N=3563 women at >=10% lifetime risk n=538 *BRCA1/2* carriers[1] Age, median (range), years: 44.6 (35-81)	• annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Skates 2017 Observational study USA, Australia	N=3449 women at increased risk N *BRCA1/2* carriers not reported[1] Age, median (range), years: not reported	• The ROCA Test with 3 monthly CA125 (TVUS annually if ROCA results normal or soon after abnormal ROCA result)	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Stirling 2005 Observational study UK	N=1048 women at increased risk N *BRCA1/2* carriers not reported[1] Age, median (range), years: not reported	• annual TVUS • annual CA125 • annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type
Woodward 2007 Observational study UK	N=179 women with>=10% lifetime risk n=31 *BRCA1/2* carriers[1] Age, median (range), years: not reported for the high-risk subgroup; in the overall cohort 66% women were below 45 years of age	• annual TVUS • annual CA125 • annual CA125 and TVUS	• Surgery with histopathology • Clinical follow-up / continued screening for those not having surgery	• Performance characteristics ○ Sensitivity ○ Specificity • Stage at diagnosis • Histological type

CA125: cancer antigen 125; HE4: human epididymis protein; RCT: randomised controlled trial; ROCA: risk of ovarian cancer algorithm; SD: standard deviation; TVUS: transvaginal ultrasound

1. Not all participants were tested for BRCA mutation status

See the full evidence tables in appendix D and summary ROC plots and other graphs in appendix E. For more information on cut-offs used to assess the performance of diagnostic tests or prediction models see Supplement 1 – Methods, Diagnostic and prediction model studies chapter.

Summary of the evidence

There was a lack of randomised trials (or observational studies that adjusted for confounders) comparing different surveillance protocols on patient outcomes such as quality of life or survival. The evidence consisted of non-comparative studies reporting the performance characteristics of surveillance protocols and the stage, grade and histological type of cancers detected. The prevalence and incidence of cancer in these studies was relatively low, which meant uncertainty around their estimates of sensitivity.

Diagnostic accuracy of methods of surveillance for women with BRCA1/2 mutations

Both CA125 + TVUS and the ROCA Test + TVUS were useful surveillance tests for ovarian cancer in this population according to the positive likelihood ratio ([LR+] > 5) and specificity (> 0,7) and a moderately useful test according to the negative likelihood ratios ([LR-] between 0.2 and 0.5) and sensitivity (between 0.6 and 0.9). The evidence quality for this was low to moderate.

Very low to low quality evidence from one study of surveillance with CA125 and the HE4 ROCA Test showed it was not a useful test for surveillance (LR+<2 and LR- >0.5) due to low sensitivity (< 0.6).

Diagnostic accuracy of methods of surveillance for women at increased risk of familial ovarian cancer

CA125 + TVUS, the ROCA Test + TVUS and CA125 were useful surveillance tests for ovarian cancer in this population according to the LR+ (> 5) and specificity (> 0.7) and moderately useful tests according to the LR- (between 0.2 and 0.5) and sensitivity (between 0.6 and 0.9). The evidence quality for this was very low to moderate.

Low to moderate quality evidence from one study of surveillance with CA125 + HE4 + TVUS showed it was a useful test for surveillance according to the LR+ (> 5) and specificity (> 0.7), but not a useful test according to the LR- (> 0.5) due to low sensitivity (< 0.6).

Very low quality evidence showed that TVUS alone is a useful test for surveillance according to the LR+ (> 5) and specificity (> 0.7), but not a useful test according to the LR- (> 0.5) and sensitivity (< 0.6).

Stage, grade and histological type of cancers detected during surveillance of women with BRCA1/2 mutations

Evidence was available for the stage, grade and histological type of ovarian cancers diagnosed in studies of surveillance with CA125 + TVUS and the ROCA Test + TVUS in women with *BRCA1/2* mutations.

There were 4 routes by which cancers were diagnosed in these studies:

- prevalence screen – cancers detected by the first round of surveillance tests
- incidence screen – cancer detected by subsequent rounds of surveillance tests
- interval cancers – cancers (typically symptomatic) not detected by surveillance tests but diagnosed between rounds of surveillance
- occult cancers at RRSO – these were asymptomatic cancers not detected by surveillance tests but picked up when the woman decided to have risk reducing surgery

There were no interval cancers reported in the studies of the ROCA Test + TVUS surveillance, suggesting that this approach can detect ovarian cancers before they become symptomatic. In studies of CA125 + TVUS surveillance, however, around 23% of cancers were interval cancers (see Figure 14).

Stage IIIa or lower

In studies of surveillance with CA125 + TVUS very low quality evidence showed that around 44% of incidence screen detected ovarian cancers were stage IIIa or lower. This compared to 47% of prevalence screen detected cancers, 13% of interval cancers and 75% of occult cancers at RRSO.

In studies of surveillance with the ROCA Test + TVUS very low quality evidence showed that around 41% of incidence screen detected ovarian cancers were stage IIIa or lower. This compared to 34% of prevalence screen detected cancers and 80% of occult cancers at RRSO. One study also reported cancers diagnosed a year or more after stopping screening, only 6% of these cancers were stage IIIa or lower.

Grade

Very low quality evidence showed that regardless of the route to diagnosis the majority of cancers detected were of high grade: 79% in studies of CA125 + TVUS surveillance and 87% in studies of the ROCA Test + TVUS surveillance.

Histological type

Very low quality evidence showed that regardless of the route to diagnosis the majority of cancers detected were of serous histological type: 64% in studies of CA125 + TVUS surveillance and 79% in studies of the ROCA Test + TVUS surveillance.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Economic

No economic studies were identified which were applicable to this review question.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Quality of life and overall survival were prioritised as critical outcomes by the committee because deferring risk reducing treatments in favour of surveillance may have a negative impact on overall survival – but this choice might be made for quality of life reasons for example preservation of fertility. Similarly, surveillance compared to no surveillance or treatment could have a positive impact on overall survival. Cancer specific and recurrence free survival were also identified as critical outcomes because the aim of surveillance is to identify ovarian cancer at a pre-symptomatic stage when it is more treatable.

Incidence of ovarian cancer, screen detected and interval related cancer were chosen as critical outcomes because they indicate whether surveillance picks up pre-symptomatic ovarian cancers (screen detected) or whether they present as symptomatic between surveillance visits (interval cancers). Stage at diagnosis and histological type were also critical outcomes because they indicate the likely prognosis and response to treatment of any cancers detected.

Performance characteristics (sensitivity, specificity, positive and negative likelihood ratio) were considered to be critical outcomes because they indicate the ability of a screening test to correctly identify and distinguish between women with and without ovarian cancer.

The committee agreed that treatment related adverse effects and test related morbidity should be important outcomes. This is due to the potential anxiety associated with waiting for surveillance test results and the possible harms associated with surgical investigation or treatment of false positive results.

Psychological outcomes and wellbeing such as patient satisfaction, acceptability and attitudes were also chosen as important outcomes because the choice of surveillance or risk reducing treatment is a trade-off between harms of risk reducing treatment such as infertility and early menopause and the risk of ovarian cancer. This trade-off will likely depend on the individual's attitudes and other factors such as age.

The committee agreed that healthcare use should be an important outcome as surveillance typically requires repeated tests and healthcare appointments.

The quality of the evidence

The quality of the evidence was assessed using modified GRADE and ranged from very low to moderate quality. This was mainly due to the imprecision around the results due to the relatively low number of cancers detected in these studies. The studies were also at serious risk of bias because asymptomatic patients with undiagnosed occult ovarian cancer but normal screening test results would not have been identified unless they opted for RRSO which could overestimate the sensitivity of the screening protocol.

There was no evidence identified for the following outcomes: quality of life, survival, treatment related adverse events, psychological outcomes and wellbeing, and healthcare use.

Benefits and harms

Accuracy

The committee discussed that the evidence showed that both CA125 (cancer antigen 125) testing + transvaginal ultrasound (TVUS) and the ROCA Test (a serial 4 monthly CA125 blood test using an algorithm to analyse results) + TVUS were useful surveillance tests for ovarian cancer (as indicated by positive likelihood ratios and specificities that were in the useful category or and negative likelihood ratios and sensitivity that were in the moderately useful category).

They discussed that there were other accurate tests such as CA125 + HE4 + TVUS and TVUS alone. However, these were only classified as useful for one set of accuracy measures LR+ and sensitivity but not LR- and specificity and the evidence quality was very low to moderate. This means that the test is not very good at correctly identifying people without the condition. This could lead to false reassurance.

They decided that on balance serial the ROCA Test would be most accurate and whilst it could still produce false positive (leading to anxiety and potentially unnecessary surgery) or false negative results (leading to a false sense of reassurance) it is less so than for other tests. The committee decided that it should be made clear to the person that a false test result is a possibility.

Staging

They also noted that the evidence showed that there were no interval cancers reported in the studies of the ROCA Test + TVUS surveillance, suggesting that this approach can detect ovarian cancers before they become symptomatic. This was not so much the case for CA125 + TVUS surveillance because around 23% of cancers were interval cancers, i.e. a large proportion was already symptomatic. The committee agreed that stage IIIa or lower versus stage IIIb or higher was a clinically relevant distinction, with patients with stage IIIa or lower having better prognosis, and in that regard they also noted that the ROCA Test + TVUS had a good detection rate of early stage ovarian cancer (stage IIIa or lower).

Given the evidence related accuracy and staging the committee agreed that, even though not assessed as being of the highest evidence quality compared to some other tests in terms of performance characteristics, the ROCA Test + TVUS surveillance would be the preferred method if the person has chosen to delay or not to have risk-reducing surgery (see also evidence review K in relation to benefits and harms of surveillance). The committee discussed that the accuracy results would mean that of all tests it would have the least false positive and negative results and it way of staging it would be the serial CA125 part (with an algorithm) that would lead to detection of earlier stage cancers because TVUS can only identify an already existing abnormal mass. They therefore recommended serial 4-monthly CA125 longitudinal testing using an algorithm and that the person should be told about what this would involve. They gave the example of the ROCA Test because they were aware that other algorithms besides the ROCA Test were in use or in development and those could be used as long as there is demonstrated accuracy. Although there was no direct evidence about the impact of surveillance on patient outcomes, the committee discussed that diagnosis at stage IIIa or lower (which was more likely with surveillance) could translate into better patient outcomes. Because the testing is 4-monthly the committee, based on experience, agreed that there need to be systems in place to coordinate such services (which would deal with invites and reviews). Given the time constraints within primary care they decided that all activities related to surveillance should be the responsibility of the familial ovarian cancer multidisciplinary team.

Cost effectiveness and resource use

There was some evidence exploring the cost-effectiveness of surveillance compared with risk reducing surgery (see evidence review K on the benefits and risks of surveillance).

However, none of the economic studies have compared different surveillance regimens in terms of their diagnostic accuracy. The recommendations on ovarian cancer surveillance are based on a broader assessment of consequences, such as cancer downstaging, which are discussed in evidence review K on the benefits and risks of surveillance.

The committee discussed the resource impact of surveillance, noting that to be implementable it will need to be based on a well-coordinated call/recall system resulting in additional infrastructure costs. This should be centrally or nationally coordinated system to ensure consistent and effective surveillance across the services.

Implementation would involve both clinical and administrative time for tasks such as sending screening invitations, scheduling appointments, interpreting test results and communicating outcomes. There will also be cost of tests (the ROCA Test is currently not available on the NHS). However, the committee explained that surveillance would be targeted at known carriers who have delayed, declined or are not able to have risk-reducing surgery, meaning that only a small number of individuals would require surveillance. Additionally, surveillance would be offered only until people choose to undergo risk-reducing surgery. The committee recommended that it is made clear to the person that surveillance is not an alternative to risk-reducing surgery, does not stop cancer developing and that there is little evidence on whether this leads to improved outcomes and saves lives. This could potentially increase the number who opt for risk-reducing surgery rather than delaying it and opting for surveillance and may mitigate some of the resource impact.

In terms of expertise, it was acknowledged that not many professionals are currently familiar with the ROCA Test. But the committee noted that the necessary expertise should be available within familial cancer multidisciplinary teams. Still, this might lead to some additional training needs.

Recommendations supported by this evidence review

This evidence review supports the final 2 bullets of recommendation 1.8.18 and the first bullet of recommendation 1.8.20 in the NICE guideline.

References – included studies

Effectiveness

Cortesi 2017

Cortesi, Laura, De Matteis, Elisabetta, Toss, Angela et al. Evaluation of Transvaginal Ultrasound plus CA-125 Measurement and Prophylactic Salpingo-Oophorectomy in Women at Different Risk Levels of Ovarian Cancer: The Modena Study Group Cohort Study. Oncology 93(6): 377-386, 2017

Evans 2009

Evans, D G, Gaarenstroom, K N, Stirling D, et al. A Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet, 46(9):593-7, 2009

Hermsen 2007

Hermsen, B B J, Olivier, R I, Verheijen, R H M et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. British journal of cancer 96(9): 1335-42, 2007

Karlan 2014

Karlan, Beth Y, Thorpe, Jason, Watabayashi, Kate et al. Use of CA125 and HE4 serum markers to predict ovarian cancer in elevated-risk women. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23(7): 1383-93, 2014

Lentz 2020

Lentz, Scott E, Powell, C Bethan, Haque, Reina et al. Development of a longitudinal two-biomarker algorithm for early detection of ovarian cancer in women with BRCA mutations. Gynecologic oncology 159(3): 804-810, 2020

Nanez 2021

Nanez, Andrea, Stram, Douglas A, Garcia, Christine et al. Ovarian cancer surveillance in the clinical follow up of women with known BRCA1 or BRCA2 pathogenic variants in a large health care system. Gynecologic oncology 163(1): 134-141, 2021

Oei 2006

Oei, A L, Massuger, L F, Bulten, J et al. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. British journal of cancer 94(6): 814-9, 2006

Philpott 2023

Philpott, Sue, Raikou, Maria, Manchanda, Ranjit, Lockley, Michelle, Singh, Naveena, Scott, Malcolm et al. The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2. J Med Genet. 60(5):440-449, 2023

Rosenthal 2017

Rosenthal, Adam N, Fraser, Lindsay S M, Philpott, Susan et al. Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study. J. Clin. Oncol. 35(13): 1411-1420, 2017

Rosenthal 2013

Rosenthal, Adam N, Fraser, Lindsay, Manchanda, Ranjit et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J. Clin. Oncol. 31(1): 49-57, 2013

Skates 2017

Skates, Steven J, Greene, Mark H, Buys, Saundra S et al. Early detection of ovarian cancer using the risk of ovarian cancer algorithm with frequent CA125 testing in women at increased familial risk - combined results from two screening trials. Clin. Cancer Res. 23(14): 3628-3637, 2017

Stirling 2005

Stirling, Diane, Evans, D Gareth R, Pichert, Gabriella et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J. Clin. Oncol. 23(24): 5588-5596, 2005

Woodward 2007

Woodward, E R, Sleightholme, H V, Considine, A M et al. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. BJOG: an international journal of obstetrics and gynaecology 114(12): 1500-9, 2007

Appendices

Appendix A Review protocol

Review protocol for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022346860
1.	Review title	Methods of surveillance for women at increased risk of familial ovarian cancer
2.	Review question	How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?
3.	Objective	To determine the optimal surveillance regime for women at increased risk of familial ovarian cancer
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language

		• Human Studies The guideline committee will decide whether to re-run the searches 6 weeks before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: Women at increased risk of familial ovarian cancer Exclusion: none

7.	Intervention	Regular screening for ovarian cancer, for example a combination of:
		• CA125 test
		• MRI
		• CT
		• transvaginal ultrasound (TVUS)
		• Prediction rules
		  ○ the ROCA Test
		  ○ multi-marker algorithms
		  ○ mathematical evaluation (other algorithms or techniques)

8.	Comparator/Reference standard	Comparisons: • A different surveillance regimen (different tests or screening frequency) • No surveillance Reference standard: • Histopathological diagnosis in those having surgery • Clinical follow-up / continued screening tests in those not having surgery
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs (test and treat studies)

		• If insufficient RCTs*:
		  ○ Quasi-randomised controlled trials
		  ○ Non-randomised controlled trials/Prospective cohort studies
		  ○ Retrospective cohort studies
		
		*Non-randomised studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest.

10.	Other exclusion criteria	**Inclusion criteria**: • Full text papers • Observational studies should adjust for baseline differences between people in different intervention groups in their analyses **Exclusion criteria**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles
11.	Context	Not applicable (no changes to scope question and no existing guidance will be updated by this review)

12.	Primary outcomes (critical outcomes) and target conditions	Primary outcomes:
		• Quality of life
		• Survival:
		  ○ cancer specific survival
		  ○ overall survival

		○ recurrence free survival (surrogates: zero residual after definitive ovarian cancer treatment) • Performance characteristics (sensitivity, specificity, PPV, NPV, AUC) Target conditions: • Ovarian cancer: ○ incidence ○ stage at diagnosis ○ screen detected and interval related cancers ○ histological type
13.	Secondary outcomes (important outcomes)	• Treatment related adverse effects and test related morbidity such as: ○ anxiety ○ investigation of false positive results • Psychological outcomes and wellbeing including ○ patient satisfaction ○ acceptability and attitudes • Healthcare use
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

		Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials • QUADAS checklist for diagnostic accuracy studies. • PROBAST tool for clinical prediction models. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for

		dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: 0.8 and 1.25 for all relative dichotomous outcomes, for continuous outcomes any published validated MIDs, if none are available then +/- 0.5x control group SD. *Diagnostic performance outcomes* Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi and midas applications in STATA and Cochrane Review Manager. Likelihood ratios or sensitivity and specificity with 95% CIs will be used as the outcomes for diagnostic test usefulness. Diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. **Decision making thresholds (for binary accuracy data)** • Sensitivity: o Useful test: 0.9 o Not a useful test 0.6

		• Specificity:
		  ○ Useful test: 0.7
		  ○ Not a useful test 0.5
		
		Decision making thresholds (for likelihood ratios [LR])
		• For positive likelihood ratios:
		  ○ Useful test LR ≥ 5.0
		  ○ Not a useful test 1 < LR < 2.0
		• For negative likelihood ratios:
		  ○ Useful test LR ≤ 0.2
		  ○ Not a useful test 0.5 < LR ≤ 1.0

17.	Analysis of sub-groups	Evidence will not be stratified.
		
		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		
		• Estimated lifetime risk of ovarian cancer (for example >10%, >20%)
		• Groups identified in the equality considerations section of the scope
		  ○ socioeconomic and geographical factors
		  ○ age
		  ○ ethnicity
		  ○ disabilities
		  ○ people for whom English is not their first language or who have other communication needs.
		  ○ trans people (particularly trans men)
		  ○ non-binary people
		  ○ Type of pathogenic variant

		○ Women who have had a BSO ○ Population based studies sub groups Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	July 2022	

22.	Anticipated completion date	September 2023		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	**5a Named contact** National Institute for Health and Care Excellence (NICE) **5b Named contact e-mail** foc@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		

25.	Review team members	Senior Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
26.	Funding sources/sponsor	This systematic review is being completed by NICE
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022346860
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE	
32.	Keywords	Familial ovarian cancer, surveillance	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

AUC: area under the curve; CA125: cancer antigen 125; CT: computer tomography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; MRI: magnetic resonance imaging; NICE: National Institute for Health and Care Excellence; NPV: negative predictive value; PPV: positive predictive value; RCT: randomised controlled trial; RoB: risk of bias; ROCA: risk of ovarian cancer algorithm; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

One literature search was performed for this review question and for review question K on the benefits and risks of surveillance for women at increased risk of familial ovarian cancer

Database: Ovid MEDLINE ALL

Date of last search: 23/03/2023

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp Breast Neoplasms/
5	exp "Neoplasms, Ductal, Lobular, and Medullary"/
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
7	or/4-6
8	3 or 7
9	exp Genetic Predisposition to Disease/
10	Pedigree/
11	exp Neoplastic Syndromes, Hereditary/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,kf.
26	exp Genes, Tumor Suppressor/
27	exp Tumor Suppressor Proteins/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	exp Fanconi Anemia Complementation Group Proteins/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.

#	Searches
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
34	Rad51 Recombinase/
35	Ataxia Telangiectasia Mutated Proteins/
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	Checkpoint Kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
42	exp Sertoli-Leydig Cell Tumor/
43	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
48	or/9-47
49	8 and 48
50	CA-125 Antigen/
51	(CA 125 or CA125).ti,ab,kf.
52	Ultrasonography/
53	(ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*).ti,ab,kf.
54	(transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*).ti,ab,kf.
55	(TVUS or TVS).ti,ab.
56	Tomography, X-Ray Computed/
57	((CAT or CT or comput* or electron beam or positron emission or PET) adj2 (scan* or x ray* or xray* or tomograph*or screen*)).ti,ab,kf.
58	exp Magnetic Resonance Imaging/
59	((magnetic resonance adj2 (imag* or scan* or screen*)) or MRI).ti,ab,kf.
60	("Risk of ovarian cancer algorithm" or ROCA).ti,ab,kf.
61	algorithms/
62	algorithm*.ti,ab,kf.
63	"predictive value of tests"/ or clinical decision rules/
64	((predict* or clinical* or decision) adj2 (value* or test* or rule* or support)).ti,ab,kf.
65	exp models, statistical/
66	((math* or statistic*) adj2 (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)).ti,ab,kf.
67	Mass Screening/ or Watchful Waiting/
68	(surveillance or watchful wait* or screen*).ti,ab,kf.
69	or/50-68
70	49 and 69
71	letter/
72	editorial/
73	news/
74	exp historical article/
75	Anecdotes as Topic/
76	comment/
77	case reports/
78	(letter or comment*).ti.
79	or/71-78

#	Searches
80	randomized controlled trial/ or random*.ti,ab.
81	79 not 80
82	animals/ not humans/
83	exp Animals, Laboratory/
84	exp Animal Experimentation/
85	exp Models, Animal/
86	exp Rodentia/
87	(rat or rats or mouse or mice or rodent*).ti.
88	or/81-87
89	70 not 88
90	limit 89 to English language
91	randomized controlled trial.pt.
92	controlled clinical trial.pt.
93	pragmatic clinical trial.pt.
94	randomi#ed.ab.
95	placebo.ab.
96	drug therapy.fs.
97	randomly.ab.
98	trial.ab.
99	groups.ab.
100	or/91-99
101	Clinical Trials as topic.sh.
102	trial.ti.
103	or/91-95,97,101-102
104	Meta-Analysis/
105	Meta-Analysis as Topic/
106	(meta analy* or metanaly* or metaanaly*).ti,ab.
107	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
108	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
109	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
110	(search* adj4 literature).ab.
111	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
112	cochrane.jw.
113	or/104-112
114	90 and (103 or 113)
115	Observational Studies as Topic/
116	Observational Study/
117	Epidemiologic Studies/
118	exp Case-Control Studies/
119	exp Cohort Studies/
120	Cross-Sectional Studies/
121	Controlled Before-After Studies/
122	Historically Controlled Study/
123	Interrupted Time Series Analysis/
124	Comparative Study.pt.
125	case control$.tw.
126	case series.tw.
127	(cohort adj (study or studies)).tw.
128	cohort analy$.tw.
129	(follow up adj (study or studies)).tw.
130	(observational adj (study or studies)).tw.
131	longitudinal.tw.

#	Searches
132	prospective.tw.
133	retrospective.tw.
134	cross sectional.tw.
135	or/115-134
136	90 and 135

Database: Ovid Embase

Date of last search: 23/03/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/
34	ATM protein/

#	Searches
35	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
36	checkpoint kinase 2/
37	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
44	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/
47	Epithelial cell adhesion molecule*.tw,kf.
48	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
49	or/8-37,40-48
50	7 and 49
51	CA 125 antigen/
52	(CA 125 or CA125).ti,ab,kf.
53	echography/ or transvaginal echography/
54	(ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*).ti,ab,kf.
55	(transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*).ti,ab,kf.
56	(TVUS or TVS).ti,ab.
57	x-ray computed tomography/
58	((CAT or CT or comput* or electron beam or positron emission or PET) adj2 (scan* or x ray* or xray* or tomograph*or screen*)).ti,ab,kf.
59	nuclear magnetic resonance imaging/
60	((magnetic resonance adj2 (imag* or scan* or screen*)) or MRI).ti,ab,kf.
61	("Risk of ovarian cancer algorithm" or ROCA).ti,ab,kf.
62	algorithm/
63	algorithm*.ti,ab,kf.
64	predictive value/
65	clinical decision rule/
66	((predict* or clinical* or decision) adj2 (value* or test* or rule* or support)).ti,ab,kf.
67	statistical model/
68	((math* or statistic*) adj2 (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)).ti,ab,kf.
69	screening/ or mass screening/ or watchful waiting/
70	(surveillance or watchful wait* or screen*).ti,ab,kf.
71	or/51-70
72	50 and 71
73	letter.pt. or letter/
74	note.pt.
75	editorial.pt.
76	case report/ or case study/
77	(letter or comment*).ti.
78	or/73-77
79	randomized controlled trial/ or random*.ti,ab.
80	78 not 79
81	animal/ not human/

#	Searches
82	nonhuman/
83	exp Animal Experiment/
84	exp Experimental Animal/
85	animal model/
86	exp Rodent/
87	(rat or rats or mouse or mice or rodent*).ti.
88	or/80-87
89	72 not 88
90	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
91	89 not 90
92	limit 91 to English language
93	random*.ti,ab.
94	factorial*.ti,ab.
95	(crossover* or cross over*).ti,ab.
96	((doubl* or singl*) adj blind*).ti,ab.
97	(assign* or allocat* or volunteer* or placebo*).ti,ab.
98	crossover procedure/
99	single blind procedure/
100	randomized controlled trial/
101	double blind procedure/
102	or/93-101
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
108	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
109	(search* adj4 literature).ab.
110	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
111	((pool* or combined) adj2 (data or trials or studies or results)).ab.
112	cochrane.jw.
113	or/103-112
114	92 and (102 or 113)
115	Clinical study/
116	Case control study/
117	Family study/
118	Longitudinal study/
119	Retrospective study/
120	comparative study/
121	Prospective study/
122	Randomized controlled trials/
123	121 not 122
124	Cohort analysis/
125	cohort analy$.tw.
126	(Cohort adj (study or studies)).tw.
127	(Case control$ adj (study or studies)).tw.
128	(follow up adj (study or studies)).tw.
129	(observational adj (study or studies)).tw.
130	(epidemiologic$ adj (study or studies)).tw.
131	(cross sectional adj (study or studies)).tw.
132	case series.tw.
133	prospective.tw.

#	Searches
134	retrospective.tw.
135	or/115-120,123-134
136	92 and 135
137	136 not 114

Database: Cochrane Database of Systematic Reviews, Issue 3 of 12, March 2023 and Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2023

Date of last search: 23/03/2023

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	(("Fanconi Anemia" or "fanconi anaemia") NEAR/3 protein*):ti,ab,kw
#32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw

#	Searches
#34	MeSH descriptor: [Rad51 Recombinase] this term only
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	(("Ataxia telangiectasia" NEAR/1 mutated NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#37	MeSH descriptor: [Checkpoint Kinase 2] this term only
#38	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#39	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#40	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or "SNF2 beta"):ti,ab,kw
#42	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#43	(((Sertoli or leydig) NEAR/3 (tumor* or tumour* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or androblastoma* or andreoblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#44	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#45	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#46	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#47	(EPCAM* or "EP CAM" or ESA or KSA or M4S1 or "MK 1" or DIAR5 or EGP* or Ly74 or gp40 or CD326 or GA733* or GA 733 or KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#48	{OR #9-#47}
#49	#8 AND #48
#50	MeSH descriptor: [CA-125 Antigen] this term only
#51	(CA 125 or CA125):ti,ab,kw
#52	MeSH descriptor: [Ultrasonography] this term only
#53	(ultrasound* or ultrason* or ultra NEXT sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*):ti,ab,kw
#54	(transvaginal or "trans vaginal" or endovaginal or "endo vaginal" or pelvic or cervi*):ti,ab,kw
#55	(TVUS or TVS):ti,ab
#56	MeSH descriptor: [Tomography, X-Ray Computed] this term only
#57	((CAT or CT or comput* or "electron beam" or "positron emission" or PET) NEAR/2 (scan* or x NEXT ray* or xray* or tomograph*or screen*)):ti,ab,kw
#58	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#59	(("magnetic resonance" NEAR/2 (imag* or scan* or screen*)) or MRI):ti,ab,kw
#60	("Risk of ovarian cancer algorithm" or ROCA):ti,ab,kw
#61	MeSH descriptor: [Algorithms] this term only
#62	algorithm*:ti,ab,kw
#63	MeSH descriptor: [Predictive Value of Tests] this term only
#64	MeSH descriptor: [Clinical Decision Rules] this term only
#65	((predict* or clinical* or decision) NEAR/2 (value* or test* or rule* or support)):ti,ab,kw
#66	MeSH descriptor: [Models, Statistical] explode all trees
#67	((math* or statistic*) NEAR/2 (model* or evaluat* or technique* or assess* or formula* or analysis or analyses or calculat*)):ti,ab,kw
#68	MeSH descriptor: [Mass Screening] this term only
#69	MeSH descriptor: [Watchful Waiting] this term only
#70	(surveillance or watchful NEXT wait* or screen*):ti,ab,kw
#71	{OR #50-#70}
#72	#49 and #71
#73	conference:pt or (clinicaltrials or trialsearch):so
#74	#72 not #73

Database: Epistemonikos

Date of last search: 23/03/2023

#	Searches
1	(title:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR abstract:(((ovarian OR breast) AND (familial OR hered*) AND cancer))
2	(title:((surveillance OR "watchful wait*" OR screen* OR CA-125 OR transvaginal OR ultrasound OR CT scan OR MRI OR ROCA OR prediction rule* OR clinical decision rule* OR algorithm* OR statistical model* OR math* analysis)) OR abstract:((surveillance OR "watchful wait*" OR screen* OR CA-125 OR transvaginal OR ultrasound OR CT scan OR MRI OR ROCA OR prediction rule* OR clinical decision rule* OR algorithm* OR statistical model* OR math* analysis))
3	1 AND 2

Database: INAHTA International HTA Database

Date of last search: 23/03/2023

#	Searches
36	#35 AND #14
35	#34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
34	((surveillance or watchful wait* or screen*))[Title] OR ((surveillance or watchful wait* or screen*))[abs]
33	"Watchful Waiting"[mh]
32	"Mass Screening"[mh]
31	(((math* or statistic*) and (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)))[Title] OR (((math* or statistic*) and (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)))[abs]
30	"Models, Statistical"[mhe]
29	(((predict* or clinical* or decision) and (value* or test* or rule* or support)))[Title] OR (((predict* or clinical* or decision) and (value* or test* or rule* or support)))[abs]
28	"Clinical Decision Rules"[mh]
27	"Predictive Value of Tests"[mh]
26	((algorithm*))[Title] OR ((algorithm*))[abs]
25	"Algorithms"[mh]
24	(("Risk of ovarian cancer algorithm" or ROCA))[Title] OR (("Risk of ovarian cancer algorithm" or ROCA))[abs]
23	(((magnetic resonance and (imag* or scan* or screen*)) or MRI))[Title] OR (((magnetic resonance and (imag* or scan* or screen*)) or MRI))[abs]
22	"Magnetic Resonance Imaging"[mhe]
21	(((CAT or CT or comput* or electron beam or positron emission or PET) and (scan* or x ray* or xray* or tomograph*or screen*)))[Title] OR (((CAT or CT or comput* or electron beam or positron emission or PET) and (scan* or x ray* or xray* or tomograph*or screen*)))[abs]
20	"Tomography, X-Ray Computed"[mh]
19	((transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*))[Title] OR ((transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*))[abs]
18	((ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*))[Title] OR ((ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*))[abs]
17	"Ultrasonography"[mh]
16	((CA 125 or CA125))[Title] OR ((CA 125 or CA125))[abs]
15	"CA-125 Antigen"[mh]
14	#13 AND #8
13	#12 OR #11 OR #10 OR #9
12	((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 OR CHEK2 or SMARCA4 or DICER or EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[Title] OR ((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 OR CHEK2 or SMARCA4 or DICER or EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[abs]

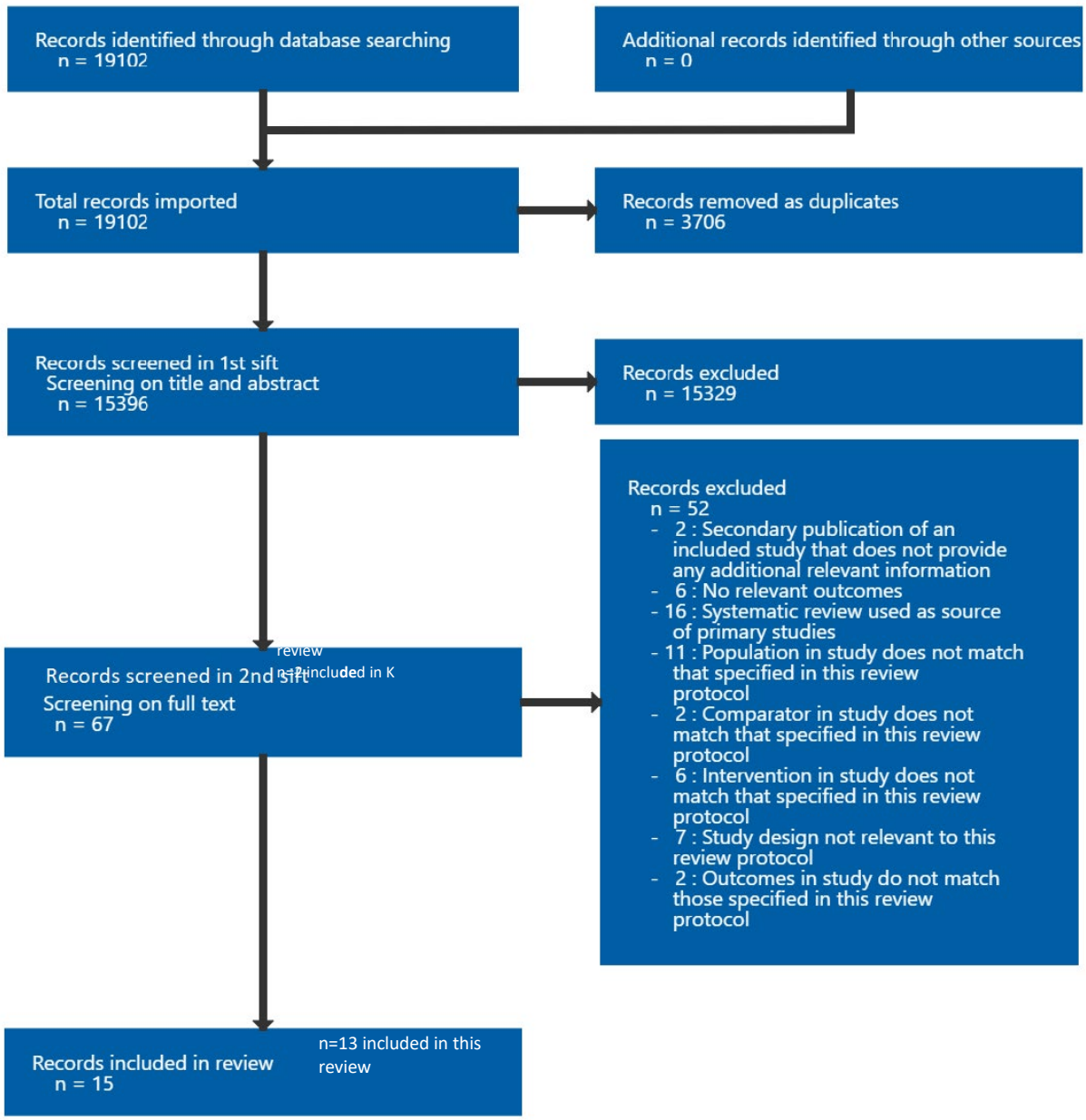
#	Searches
11	(((carrier* or gene*) and mutat*))[Title] OR (((carrier* or gene*) and mutat*))[abs]
10	((family and histor* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((family and histor* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
9	(((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
8	#7 OR #3
7	#6 OR #5 OR #4
6	(((breast* or mammary) and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[Title] OR (((breast* or mammary) and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[abs]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]
4	"Breast Neoplasms"[mhe]
3	#2 OR #1
2	((ovar* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((ovar* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
1	"Ovarian Neoplasms"[mhe]

Appendix C Diagnostic evidence study selection

Study selection for: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

One literature search was performed for the review questions K and L, which is what is reflected in Figure 1. Studies included in this review were excluded from review K and studies included in review K were excluded from this review, however, these studies do not appear in the 'Records excluded' box in Figure 1, or in the respective excluded studies tables (Appendix J).

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

Cortesi, 2017

Bibliographic Reference	Cortesi, Laura; De Matteis, Elisabetta; Toss, Angela; Marchi, Isabella; Medici, Veronica; Contu, Giannina; Xholli, Anjeza; Grandi, Giovanni; Cagnacci, Angelo; Federico, Massimo; Evaluation of Transvaginal Ultrasound plus CA-125 Measurement and Prophylactic Salpingo-Oophorectomy in Women at Different Risk Levels of Ovarian Cancer: The Modena Study Group Cohort Study.; Oncology; 2017; vol. 93 (no. 6); 377-386

Study details

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Between 2002 and 2014
Inclusion criteria	Carriers of *BRCA1* or *BRCA2*, *TP53*, *MLH1*, or *MSH2* mutations or subjects at risk and at least 18 years of age. Family histories of BC and/or OC were classified according to the following criteria: • at least three relatives diagnosed with BC or OC in two different generations; • at least one of the three relatives must be a first-degree relative of one of the other two; in the case of male interposition, a relationship of different degree is allowed; • at least one BC must be diagnosed before the age of 40 years or be bilateral; • at least one BC diagnosed at age ≤ 35 years, regardless of family history; • at least one BC and one OC diagnosed in the same woman, regardless of family history; • at least one male BC, regardless of family history;

	• one sporadic BC or OC.
Exclusion criteria	Patients who had a personal history of OC were excluded and among women classified as high, intermediate, or slightly increased risk, only those with OC reported in the family were considered for the study. Women who had RRSO (n=41) were analysed separately from the surveillance group and their results are not included here.
Patient characteristics	N=620 women at increased risk; n=101 *BRCA1/2* pathogenic mutation carriers **Gender:** Women **Age (years (median (range)):** surveillance group: 50 (25-85) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation (n):** 101 (16%)
Index test(s)	• 6 – 12 monthly CA-125 and TVUS. This was offered starting at 25 years of age with 6-monthly serum CA-125 measurement and TVUS to mutation carriers and annual testing to the rest (high-, intermediate-, and slightly-increased-risk group). Every patient received CA-125 measurement and TVUS at the same centre. Serum CA-125 cut-off was 35 U/mL. The ultrasound features for predicting malignant lesions were the following: increased size of adnexa, irregular solid tumour, or multilocular solid cyst with at least one papillary projection, and multicyctic lesion with at least score 2 of blood flow into the septa by colour Doppler examination.

Reference standard(s)	• Surgery and histopathology (N=73; 12%) performed by laparoscopy, after a previous examination of abdominal and pelvic units, considering liver, omentum, and peritoneum surface • Clinical follow-up / continued screening for those not having surgery (N=547; 88%)
Duration of follow-up	Median follow up (months (range)): • 112 (1-263) Lost to follow-up: • 35%
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (*women choosing RRSO were excluded from the surveillance group results and analysed separately; could overestimate sensitivity)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test results were interpreted without knowledge of the results of the reference standard)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(different reference standards depending on screening test results or symptoms; 35% of women were lost to follow-up in the surveillance group and 21% in the surgery group)*

Evans, 2009

Bibliographic Reference	Evans, D G; Gaarenstroom, K N; Stirling, D; Shenton, A; Maehle, L; Dorum, A; Steel, M; Lalloo, F; Apold, J; Porteous, M E; Vasen, H F A; van Asperen, C J; Moller, P; Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers.; Journal of medical genetics; 2009; vol. 46 (no. 9); 593-7

Study details

Country/ies where study was carried out	UK, the Netherlands, Norway
Study type	Prospective cohort study
Study dates	Between January 1991 and March 2007

Inclusion criteria	Women assessed as being at increased risk of ovarian cancer (usually at least a 10% lifetime risk as assessed by clinical genetics services), requiring more than just a single close relative with ovarian cancer.
Exclusion criteria	Not reported
Patient characteristics	N=3532 women at increased risk of ovarian cancer **Gender:** Women **Age:** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers (n):** 981
Index test(s)	• annual CA125 and TVUS, starting at either 30 or 35 years of age. No cut-off value for CA125 reported.
Reference standard(s)	• Surgery and histopathology (number not reported) • Clinical follow-up / continued screening for those not having surgery (number not reported)
Duration of follow-up	5 and 10 years for survival outcomes
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test results were interpreted without knowledge of the results of the reference standard; no cut-off value for CA125 reported)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear (*different reference standards depending on screening test results, symptoms and choice of risk reducing surgery)*

Hermsen, 2007

Bibliographic Reference	Hermsen, B B J; Olivier, R I; Verheijen, R H M; van Beurden, M; de Hullu, J A; Massuger, L F; Burger, C W; Brekelmans, C T; Mourits, M J; de Bock, G H; Gaarenstroom, K N; van Boven, H H; Mooij, T M; Rookus, M A; No efficacy of annual

gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study.; British journal of cancer; 2007; vol. 96 (no. 9); 1335-42

Study details

Country/ies where study was carried out	the Netherlands
Study type	Prospective cohort study
Study dates	Between 1993 and 2005
Inclusion criteria	*BRCA1/2* mutation carriers
Exclusion criteria	Women presenting with complaints at first gynaecologist visit and those who visited the gynaecologist only once
Patient characteristics	N=883 however only n=601 women had full data on each single visit; n=118 women visited the centre once, n=24 women were not screened with both CA125 and TVUS. Detailed results presented for n = 459 women with 1116 regular screening visits **Gender:** Women **Age (years, median (range)):** not reported for the 459 included in the analysis **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers (n):** Overall *BRCA1* = 683, *BRCA2* = 200

Index test(s)	• annual CA-125 and TVUS Serum CA125 cut-off was 35 IU/mL. CA125 levels above this threshold were scored as abnormal if the clinical decision based on these findings was an extra-screening visit or a diagnostic surgery (laparoscopy or laparotomy). Prophylactic surgery that followed a visit within 3 months, while at this visit abnormalities were detected, was classified as diagnostic surgery. TVUS findings were classified as abnormal for ovaries or fallopian tubes, or normal including non-visualized ovaries.
Reference standard(s)	• Surgery and histopathology (N=311; 68%) • Clinical follow-up / continued screening for those not having surgery (N=148; 32%)
Duration of follow-up	1473 women-years of follow-up
Sources of funding	This study was partly supported by the Biocare Foundation (Grant no. 02-22)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test results were interpreted without knowledge of the results of the reference standard)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear (*different reference standards depending on screening test results, symptoms and choice of risk reducing surgery)*

Karlan, 2014

Bibliographic Reference	Karlan, Beth Y; Thorpe, Jason; Watabayashi, Kate; Drescher, Charles W; Palomares, Melanie; Daly, Mary B; Paley, Pam; Hillard, Paula; Andersen, M Robyn; Anderson, Garnet; Drapkin, Ronny; Urban, Nicole; Use of CA125 and HE4 serum markers to predict ovarian cancer in elevated-risk women.; Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; 2014; vol. 23 (no. 7); 1383-93

Study details

Country/ies where study was carried out	USA, Sweden
Study type	Randomised controlled trial (RCT)
Study dates	Results were analysed as of October 31, 2013; the trial is ongoing. The study population was enrolled between February 2010 and October 2013
Inclusion criteria	• women at increased risk aged 25 to 80

	• those who provided informed consent, signed a medical records release form, and identified a care provider who agreed to receive screening results
Exclusion criteria	• women with a personal history of epithelial OC, • no ovaries, • abdominal surgery within the last 3 months, • a current pregnancy, • a medical condition precluding phlebotomy, • untreated malignancy (other than non-melanoma skin cancer), • receipt of adjuvant chemotherapy or radiation therapy for cancer (tamoxifen, aromatase inhibitors, and/or GnRH agonist were allowed) within 3 months
Patient characteristics	N=1172 (CA125 + HE4 n=582; CA125 n= 590) women at increased risk ; all included women had at least 1 screen and were included in the analyses **Gender:** Women **Age (years, mean (SD)):** 52 (11.5) **Ethnicity:** CA125 + HE4: White Caucasian = 89.3%, Ashkenazi Jewish = 20.4%, Hispanic = 5.1%; CA125: White Caucasian = 89.3% Ashkenazi Jewish = 17.8%, Hispanic = 4.3% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers:** CA125 + HE4: 18.2%; CA125: 17.3%
Index test(s)	• 6 monthly HE4 + CA125 – followed by TVUS if either positive • 6 monthly CA125 alone (with 2nd line HE4 test) – followed by TVUS if either positive

	CA125 and HE4 were interpreted using the PEB longitudinal algorithm (above a threshold corresponding to 90%, 95% or 99% specificity) to take advantage of rising trends in an individual woman's marker level as a signal of disease. The PEB determines the expected value of a marker for each individual woman based on her reference population and marker history. Age below or above 50 was used to define reference populations for the PEB, rather than pre- and post-menopause.
Reference standard(s)	• Surgery with pathology (N=100; 9%) • Clinical follow-up / continued screening for those not having surgery (N=1079; 91%)
Duration of follow-up	Not clear
Sources of funding	Support from the Canary Foundation, Marsha Rivkin Center for Ovarian Cancer Research, NCI P50 CA083636 (to NU), NCI U01 CA152637 (to CL), and NIH/NCATS Grant# UL1TR000124, American Cancer Society Clinical Research Professorship (SIOP-06-258-01-COUN) (to BYK), and a grant of no-charge study materials from Abbott Laboratories. Financial Support: NCI P50 CA083636 (to NU), NCI U01 CA152637 (to CL), NIH/NCATS Grant# UL1TR000124 and SIOP-06-258-01-COUN (to BYK)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear (*different reference standards depending on screening test results, symptoms and choice of risk reducing surgery)*

Lentz, 2020

Bibliographic Reference	Lentz, Scott E; Powell, C Bethan; Haque, Reina; Armstrong, Mary Anne; Anderson, Meredith; Liu, Yiling; Jiang, Wenqing; Chillemi, Giulia; Shaw, Sally; Alvarado, Monica M; Kushi, Lawrence H; Skates, Steven J; Development of a longitudinal two-biomarker algorithm for early detection of ovarian cancer in women with BRCA mutations.; Gynecologic oncology; 2020; vol. 159 (no. 3); 804-810

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	Between June 2016 and September 2017, follow-up until June 30, 2018

Inclusion criteria	• *BRCA1* and/or *BRCA2* mutation carrier, • age ≥ 30 years, • English-speaking • presence of at least one ovary • declined preventative ovarian removal at the time of enrolment
Exclusion criteria	Not reported
Patient characteristics	N=149 women agreed to surveillance with ROCA and underwent CA 125 and HE4 blood tests; n=43 were enrolled in a standard surveillance care group **Gender:** Women **Age (years, mean (SD)):** 41.3 (12.1) **Ethnicity:** *BRCA1*: African American = 4.2%, Latino = 15.7%, Caucasian = 60%, Asian = 10%, Filipino = 0%, Multiracial = 4.2%. other = 5.7%; *BRCA2*: African American = 2.5%, Latino = 24.1%, Caucasian = 48.1%, Asian = 7.5%, Filipino = 5.1%, Multiracial = 11.3%. other = 1.2% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers (n):** *BRCA1* = 70 (46.98%), *BRCA2* = 79 (53.02%)
Index test(s)	• 4 monthly CA125 + HE4 ROCA (high risk ROCA) • 6 monthly CA-125 and TVUS (CA125 cut-off >35 U/mL) (standard surveillance care) - insufficient detail reported to extract outcomes for this group
Reference standard(s)	• Surgery and histopathology (N=12; 8%)

	• Clinical follow-up / continued screening for those not having surgery (N=137; 92%)
Duration of follow-up	The maximum period for surveillance for enrolled women was 24 months for both groups
Sources of funding	This work was supported by the Kaiser Permanente Garfield Memorial Fund and a KPNC Community Benefit Grant, Principal Investigator C Bethan Powell. After support for Dr. Skates from these funds ended, he received additional support from The Concord (MA) Detect Ovarian Cancer Early Fund, from PROMISE- funded through Cancer Research UK PRC Program Grant A12677 and by the Eve Appeal, and from the NCI Early Detection Research Network grant (CA152990)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(different reference standards depending on screening test results, symptoms and choice of risk reducing surgery.)*

Nanez, 2021

Bibliographic Reference	Nanez, Andrea; Stram, Douglas A; Garcia, Christine; Powell, C Bethan; Ovarian cancer surveillance in the clinical follow up of women with known BRCA1 or BRCA2 pathogenic variants in a large health care system.; Gynecologic oncology; 2021; vol. 163 (no. 1); 134-141

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Between January 2001 and December 2017
Inclusion criteria	• women were identified from the Breast Cancer Tracking and Surveillance (BCTS) database. All female patients with a *BRCA1*/2PV diagnosed between 1/1/2003 and 12/ 31/2017 were identified • over age 18 • had at least one intact ovary at the time of genetic testing
Exclusion criteria	• bilateral salpingo-oophorectomy • history of epithelial ovarian cancer prior to genetic testing • left Kaiser within the first year
Patient characteristics	N=530 women with any surveillance (n=108 with regular surveillance) **Gender:** Women

	Age (years, median (range)): 38 (37-40) **Ethnicity:** White = 60%, Hispanic/Latino = 16%, Asian/Pacific Islander = 13%, African American = 5%, other = 6% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers (n):** *BRCA1* = 243 (46%), *BRCA2* = 287 (54%)
Index test(s)	• 6 monthly CA-125 and TVUS CA125 cut-off >35 U/mL. Ultrasounds classified as “normal” included reported small simple cysts and cysts with classic ultrasound features of a haemorrhagic cyst. Ultrasounds reporting adnexal masses outside of these categories were considered abnormal.
Reference standard(s)	• Surgery and histopathology (N=60; 56%) • Clinical follow-up / continued screening for those not having surgery (N=48; 44%)
Duration of follow-up	For women with any surveillance median follow-up 2.9 (range 2.7-3.2)
Sources of funding	Kaiser Permanente Garfield Memorial Fund (CBP), a private donation from Stephen Gomez in honour of Lee Caudill (CBP) and the Kaiser Permanente Northern California (KPNC) Residency Program, Kaiser Foundation Hospital (AN, DS).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(different reference standards depending on screening test results, symptoms and choice of risk reducing surgery.)*

Oei, 2006

Bibliographic Reference	Oei, A L; Massuger, L F; Bulten, J; Ligtenberg, M J; Hoogerbrugge, N; de Hullu, J A; Surveillance of women at high risk for hereditary ovarian cancer is inefficient.; British journal of cancer; 2006; vol. 94 (no. 6); 814-9

Study details

Country/ies where study was carried out	the Netherlands
Study type	Prospective cohort study
Study dates	Between January 1995 and January 2005
Inclusion criteria	Criteria for referral to the gynaecologist for ovarian surveillance: • women with a proven *BRCA1* and/or a *BRCA2* mutation, • women from a family with a proven BRCA mutation but who are not (yet) tested for a mutation, • women with first- or second-degree relatives with breast cancer before the age of 50 and ovarian cancer in the family • 2 first-degree relatives or 1 first-degree and 1 second-degree relative with ovarian cancer, independent of age
Exclusion criteria	Not reported
Patient characteristics	N=512 at high risk of ovarian cancer **Gender:** Women **Age (years, median (range)):** 42 (20-75) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutation carriers (n):** *BRCA1* = 180 (34.2%), *BRCA2* = 84 (16%), *BRCA1* and *BRCA2* = 1 (0.2%)

Index test(s)	• annual CA125 and TVUS TVUS was abnormal in case of the following morphological abnormalities: multiple cysts, cyst with thick septa, papillary projection, irregular patterns or a variety in sonoluency. Cut-off value for CA-125 was 35 IU/mL
Reference standard(s)	• Surgery and histopathology (N=193; 38%) . Patients who preferred Bilateral SO underwent laparoscopy and the ovaries as well as the fallopian tubes were removed. Hysterectomy was not part of the standard operation. • Clinical follow-up / continued screening for those not having surgery (N=319; 62%)
Duration of follow-up	Median follow-up: 2.07 years (range 0-9.4)
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(different reference standards depending on screening test results, symptoms and choice of risk reducing surgery.)*

Philpott, 2023

Bibliographic Reference	Philpott S; Raikou M; Manchanda R; Lockley M; Singh N; Scott M; Evans DG; Adlard J; Ahmed M; Edmondson R; Woodward ER; Lamnisos A; Balega J; Brady AF; Sharma A; Izatt L; Kulkarni A; Tripathi V; Solomons JS; Hayes K; Hanson H; Snape K; Side L; Skates S; McGuire A; Rosenthal AN; The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2.; Journal of medical genetics; 2023; vol. 60 (no. 5)

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	2018 to 2020
Inclusion criteria	Women with documented pathogenic germline *BRCA1/2* variants. Age 35 to 85 years. Had not had bilateral salpingo-oophorectomy (salpingectomy was permitted). Able to travel to participating hospitals if TVUS was needed.
Exclusion criteria	None reported
Patient characteristics	Women with *BRCA1/2* pathogenic variants, N=819 were recruited, N=767 had at least one test. *BRCA* status was known for N=755: n=399 (44.7%) *BRCA1* carriers; n=410 (54.1%) *BRCA2* carriers; n=6 (0.8%) *BRCA1+2* carriers

	Gender: Women **Age, median (range):** 40 years (34.5 to 85) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (e.g. not English 1st language):** not reported **Non-binary people:** not reported **Menopausal status (n):** premenopausal = 590 (77.2%)

Index test(s)	• ROCA surveillance: 4 monthly CA125 test results were processed by Abcodia Ltd (Cambridge, UK). The tests were classified as:
	  ○ Normal - continue with 4 monthly surveillance
	  ○ Mildly elevated – repeat the ROCA Test in 6 weeks
	  ○ Moderately elevated – repeat the ROCA Test and TVUS in 6 weeks
	  ○ Significantly elevated - urgent referral to gynaecologist plus TVUS

Reference standard(s)	• Surgery and histopathology (N=100; 13%) : for any women undergoing adnexal surgery the surgical documentation (indication, operation notes, histopathology/cytopathology reports) was reviewed by a consultant gynaecologist and gynaecological pathologist. Diagnoses were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, and the FIGO (2018) ovarian cancer staging system • Clinical follow-up / continued screening for those not having surgery (N=667; 87%)
Duration of follow-up	Median of 1.9 screening years per woman (range 0.04 to 2.72 screening years)
Sources of funding	Abcodia Ltd and North Central London Cancer Alliance
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(not reported whether reference standard results interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(not all patients received the same reference standard - potential for false negatives)*

Rosenthal, 2017

Bibliographic Reference	Rosenthal, Adam N; Fraser, Lindsay S M; Philpott, Susan; Manchanda, Ranjit; Burnell, Matthew; Badman, Philip; Hadwin, Richard; Rizzuto, Ivana; Benjamin, Elizabeth; Singh, Naveena; Evans, D Gareth; Eccles, Diana M; Ryan, Andy; Liston, Robert; Dawnay, Anne; Ford, Jeremy; Gunu, Richard; Mackay, James; Skates, Steven J; Menon, Usha; Jacobs, Ian J;

collaborators, United Kingdom Familial Ovarian Cancer Screening Study; Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study; J. Clin. Oncol.; 2017; vol. 35 (no. 13); 1411-1420

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Phase II between June 2007 and May 2012
Inclusion criteria	Women at an estimated minimum 10% lifetime ovarian caner risk dependent on family history or predisposing mutations.
Exclusion criteria	• borderline and non-epithelial ovarian cancer • women who had bilateral salpingo-oophorectomy • <35 years of age • were participating in other ovarian cancer screening trials
Patient characteristics	N=4,531 women (from Phase I n=2,362 [52.1%]); total screened n=4,348 (96%) (13,728 woman screening years; median 3.26 screen-years per woman) Withdrew n=977 (22.5%) **Gender:** Women **Age (median):** 45.5 years (range 34.2-84.8) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported

	People with communication needs (for example not English 1st language): not reported **Non-binary people:** not reported **BRCA mutation:** 734 had known *BRCA1/2* mutation Most frequent indications for inclusion: 40.5% were included because of breast/ovarian family history; no known mutation 23.8% were included because of ovarian only family history; no known mutation
Index test(s)	• 4 monthly ROCA screening (TVS annually if ROCA results normal or within 2 months of an abnormal ROCA result) True positive: cases in which abnormal screening results prompted surgery if invasive epithelial ovarian/fallopian tube cancer was diagnosed. False positive: all other diagnoses (including borderline/benign ovarian tumours) resulting from surgery prompted by abnormal test results. True negative: women in whom the last screen was normal and no diagnosis of ovarian/fallopian tube cancer was made in the subsequent 365 days. False negative (interval cancers): those presenting clinically between screens or <365 days after the final screen.
Reference standard(s)	• Surgery with histopathology (N=775; 18%) • Clinical follow-up / continued screening for those not having surgery (N=3573; 82%)
Duration of follow-up	Median follow-up beyond last screen/withdrawal 4.7 years (range 0 to 8.7) 13,728 woman screening years; median 3.26 screen-years per woman
Sources of funding	Supported by Cancer Research UK (Grants No. C315/A2621 and C1005/A6383), the UK Department of Health, and the Eve Appeal and in part by the National Cancer Institute Early Detection Research Network (Grants No. CA152990 and CA086381) and the National Institute for Health Research University College London (UCL) Hospitals/ UCL Comprehensive Biomedical Research Centre (research team at UCL coordinating centre)

Other information	Screening strategy: • serum CA125 tests every 4 months • 4 monthly ROCA screening (TVS annually if ROCA results normal or within 2 months of an abnormal ROCA result) Initial risk of ovarian cancer (ROC) was based on initial CA125 level and estimated age-specific ovarian cancer incidence. Subsequently, ROC was based on absolute CA125 level and rate of change. Initially high or increasing CA125 levels (even <30 iU/ml) generated a high ROC, whereas initially low, stable-high (even >30 iU/ml), or decreasing levels generated low ROCs.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test results were interpreted without knowledge of the results of the reference standard)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(asymptomatic patients with occult undiagnosed ovarian cancer & normal screening tests would not have been identified unless they opted for RRSO. Could overestimate the sensitivity of the screening protocol.)*

Rosenthal, 2013

Bibliographic Reference	Rosenthal, Adam N; Fraser, Lindsay; Manchanda, Ranjit; Badman, Philip; Philpott, Susan; Mozersky, Jessica; Hadwin, Richard; Cafferty, Fay H; Benjamin, Elizabeth; Singh, Naveena; Evans, D Gareth; Eccles, Diana M; Skates, Steven J; Mackay, James; Menon, Usha; Jacobs, Ian J; Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule; J. Clin. Oncol.; 2013; vol. 31 (no. 1); 49-57

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Phase I between May 2002 and January 2008
Inclusion criteria	Women at an estimated minimum 10% lifetime ovarian cancer risk on the basis of family history or predisposing mutations, including Lynch syndrome-associated mutations. Ovarian cancer in the family was defined as epithelial ovarian cancer, fallopian tube or primary peritoneal cancer.
Exclusion criteria	• borderline and non-epithelial ovarian cancer

	• women who had bilateral salpingo-oophorectomy • <35 years of age • were participating in other ovarian cancer screening trials
Patient characteristics	N=3,563 women (11,366 woman screening years) **Gender:** Women **Age (median):** 44.6 years (range 35-81) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **Mutation status (n):** *BRCA1* = 282 (7.9%), *BRCA2* = 250 (7%), *BRCA1/2* = 6 (0.2%), *MLH1* = 28 (0.8%), *MSH2* = 33 (0.9%), *MSH6* = 4 (0.1%) Most frequent indications for inclusion: 42.1% were included because of breast/ovarian family history; no known mutation 25% were included because of ovarian only family history; no known mutation
Index test(s)	• annual CA125 and TVUS Serum CA125 was measured using preferred assays at collaborating clinical laboratories. Cut-offs of 35 and 30 IU/mL in premenopausal and postmenopausal women, respectively, were recommended.

Reference standard(s)	• Surgery and histopathology / cytopathology (N=637; 18%). Whenever women underwent salpingo-oophorectomy, the coordinating centre obtained documentation explaining surgical indication, whether CA125 and/or TVS results had prompted surgery, the operation note, and histopathology and cytopathology reports. • Clinical follow-up / continued screening for those not having surgery (N=2926; 82%)
Duration of follow-up	Not clear 11,366 women screen–years; mean screening 3.2 years per woman
Sources of funding	Supported by Cancer Research UK (Grants No. C315/A2621 and C1005/A6383), the UK Department of Health, and the Eve Appeal and in part by the National Cancer Institute Early Detection Research Network (Grants No. CA152990 and CA086381) and the National Institute for Health Research University College London (UCL) Hospitals/ UCL Comprehensive Biomedical Research Centre (research team at UCL coordinating centre)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test results were interpreted without knowledge of the results of the reference standard)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard results were interpreted without knowledge of the results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Asymptomatic patients with undiagnosed occult ovarian cancer & normal screening tests would not have been identified unless they opted for RRSO. Could overestimate the sensitivity of the screening protocol.)*

Skates, 2017

Bibliographic Reference	Skates, Steven J; Greene, Mark H; Buys, Saundra S; Mai, Phuong L; Brown, Powel; Piedmonte, Marion; Rodriguez, Gustavo; Schorge, John O; Sherman, Mark; Daly, Mary B; Rutherford, Thomas; Brewster, Wendy R; O'Malley, David M; Partridge, Edward; Boggess, John; Drescher, Charles W; Isaacs, Claudine; Berchuck, Andrew; Domchek, Susan; Davidson, Susan A; Edwards, Robert; Elg, Steven A; Wakeley, Katie; Phillips, Kelly-Anne; Armstrong, Deborah; Horowitz, Ira; Fabian, Carol J; Walker, Joan; Sluss, Patrick M; Welch, William; Minasian, Lori; Horick, Nora K; Kasten, Carol H; Nayfield, Susan; Alberts, David; Finkelstein, Dianne M; Lu, Karen H; Early detection of ovarian cancer using the risk of ovarian cancer algorithm with frequent CA125 testing in women at increased familial risk - combined results from two screening trials; Clin. Cancer Res.; 2017; vol. 23 (no. 14); 3628-3637

Study details

Country/ies where study was carried out	USA & Australia
Study type	Prospective cohort study
Study dates	The Cancer Genetics Network (CGN) study: between 2001 and 2011

	The Gynecologic Oncology Group (GOG): between 2003 and 2006
Inclusion criteria	CGN study: women from families with a deleterious *BRCA1/2* mutation, and/or multiple ovarian and/or breast cancers in first- or second-degree blood relatives. GOG study: women from families with a deleterious *BRCA1/2* mutation, and/or multiple ovarian and/or breast cancers in first- or second-degree blood relatives.
Exclusion criteria	CGN study: women who had previously undergone bilateral oophorectomy (n=278) were eligible for screening for primary peritoneal cancer but were excluded from the analysis GOG study: women without ovaries
Patient characteristics	N=3,449 women at increased risk (13,080 woman-screening years) **Gender:** Women **Age (average):** not reported **Ethnicity (n):** Asian 17, Black 73, White 1,761, other 120, unknown/not reported 21; Hispanic ethnicity (n): not Hispanic/Latino 1,945, Hispanic/Latino 46, unknown/not reported: 57; Ashkenazi Jewish Descent (n): 365 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• 3 monthly CA125 ROCA screening (TVUS annually if ROCA results normal or soon after abnormal ROCA result) The screening strategy implemented the ROCA Test (risk of ovarian cancer algorithm). For any sequence of CA125 results and test intervals, ROCA calculated the risk that serum CA125 had a change-point profile which had increased significantly above baseline vs a flat profile which varies stably around the baseline. An increased change-point risk raised suspicion for

	an undetected tumour. All screening decisions regarding ROCA scheduling or more detailed ultrasound or gynaecologic evaluation were based on the ROCA risk level and not the most recent CA125 test result. After each new CA125, ROCA risk was re-calculated, adding the current CA125 to all previous results, subject's age and menopausal status, and the subject was re-triaged: normal-risk women (<1% risk of having ovarian cancer) returned in 3 months for the next CA125; those with an intermediate risk (1–10%) were referred for TVS; and those with an elevated risk (>10%) received TVS and evaluation by a gynaecologic oncologist or study site PI. Women with above-normal risks were referred to more intensive follow-up, commensurate with their risk score. The updated ROCA resulted in rapid referral of women with CA125 levels rising significantly above their baseline, including increases within the so-called normal range (≤35 U/mL), to TVS or TVS with gynaecologic oncologist review.
Reference standard(s)	• Surgery and histopathology (N=696; 20%) • Clinical follow-up / continued screening for those not having surgery (N=2725; 80%)
Duration of follow-up	Median follow-up 6 years Total 13,080 woman-screening years CGN study: 6,979 woman-years of screening (median 2.9 yrs; range 0–10.3 yrs) GOG study: 6,101 woman-years of screening (median 5.0 yrs, range 0–6.9 yrs)
Sources of funding	Fujirebio Diagnostics Inc; NCI/NIH
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear if the index test was interpreted without the knowledge of the reference standard)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear if the reference standard was interpreted without the knowledge of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(N=3692 were screened, included n=3448; asymptomatic patients with ovarian cancer & normal screening tests would not have been identified unless they opted for RRSO. Could overestimate the sensitivity of the screening protocol.)*

Stirling, 2005

Bibliographic Reference	Stirling, Diane; Evans, D Gareth R; Pichert, Gabriella; Shenton, Andrew; Kirk, Elaine N; Rimmer, Sylvia; Steel, C Michael; Lawson, Sheila; Busby-Earle, R M Camille; Walker, Jane; Lalloo, Fiona I; Eccles, Diana M; Lucassen, Anneke M; Porteous, Mary E; Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system; J. Clin. Oncol.; 2005; vol. 23 (no. 24); 5588-5596

Study details

Country/ies where study was carried out	UK

Study type	Prospective cohort study
Study dates	Between January 1991 and March 2004
Inclusion criteria	Women with a first-degree relative (mother, father, sister, brother, daughter, or son) affected by cancer within a family that meets one of the following criteria: • 1 individual with ovarian cancer at any age, and one with breast cancer diagnosed younger than age 50 years, who are first-degree relatives of each other#, • 1 relative with ovarian cancer at any age, and 2 with breast cancer diagnosed younger than age 60 years, who are connected by first-degree relationships#, • known hMLH1, hMSH2 mutation carrier, • 2 or more individuals with ovarian cancer, who are first-degree relatives of each other, • an individual with both breast and ovarian cancer • 3 or more individuals with breast or ovarian cancer over three generations (one must have ovarian cancer), known *BRCA1*, *BRCA2* mutation carrier #in these categories a second-degree relative may be counted if the transmission is via the paternal line (eg, a sister and a paternal aunt or a sister and two paternal aunts)
Exclusion criteria	None reported
Patient characteristics	Women at increased risk of ovarian cancer were screened, n=1048 had TVUS; n=760 had CA125 measurements **Gender:** Women **Age:** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported

	Non-binary people: not reported **Menopausal status (n):** premenopausal = 614, perimenopausal = 100, post-menopausal = 140, no status recorded = 194 **Mutation status:** N BRCA1/2 carriers not reported
Index test(s)	• annual TVUS • annual CA125 • annual CA125 and TVUS Cut-off values for CA125 varied between centres and even with time in the same centre, as new assays were developed, but generally were between 15 and 35 U/mL. Wherever possible, ultrasound scans were performed transvaginally. Ovarian volume was noted along with any morphologic abnormalities. Cysts were noted to be unilocular, multilocular, or complex, and the wall was noted to be smooth or irregular with or without septations. The volume of the cyst was also noted. In premenopausal women, any cyst larger than 2.5 cm was reviewed in 6 weeks.
Reference standard(s)	• Surgery with histopathology (N not reported) • Clinical follow-up / continued screening for those not having surgery (N not reported)
Duration of follow-up	Not reported
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Asymptomatic patients with ovarian cancer & normal screening tests would not have been identified unless they opted for RRSO. Could overestimate the sensitivity of the screening protocol.)*

Woodward, 2007

Bibliographic Reference	Woodward, E R; Sleightholme, H V; Considine, A M; Williamson, S; McHugo, J M; Cruger, D G; Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective.; BJOG : an international journal of obstetrics and gynaecology; 2007; vol. 114 (no. 12); 1500-9

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	Between April 1996 and March 2005
Inclusion criteria	• women registered by the gynaecological radiology department as attending for TVU in view of a reported family history of ovarian cancer
Exclusion criteria	• women symptomatic at enrolment
Patient characteristics	N=179 women with a >=10% lifetime risk **Gender:** Women **Age at 1st TVUS (years, n) in the whole cohort (including those with a moderate and near population risk, N=341):** <45 = 224 (65.7%), <40 = 165 (48.7%), older than 50 = 64 (19%) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **Mutation carriers (n), total 52.5%:** *BRCA1* = 20, *BRCA2* = 11, *MLH1* = 4, *MSH2* = 3, Amsterdam Positive = 7, *BRCA*-like = 134
Index test(s)	• annual TVUS • annual CA125

	• annual CA126 and TVUS Women with simple cysts or features to suggest a haemorrhagic corpus luteum had repeat scans at 6 weeks. Women with multilocular or complex cysts were referred at screening to a gynae oncologist as were those with increasing or persisting ovarian abnormalities at repeat TVUS. CA125 data were only available from May 1998 onwards. CA125 threshold not reported.
Reference standard(s)	• Surgery with histopathology (N=90; 50%) • Clinical follow-up / continued screening for those not having surgery (N=89; 50%)
Duration of follow-up	Mean follow-up time 29.4 months (standard error 1.6), median follow-up time 23.0 months (range 0–100.0 months)
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear (*unclear whether index tests were interpreted without knowledge of reference standard)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear *(unclear what threshold was used)*

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Asymptomatic patients with undiagnosed occult ovarian cancer & normal screening tests would not have been identified unless they opted for RRSO. Could overestimate the sensitivity of the screening protocol.)*

Appendix E Forest plots and SROC plots

Forest plots for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

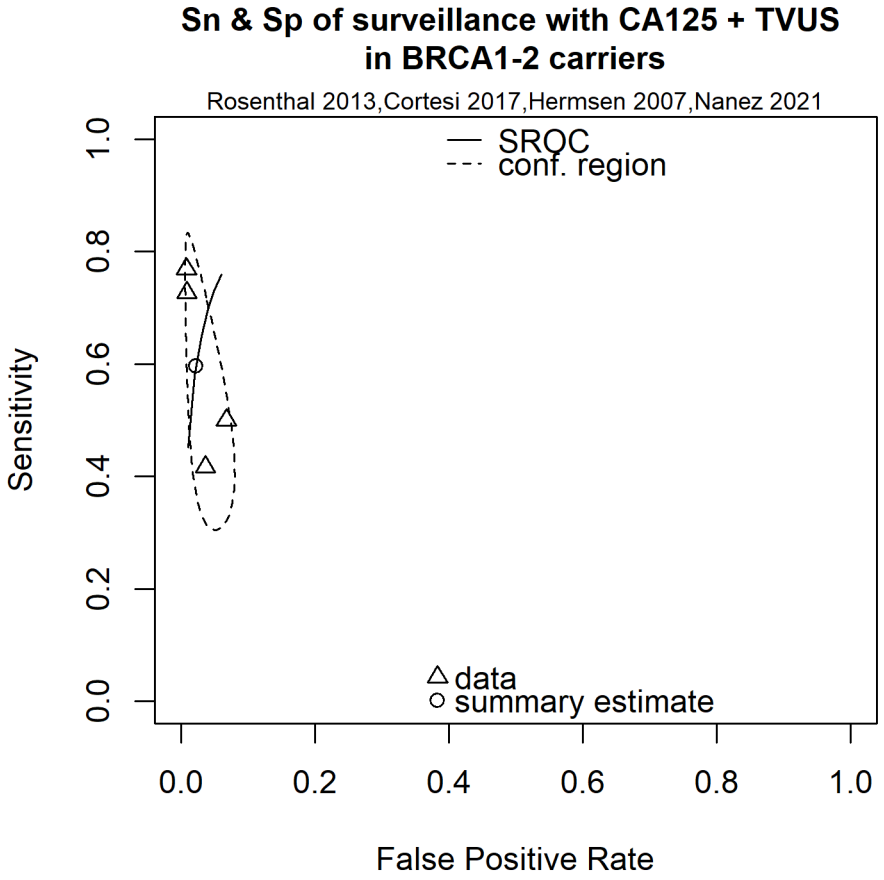
This section includes forest and SROC plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Sensitivity and specificity of surveillance with CA125 and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in BRCA1/2 carriers

Study	TP	FP	FN	TN	Sens (95% CI)	Spec (95% CI)
Hermsen 2007	5	16	7	431	0.42 (0.20-0.68)	0.96 (0.94-0.97)
Nanez 2021	2	7	2	97	0.50 (0.15-0.85)	0.93 (0.86-0.97)
Cortesi 2017	8	1	3	115	0.73 (0.44-0.90)	0.99 (0.95-1.00)
Rosenthal 2013	10	4	3	509	0.77 (0.50-0.92)	0.99 (0.98-1.00)
Summary (bivariate model)					0.60 (0.36-0.80)	0.98 (0.94-0.99)

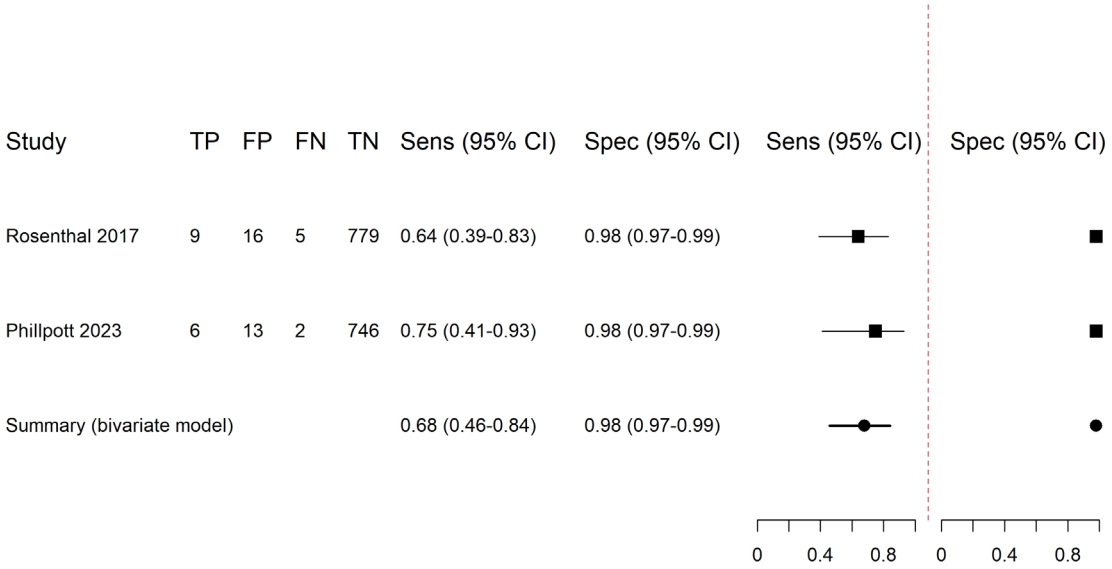
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 3: Summary ROC of surveillance with CA125 and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in BRCA1/2 carriers



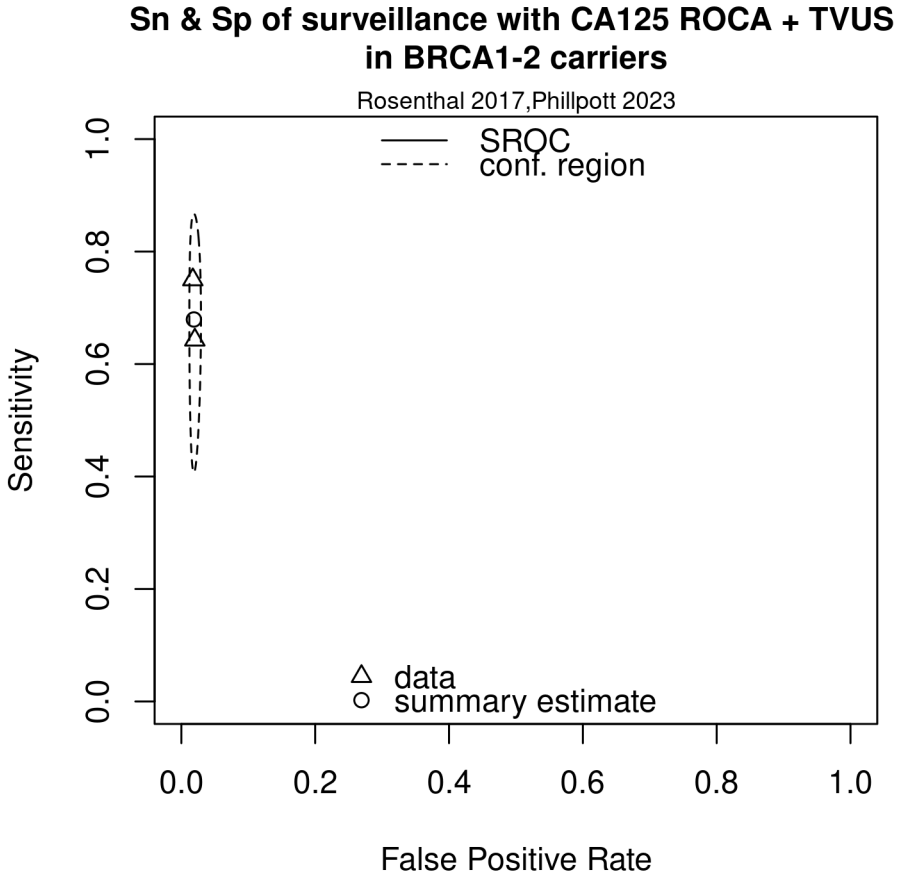
Sn: sensitivity; Sp: specificity; SROC: Summary receiver operating characteristic curve; TVUS: transvaginal ultrasound

Figure 4: Sensitivity and specificity of surveillance with the ROCA Test and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in BRCA1/2 carriers



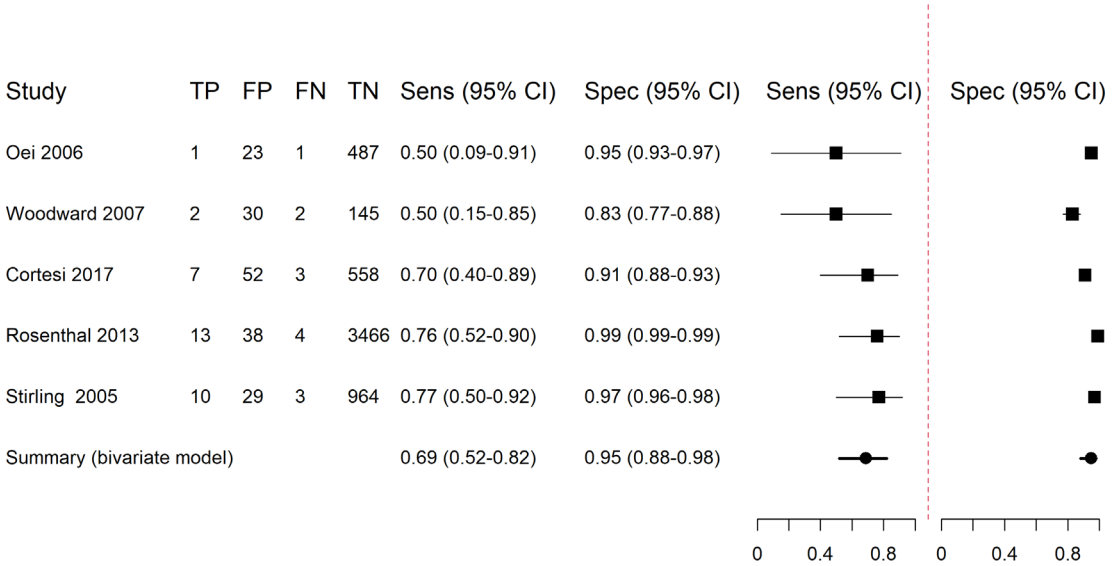
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 5: Summary ROC of surveillance with the ROCA Test and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in *BRCA1/2* carriers



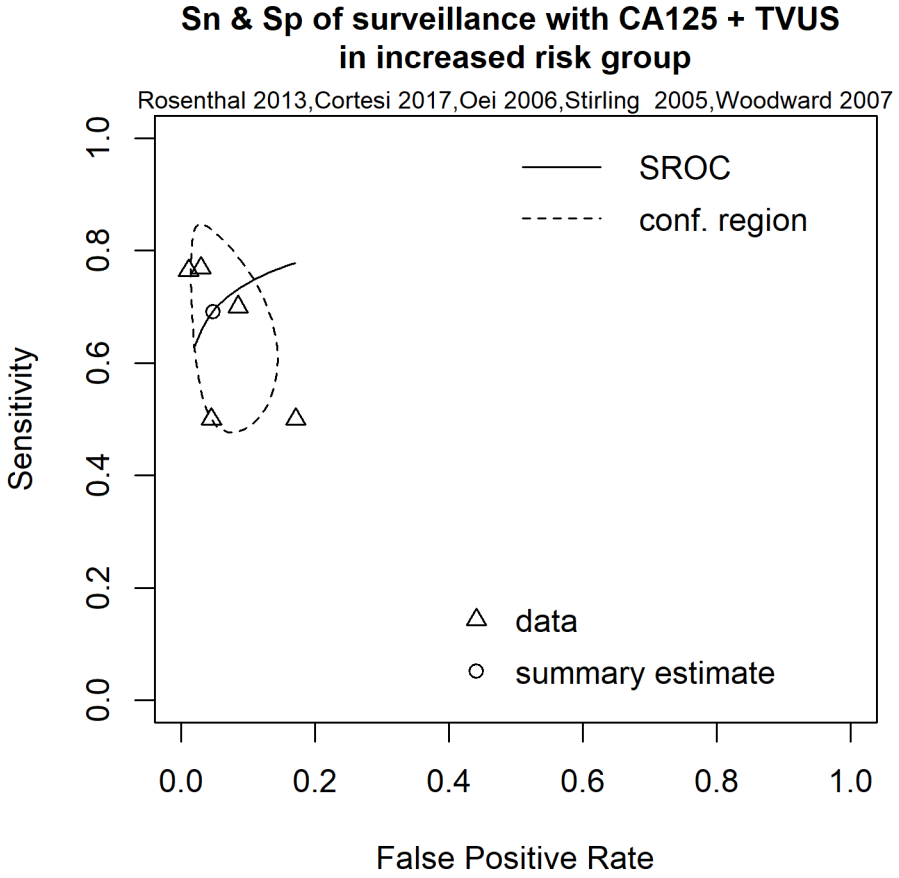
Sn: sensitivity; Sp: specificity; ROCA: risk of ovarian cancer algorithm; SROC: Summary receiver operating characteristic curve; TVUS: transvaginal ultrasound

Figure 6: Sensitivity and specificity of surveillance with CA125 and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



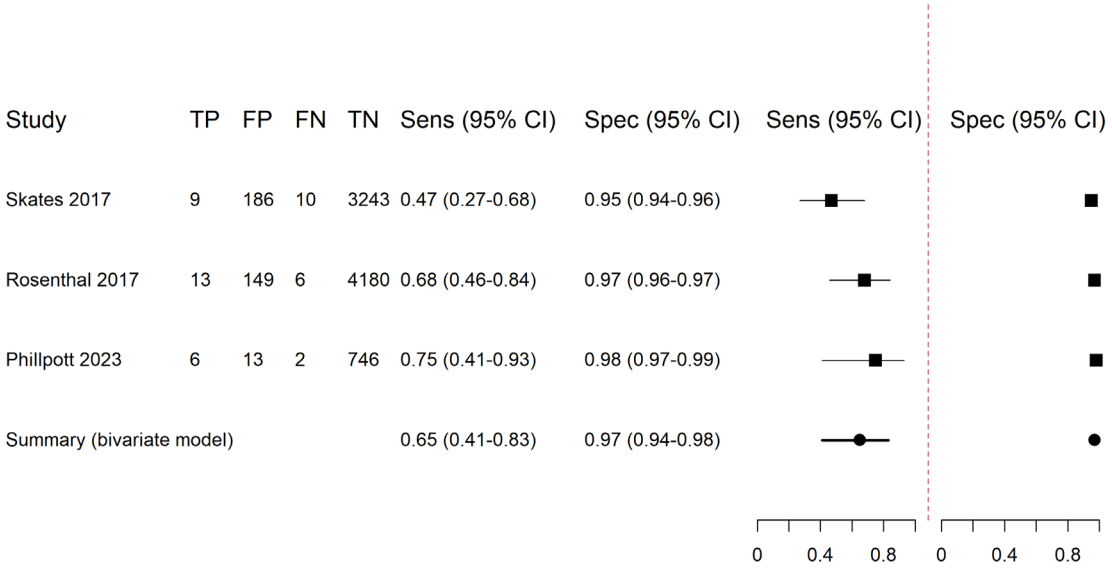
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 7: Summary ROC of surveillance with CA125 and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



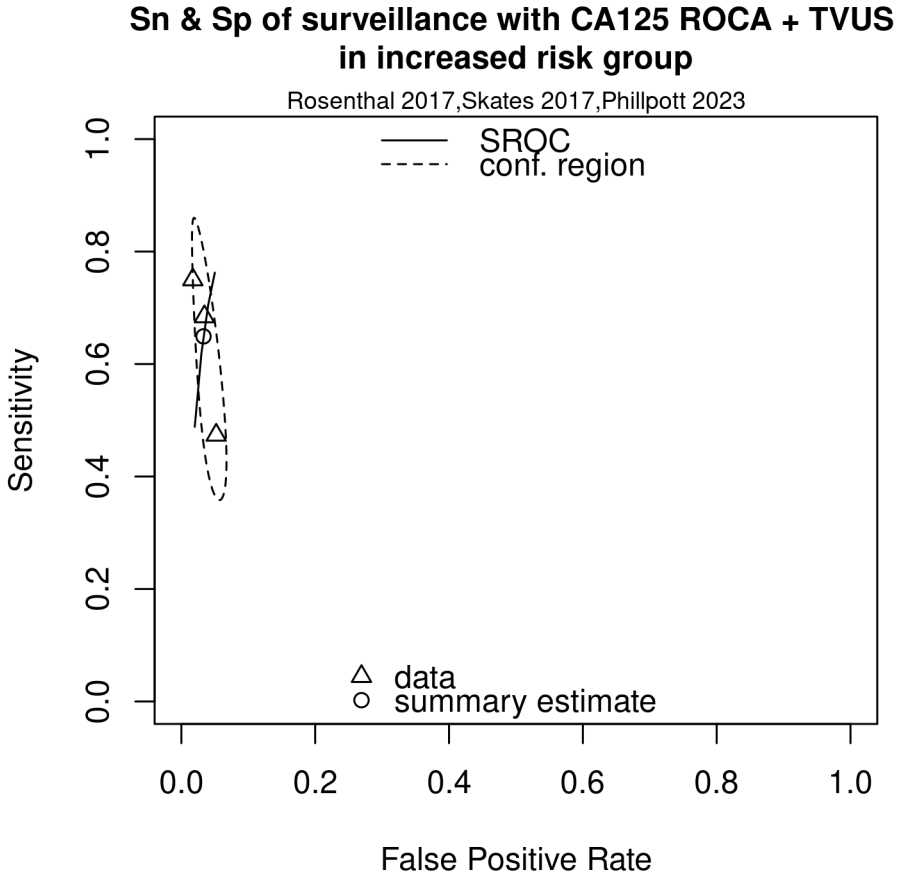
Sn: sensitivity; Sp: specificity; SROC: Summary receiver operating characteristic curve; TVUS: transvaginal

Figure 8: Sensitivity and specificity of surveillance with the ROCA Test and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



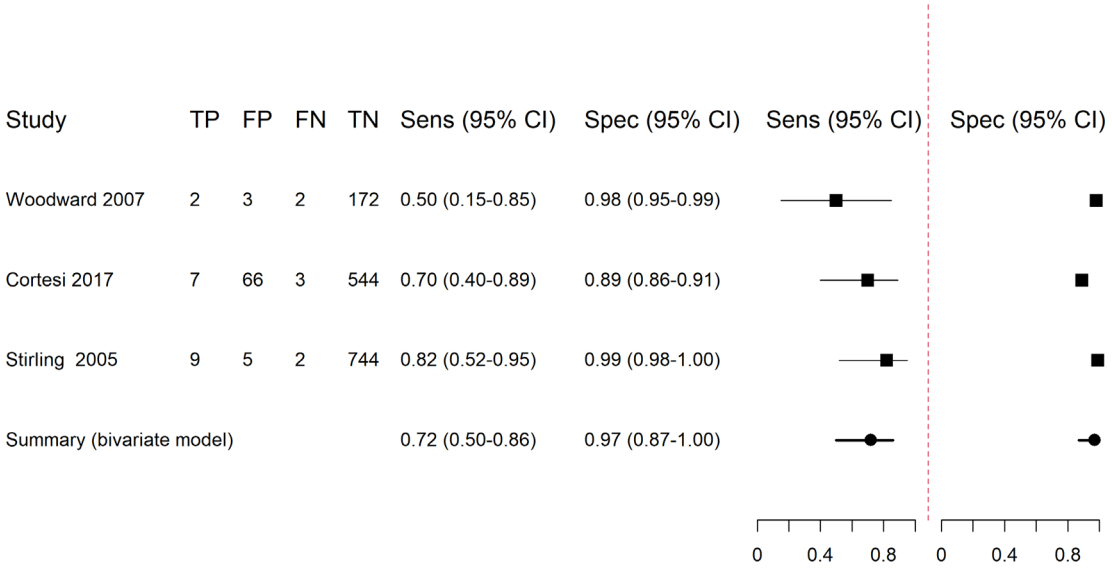
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 9: Summary ROC of surveillance with the ROCA Test and TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



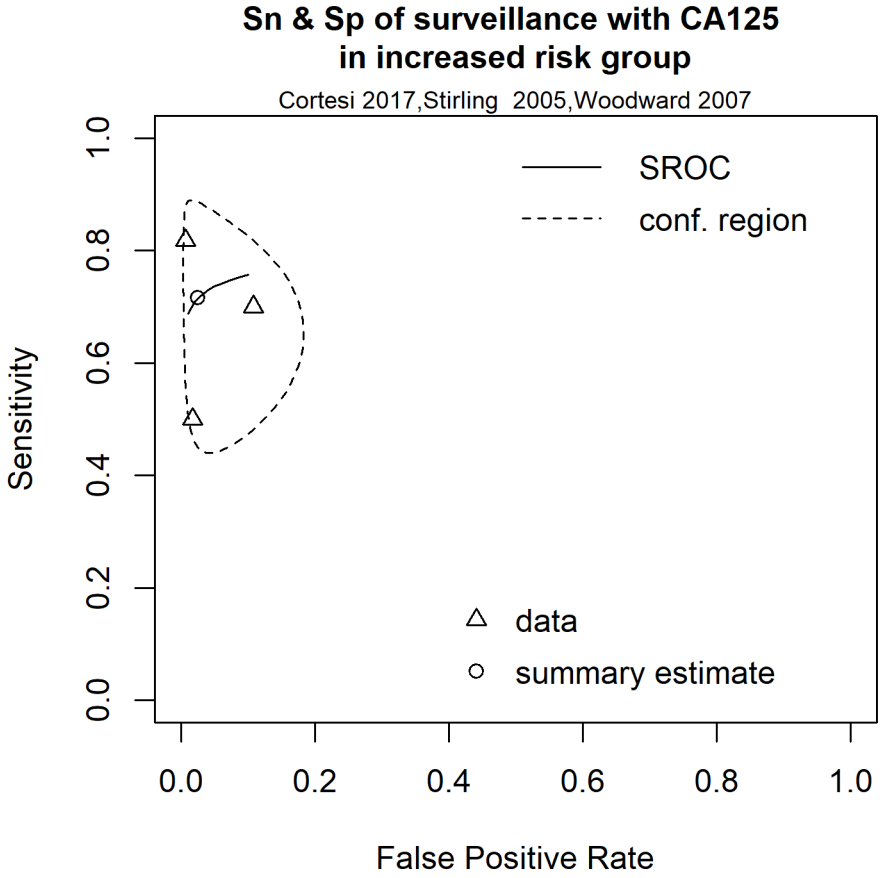
Sn: sensitivity; Sp: specificity; ROCA: risk of ovarian cancer algorithm; SROC: Summary receiver operating characteristic curve; TVUS: transvaginal ultrasound

Figure 10: Sensitivity and specificity of surveillance with CA125 for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



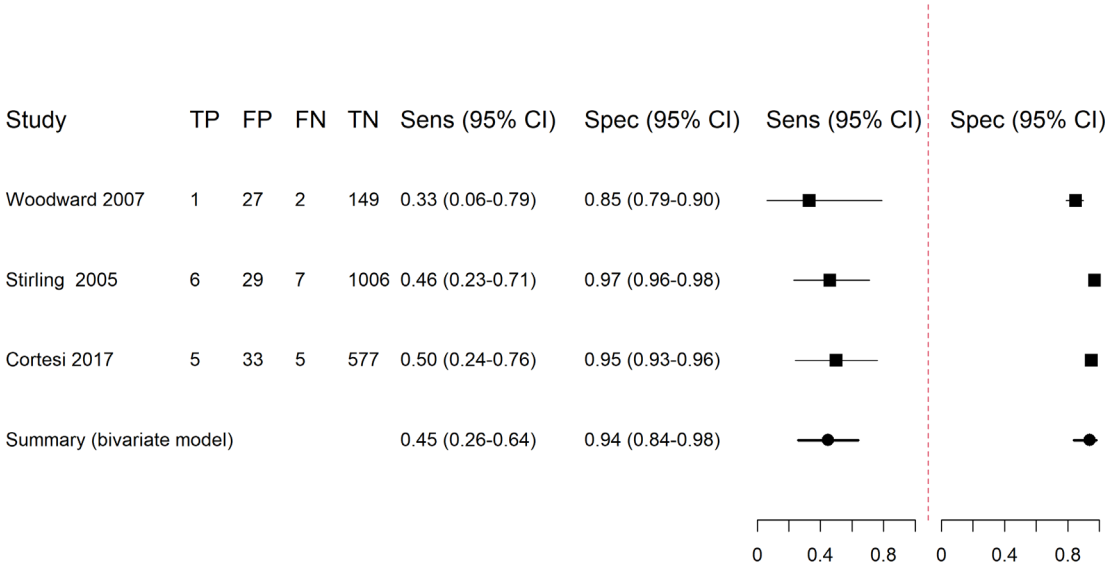
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 11: Summary ROC of surveillance with CA125 for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



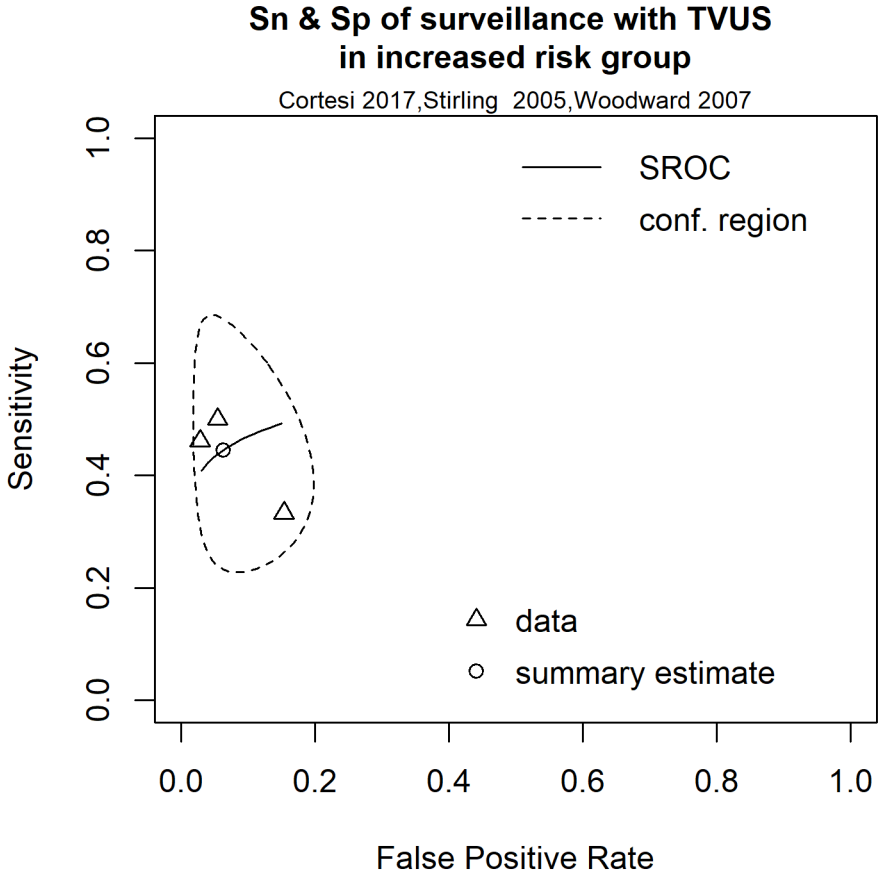
Sn: sensitivity; Sp: specificity; SROC: Summary receiver operating characteristic curve

Figure 12: Sensitivity and specificity of surveillance with TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



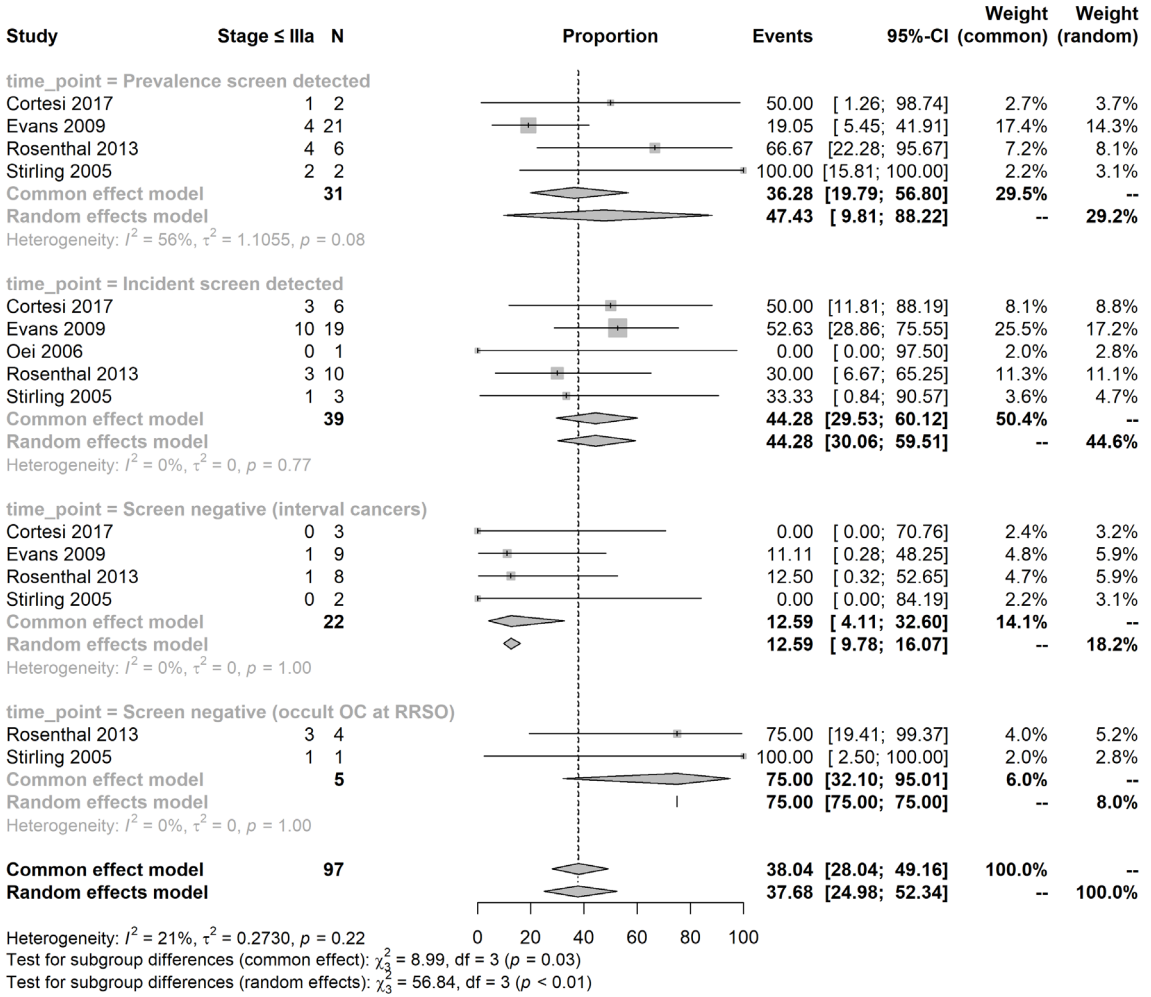
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 13: Summary ROC of surveillance with TVUS for the detection of ovarian, fallopian tube and peritoneal cancers in women at increased risk



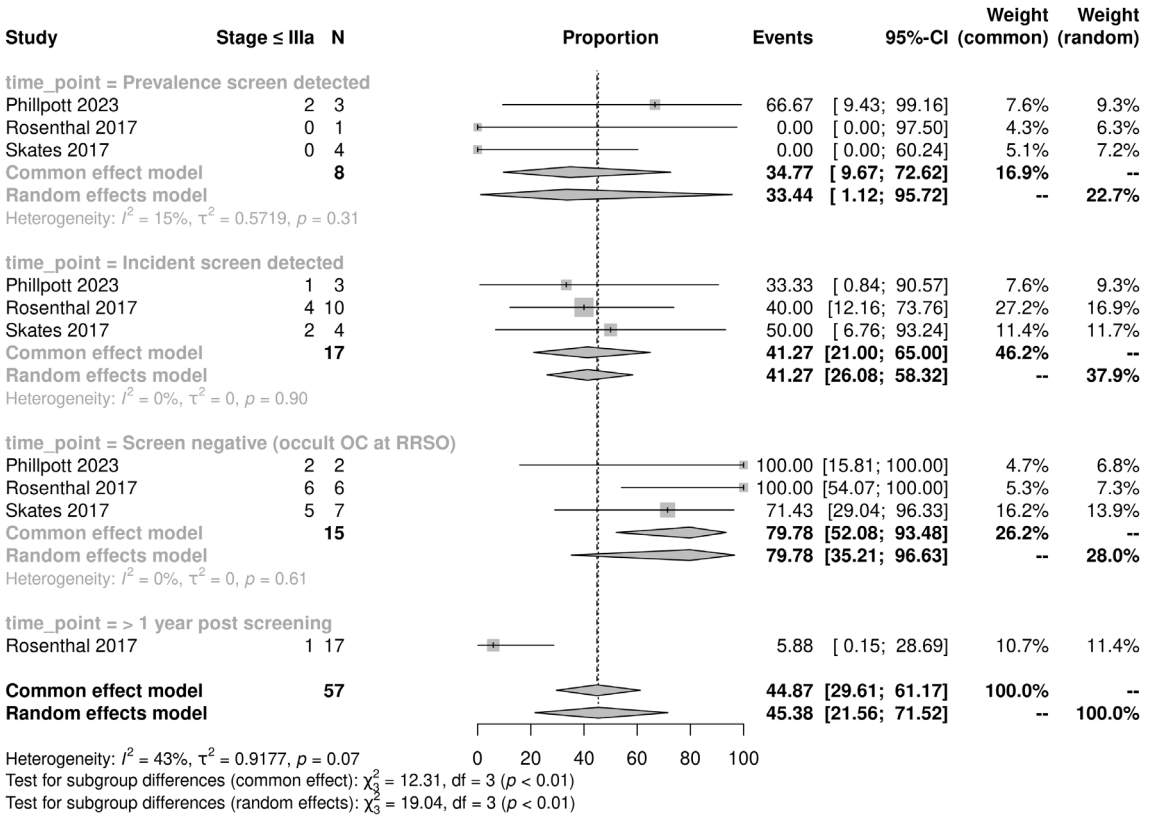
Sn: sensitivity; Sp: specificity; SROC: Summary receiver operating characteristic curve; TVUS: transvaginal ultrasound

Figure 14: Proportion of cancers diagnosed at stage IIIa or lower during studies of surveillance using CA125 and TVUS in *BRCA1/2* carriers



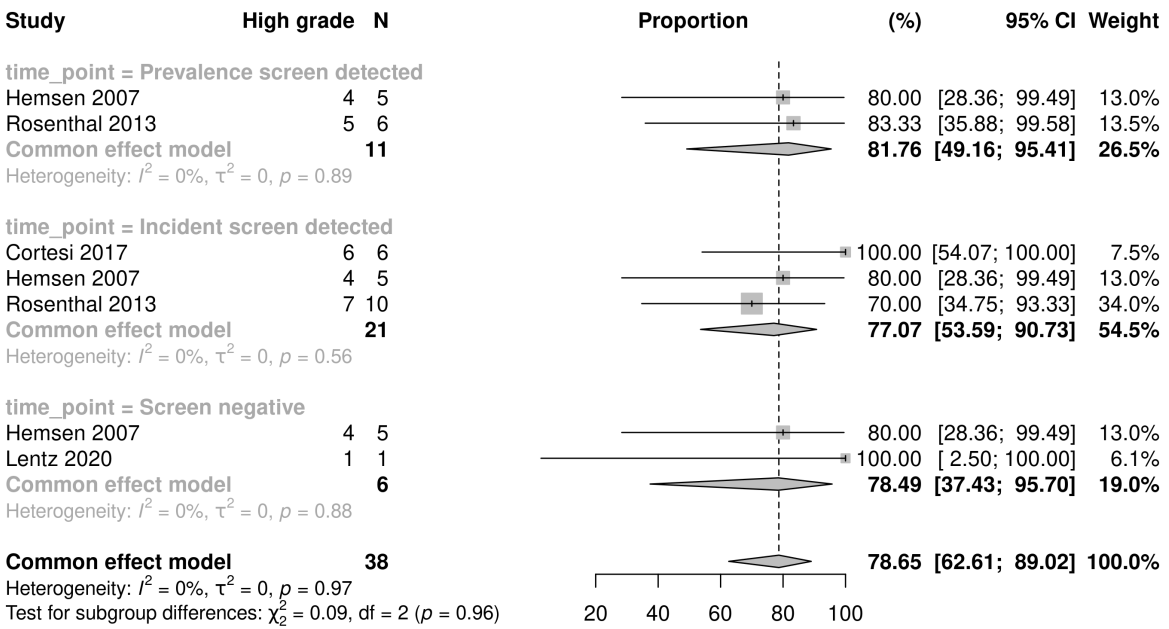
CI: confidence interval; OC: ovarian cancer; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Figure 15: Proportion of cancers diagnosed at stage IIIa or lower during studies of surveillance using the ROCA Test and TVUS in *BRCA1/2* carriers



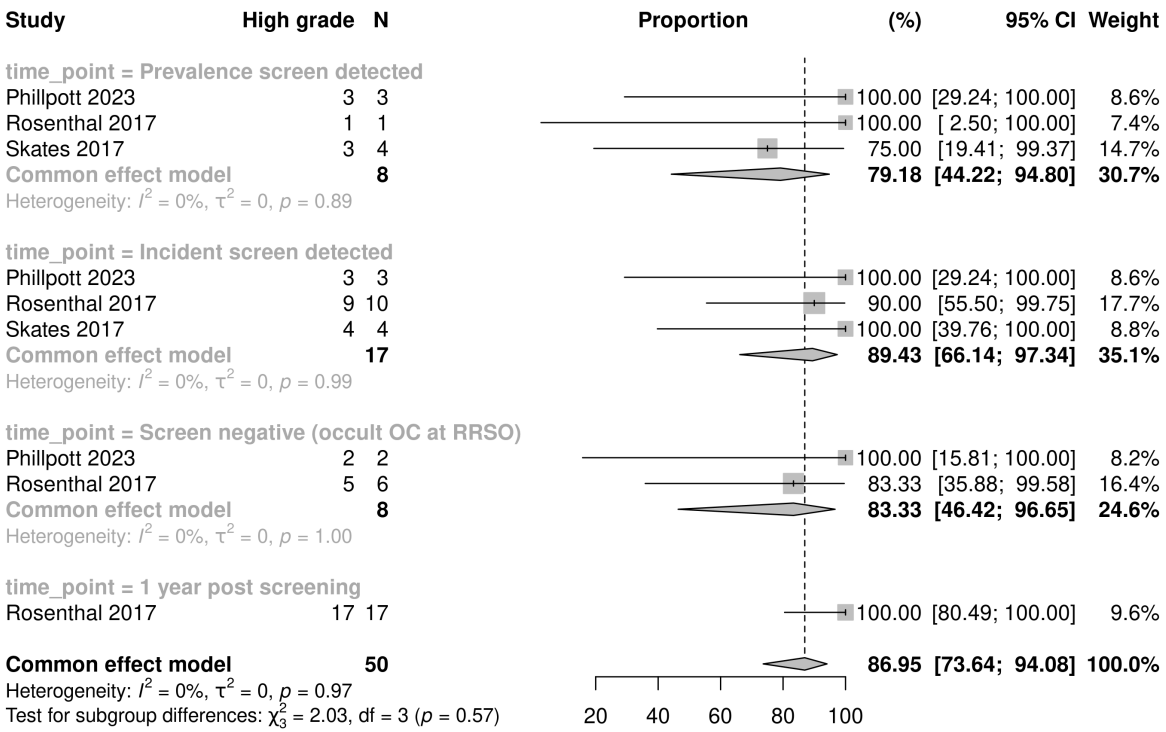
CI: confidence interval; OC: ovarian cancer; ROCA: risk of ovarian cancer algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Figure 16: Proportion of cancers diagnosed as high-grade during studies of surveillance using CA125 and TVUS in *BRCA1/2* carriers



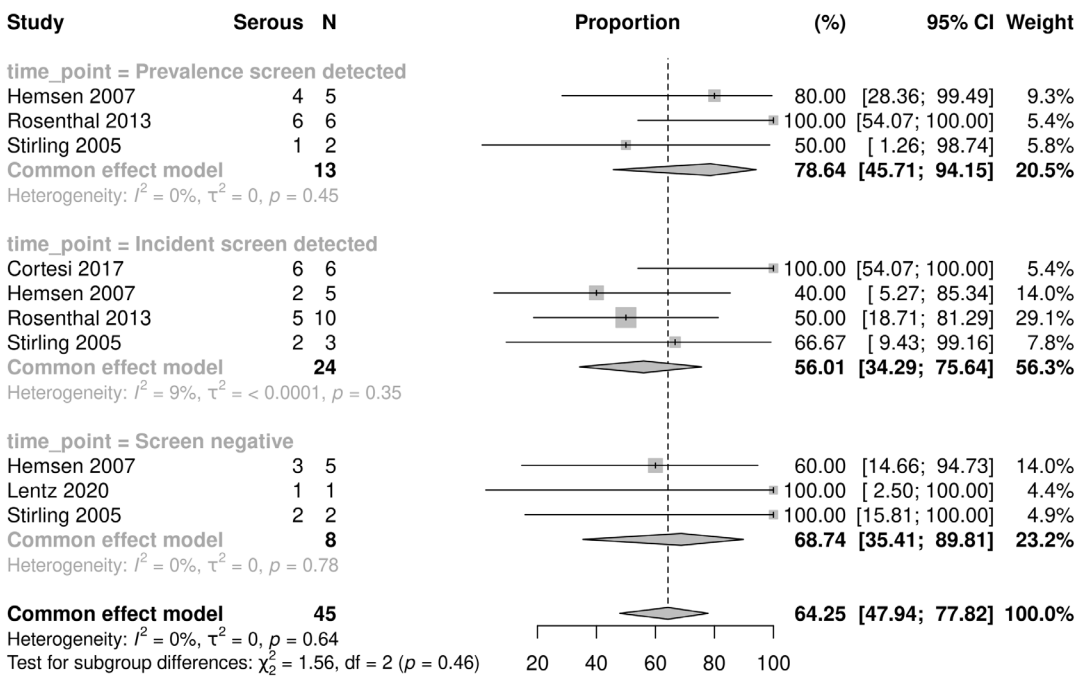
CI: confidence interval; OC: ovarian cancer; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Figure 17: Proportion of cancers diagnosed as high-grade during studies of surveillance using the ROCA Test and TVUS in *BRCA1/2* carriers



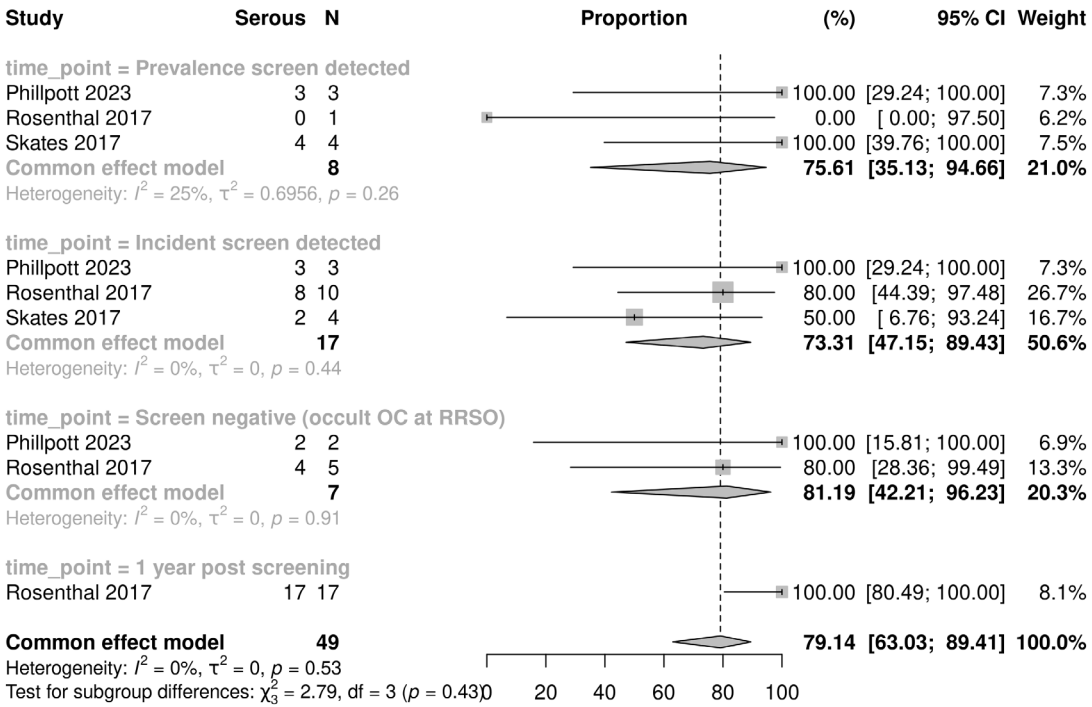
CI: confidence interval; OC: ovarian cancer; ROCA: risk of ovarian cancer algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Figure 18: Proportion of cancers diagnosed as serous histological type during studies of surveillance using CA125 and TVUS in *BRCA1/2* carriers



CI: confidence interval; OC: ovarian cancer; TVUS: transvaginal ultrasound

Figure 19: Proportion of cancers diagnosed as serous histological type during studies of surveillance using the ROCA Test and TVUS in *BRCA1/2* carriers



CI: confidence interval; OC: ovarian cancer; ROCA: risk of ovarian cancer algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Appendix F Modified GRADE tables

GRADE tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

Table 4: Evidence profile for performance characteristics (diagnostic accuracy) of methods of surveillance for *BRCA1/2* carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Surveillance with CA125 and TVUS to identify ovarian, fallopian tube or peritoneal cancer											
4[2]	Cohort studies	1877	0.60 [0.36 to 0.80]	0.98 [0.94 to 0.99]	LR+ 33.0 [6.61 to 96.70]	Serious[3]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.42 [0.21 to 0.67]	Serious[3]	Not serious	Not serious	Serious[4]	LOW	CRITICAL
Surveillance with the ROCA Test and TVUS to identify ovarian, fallopian tube or peritoneal cancer											
2[5]	Cohort studies	1576	0.68 [0.46 to 0.84]	0.98 [0.97 to 0.99]	LR+ 36.5 [21.6 to 55.5]	Serious[3]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.34 [0.16 to 0.55]	Serious[3]	Not serious	Not serious	Serious[4]	LOW	CRITICAL
Surveillance with CA125 and the HE4 ROCA Test to identify ovarian, fallopian tube or peritoneal cancer											
Lentz 2020	Cohort study	149	0.17 [0.02 to 0.69][6]	0.84 [0.77 to 0.89]	LR+ 1.05 [0.08 to 13.5]	Serious[3]	Not serious	Not serious	Very serious[5]	VERY LOW	CRITICAL
					LR- 0.99 [0.59 to 1.65]	Serious[3]	Not serious	Not serious	Serious[4]	LOW	CRITICAL

CI, confidence interval; FP: false positive; LR+, positive likelihood ratio; LR-, negative likelihood ratio; ROCA: risk of ovarian cancer algorithm; TP: true positive; TVUS: transvaginal ultrasound

1 Imprecision judgement based on likelihood ratios

2 Rosenthal 2013, Cortesi 2017, Hemsen 2007, Nanez 2021

3 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS2

4 95% CI crosses 1 decision making threshold

5 Philpott 2013, Rosenthal 2023

5 95% CI crosses 2 decision making thresholds

6 No cancers detected by screening in Lentz 2020 – sensitivity estimate uses continuity correction (adding 0.5 to TP and FP counts)

Table 5: Evidence profile for performance characteristics (diagnostic accuracy) of methods of surveillance for women at increased risk

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[7]	Quality	Importance
Surveillance with CA125 and TVUS to identify ovarian, fallopian tube or peritoneal cancer											
5[1]	Cohort study	5838	0.69 [0.52 to 0.82]	0.95 [0.88 to 0.98]	LR+ 16.7 [5.13 to 41.3]	Serious[2]	Serious[3]	Not serious	Not serious	LOW	CRITICAL
					LR- 0.33 [0.19 to 0.52]	Serious[2]	Serious[3]	Not serious	Serious[4]	VERY LOW	CRITICAL
Surveillance with the ROCA Test and annual TVUS to identify ovarian, fallopian tube or peritoneal cancer											
3[5]	Cohort study	8709	0.65 [0.41 to 0.83]	0.97 [0.94 to 0.98]	LR+ 21.0 [7.57 to 43.3]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.37 [0.18 to 0.62]	Serious[2]	Not serious	Not serious	Serious[4]	LOW	CRITICAL
Surveillance with CA125, HE4 and TVUS to identify ovarian, fallopian tube or peritoneal cancer											
Karlan 2014	RCT[6]	1179	0.28 [0.09 to 0.6]	0.99 [0.98 to 1]	LR+ 31.0 [9.21 to 104]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.73 [0.49 to 1.09]	Serious[2]	Not serious	Not serious	Serious[4]	LOW	CRITICAL
Surveillance with CA125 to identify ovarian, fallopian tube or peritoneal cancer											
3[5]	Cohort study	1559	0.72 [0.50 to 0.86]	0.97 [0.87 to 1.00]	LR+ 42.6 [4.97 to 168]	Serious[2]	Serious[3]	Not serious	Serious[4]	VERY LOW	CRITICAL
					LR- 0.31 [0.14 to 0.54]	Serious[2]	Serious[3]	Not serious	Serious[4]	VERY LOW	CRITICAL
Surveillance with TVUS to identify ovarian, fallopian tube or peritoneal cancer											
3[6]	Cohort study	1847	0.45 [0.26 to 0.64]	0.94 [0.84 to 0.98]	LR+ 8.42 [2.21 to 22.7]	Serious[2]	Serious[3]	Not serious	Serious[4]	VERY LOW	CRITICAL
					LR- 0.60 [0.38 to 0.82]	Serious[2]	Serious[3]	Not serious	Serious[4]	VERY LOW	CRITICAL

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; RCT: randomised controlled trial; ROCA: risk of ovarian cancer algorithm; TVUS: transvaginal ultrasound

1 Rosenthal 2013, Cortesi 2017, Oei 2006, Stirling 2005, Woodward 2007

2 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS2

3 Serious heterogeneity not explained by subgroup analysis

4 95% CI crosses 1 decision making threshold

5 Philpott 2023, Rosenthal 2017, Skates 2017

6 Cortesi 2017, Stirling 2005, Woodward 2007

7 *Imprecision judgement based on likelihood ratios*

Table 6: Stage, grade and histological type of cancers diagnosed during ovarian cancer surveillance studies

No. of studies	Study design	No. of with characteristic / No. of cancers	Proportion (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Proportion of prevalence screen detected cancers stage IIIa or lower in surveillance using CA125 and TVUS in BRCA1/2 carriers									
4[1]	Cohort studies	11/31	47.43% (9.81 to 88.22)	Serious[2]	Serious[3]	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of incidence screen detected cancers stage IIIa or lower in surveillance using CA125 and TVUS in BRCA1/2 carriers									
5[5]	Cohort studies	17/39	44.28% (29.53 to 60.12)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of screen negative (interval) cancers stage IIIa or lower in surveillance using CA125 and TVUS in BRCA1/2 carriers									
4[1]	Cohort studies	2/22	12.59% (4.11 to 32.60)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of screen negative (occult OC at RRSO) cancers stage IIIa or lower in surveillance using CA125 and TVUS in BRCA1/2 carriers									
2[6]	Cohort studies	4/5	75.00% (32.10 to 95.01)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of prevalence screen detected cancers stage IIIa or lower in surveillance using the ROCA Test and TVUS in BRCA1/2 carriers									
3[7]	Cohort studies	2/8	33.77% (9.67 to 72.62)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of incidence screen detected cancers stage IIIa or lower in surveillance using the ROCA Test and TVUS in BRCA1/2 carriers									
3[7]	Cohort studies	6/17	41.27% (21.00 to 65.00)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of screen negative (occult OC at RRSO) cancers stage IIIa or lower in surveillance using the ROCA Test and TVUS in BRCA1/2 carriers									
3[7]	Cohort studies	13/15	79.78% (52.08 to 93.48)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of cancers stage IIIa or lower diagnosed ≥ 1 year after stopping surveillance with the ROCA Test and TVUS in BRCA1/2 carriers									
Rosenthal 2017	Cohort study	1/17	5.88% (0.15 to 28.69)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of cancers diagnosed as high-grade during surveillance using CA125 and TVUS in BRCA1/2 carriers									

No. of studies	Study design	No. of with characteristic / No. of cancers	Proportion (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
4[8]	Cohort studies	31/38	78.65% (62.61 to 89.02)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of cancers diagnosed as high-grade during surveillance using the ROCA Test and TVUS in BRCA1/2 carriers									
3[7]	Cohort studies	47/50	86.95% (73.64 to 94.08)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of cancers diagnosed as serous histological type during surveillance using CA125 and TVUS in BRCA1/2 carriers									
5[9]	Cohort studies	32/45	64.25% (47.94 to 77.82)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL
Proportion of cancers diagnosed as serous histological type during surveillance using the ROCA Test and TVUS in BRCA1/2 carriers									
3[7]	Cohort study	43/49	79.14% (63.03 to 89.41)	Serious[2]	Not serious	Not serious	Very serious[4]	VERY LOW	CRITICAL

CI: confidence interval; ROCA: risk of ovarian cancer algorithm; TVUS, transvaginal ultrasound
1 Cortesi 2017, Evans 2009, Rosenthal 2013
2 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS2
3 Serious heterogeneity unexplained by subgroup analysis
4 Sample size < 200
5 Cortesi 2017, Evans 2009, Oei 2006, Rosenthal 2013, Stirling 2005
6 Rosenthal 2013, Stirling 2005
7 Philpott 2023, Rosenthal 2017, Skates 2017
8 Cortesi 2017, Hemsen 2007, Lentz 2020, Rosenthal 2013
9 Cortesi 2017, Hemsen 2007, Lentz 2020, Rosenthal 2013, Stirling 2005

Appendix G Economic evidence study selection

Study selection for: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

One global search was undertaken – please see Supplement 2 for details on study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

No economic evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

Excluded effectiveness/diagnostic studies

One literature search was performed for the review questions K and L. Studies included in this review were excluded from review K and studies included in review K were excluded from this review however, these studies do not appear in the 'Records excluded' box in Figure 1, or in the respective excluded studies tables below.

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Andersen, M Robyn, Drescher, Charles W, Zheng, Yingye et al. (2007) Changes in cancer worry associated with participation in ovarian cancer screening. Psycho-oncology 16(9): 814-20	- Population in study does not match that specified in this review protocol *Women not at increased risk of familial ovarian cancer*
Andersen, M Robyn, Karlan, Beth Y, Drescher, Charles W et al. (2019) False-positive screening events and worry influence decisions about surgery among high-risk women. Health psychology: official journal of the Division of Health Psychology, American Psychological Association 38(1): 43-52	- Outcomes in study do not match those specified in this review protocol *Secondary analysis of Karlan 2014*
Auranen, Annika and Joutsiniemi, Titta (2011) A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta obstetricia et gynecologica Scandinavica 90(5): 437-44	- Systematic review used as source of primary studies
Belkic, K.L., Cohen, M., Marquez, M. et al. (2010) Screening of high-risk groups for breast and ovarian cancer in Europe: A focus on the Jewish population. Oncology Reviews 4(4): 233-267	- Systematic review used as source of primary studies
Bermejo-Perez, M J; Marquez-Calderon, S; Llanos-Mendez, A (2007) Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. International journal of cancer 121(2): 225-31	- Systematic review used as source of primary studies
Bermejo-Perez, M J; Marquez-Calderon, S; Llanos-Mendez, A (2008) Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review. The British journal of radiology 81(963): 172-9	- Systematic review used as source of primary studies
Blyuss, Oleg, Burnell, Matthew, Ryan, Andy et al. (2018) Comparison of Longitudinal CA125 Algorithms as a First-Line Screen for Ovarian Cancer in the General Population. Clinical cancer research : an official journal of the American Association for Cancer Research 24(19): 4726-4733	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Bourne, T H, Campbell, S, Reynolds, K et al. (1994) The potential role of serum CA 125 in an ultrasound-based screening program for familial ovarian cancer. Gynecologic oncology 52(3): 379-85	- Outcomes in study do not match those specified in this review protocol *Outcomes reported for screening group only*
Buys, Saundra S, Partridge, Edward, Black, Amanda et al. (2011) Effect of screening on ovarian cancer mortality: the Prostate, Lung,	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 305(22): 2295-2303	*Results not reported separately for the subgroup s of women with a family or personal history of ovarian cancer. Trialists contacted to ask for this subgroup data*
Debniak, Tadeusz, Gromowski, Tomasz, Scott, Rodney J et al. (2015) Management of ovarian and endometrial cancers in women belonging to HNPCC carrier families: review of the literature and results of cancer risk assessment in Polish HNPCC families. Hereditary cancer in clinical practice 13(1): 3	- Intervention in study does not match that specified in this review protocol *No details of surveillance protocol used for ovarian cancer*
Drescher, Charles W, Nelson, Judy, Peacock, Sue et al. (2004) Compliance of average- and intermediate-risk women to semiannual ovarian cancer screening. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 13(4): 600-6	- Outcomes in study do not match those specified in this review protocol *Compliance with screening only*
Eikenboom, E.L., Van Doorn, H.C., Dinjens, W.N.M. et al. (2021) Gynecological surveillance and surgery outcomes in dutch lynch syndrome carriers. Cancers 13(3): 1-16	- Intervention in study does not match that specified in this review protocol *Study assesses gynaecological tumours and gynaecological management in Lynch Syndrome carriers*
Eleje, George U, Eke, Ahizechukwu C, Ezebialu, Ifeanyichukwu U et al. (2018) Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. The Cochrane database of systematic reviews 8: cd012464	- Intervention in study does not match that specified in this review protocol *RRSO is compared to general surveillance or non-RRSO - but no details of surveillance protocols are given*
Fatouros, Michael; Baltoyiannis, Georgios; Roukos, Dimitrios H (2008) The predominant role of surgery in the prevention and new trends in the surgical treatment of women with BRCA1/2 mutations. Annals of surgical oncology 15(1): 21-33	- Systematic review used as source of primary studies
Fries, Melissa H, Hailey, B Jo, Flanagan, Judith 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): 411-6	- Comparator in study does not match that specified in this review protocol *Does not compare surveillance to an alternative strategy*
Fry, A, Busby-Earle, C, Rush, R et al. (2001) Prophylactic oophorectomy versus screening: psychosocial outcomes in women at increased risk of ovarian cancer. Psycho-oncology 10(3): 231-41	- Study design does not match that specified in this review protocol *Non-randomised study, does not adjust for confounders in the analysis*
Gentry-Maharaj, A., Blyuss, O., Ryan, A. et al. (2020) Multi-marker longitudinal algorithms incorporating HE4 and CA125 in ovarian cancer screening of postmenopausal women. Cancers 12(7): 1-12	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*

Study	Reason for exclusion
Gentry-Maharaj, A, Sharma, A, Burnell, M et al. (2013) Acceptance of transvaginal sonography by postmenopausal women participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 41(1): 73-9	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Gopie, Jessica P; Vasen, Hans F A; Tibben, Aad (2012) Surveillance for hereditary cancer: does the benefit outweigh the psychological burden?--A systematic review. Critical reviews in oncology/hematology 83(3): 329-40	- Systematic review used as source of primary studies
Grandi, Giovanni, Fiocchi, Federica, Cortesi, Laura et al. (2021) The challenging screen detection of ovarian cancer in BRCA mutation carriers adhering to a 6-month follow-up program: results from a 6-years surveillance. Menopause (New York, N.Y.) 29(1): 63-72	- Secondary publication of an included study that does not provide any additional relevant data *See Cortesi 2017*
Gronwald, Jacek, Lubinski, Jan, Huzarski, Tomasz et al. (2019) A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy. Gynecologic oncology 155(2): 270-274	- Study design does not match that specified in this review protocol *Comparisons between groups not adjusted for baseline differences*
Haque, Reina, Skates, Steven J, Armstrong, Mary Anne et al. (2020) Feasibility, patient compliance and acceptability of ovarian cancer surveillance using two serum biomarkers and Risk of Ovarian Cancer Algorithm compared to standard ultrasound and CA 125 among women with BRCA mutations. Gynecologic oncology 157(2): 521-528	- Secondary publication of an included study that does not provide any additional relevant data *See Lentz 2020*
Henderson, J.T.; Webber, E.M.; Sawaya, G.F. (2018) Screening for ovarian cancer updated evidence report and systematic review for the US preventive services task force. JAMA - Journal of the American Medical Association 319(6): 595-606	- Systematic review used as source of primary studies
Jacobs, Ian J, Menon, Usha, Ryan, Andy et al. (2016) Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet (London, England) 387(10022): 945-956	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Kobayashi, H, Yamada, Y, Sado, T et al. (2008) A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int. J. Gynecol. Cancer 18(3): 414-420	- Population in study does not match that specified in this review protocol *Participants not at increased risk of familial ovarian cancer. No subgroup analysis of increased risk groups*
Lacey Jr., J.V., Greene, M.H., Buys, S.S. et al. (2006) Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstetrics and Gynecology 108(5): 1176-1184	- Outcomes in study do not match those specified in this review protocol *Insufficient data to calculate diagnostic outcomes*
Laframboise, Stephane, Nedelcu, R, Murphy, J et al. (2002) Use of CA-125 and ultrasound in high-risk women. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 12(1): 86-91	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
	Insufficient data to calculate diagnostic outcomes
Li, Jiaxin, Jia, Ziqi, Zhang, Menglu et al. (2021) Cost-Effectiveness Analysis of Imaging Modalities for Breast Cancer Surveillance Among BRCA1/2 Mutation Carriers: A Systematic Review. Frontiers in oncology 11: 763161	- Systematic review used as source of primary studies
Lim, Natalie, Hickey, Martha, Young, Graeme P et al. (2022) Screening and risk reducing surgery for endometrial or ovarian cancers in Lynch syndrome: a systematic review. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 32(5): 646-655	- Outcomes in study do not match those specified in this review protocol *Insufficient data to calculate diagnostic outcomes*
Lockwood, S. and Ritzert, B. (2013) Cost-effectiveness of serum CA125 compared to transvaginal ultrasound as a screening test for ovarian cancer: A systematic review protocol. JBI Library of Systematic Reviews 11(10): 89-106	- Study design does not match that specified in this review protocol *Systematic review protocol*
Mallen, Adrianne, Soong, T Rinda, Townsend, Mary K et al. (2018) Surgical prevention strategies in ovarian cancer. Gynecologic oncology 151(1): 166-175	- Systematic review used as source of primary studies
Marchetti, C., De Felice, F., Perniola, G. et al. (2018) Screening program in ovarian cancer: A logical step in clinical management? A meta-analysis. Current Problems in Cancer 42(2): 235-240	- Systematic review used as source of primary studies
Menon, Usha, Gentry-Maharaj, Aleksandra, Burnell, Matthew et al. (2021) Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet (London, England) 397(10290): 2182-2193	- Population in study does not match that specified in his review protocol *Women with increased risk of familial ovarian cancer were excluded*
Menon, Usha, Gentry-Maharaj, Aleksandra, Hallett, Rachel et al. (2009) Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The Lancet. Oncology 10(4): 327-40	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Menon, Usha, Ryan, Andy, Kalsi, Jatinderpal et al. (2015) Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 33(18): 2062-71	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Moller, Pal, Seppala, Toni, Bernstein, Inge et al. (2017) Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 66(3): 464-472	- Intervention in study does not match that specified in this review protocol *Colonoscopic surveillance*
Pinsky, Paul F, Yu, Kelly, Kramer, Barnett S et al. (2016) Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecol. Oncol. 143(2): 270-275	- Population in study does not match that specified in this review protocol *Results not reported separately for the subgroup of women with a family history of breast or ovarian cancer*

Study	Reason for exclusion
Ramamurthy, C.; Chertock, Y.; Hall, M.J. (2017) Randomized Controlled Trials in Hereditary Cancer Syndromes. Surgical Oncology Clinics of North America 26(4): 729-750	- Systematic review used as source of primary studies
Reade, C.J., Riva, J.J., Busse, J.W. et al. (2013) Risks and benefits of screening asymptomatic women for ovarian cancer: A systematic review and meta-analysis. Gynecologic Oncology 130(3): 674-681	- Systematic review used as source of primary studies
Renaud, M.-C. and Le, T. (2018) No. 291-Epidemiology and Investigations forSuspected Endometrial Cancer. Journal of Obstetrics and Gynaecology Canada 40(9): e703-e711	- Study design does not match that specified in this review protocol *Clinical practice guideline*
Salhab, Mohamed; Bismohun, Selina; Mokbel, Kefah (2010) Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery. BMC women's health 10: 28	- Systematic review used as source of primary studies
Schmeler, KM, Sun, CC, Bodurka, DC et al. (2006) Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. Obstetrics and gynecology 108(3pt1): 515-520	- Study design does not match that specified in this review protocol *Analysis does not adjust for baseline differences between groups*
Sherman, Mark E, Piedmonte, Marion, Mai, Phuong L et al. (2014) Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 32(29): 3275-83	- Comparator in study does not match that specified in this review protocol *Outcomes reported for RRSO group only*
Sroczynski, Gaby, Gogollari, Artemisa, Kuehne, Felicitas et al. (2020) A Systematic Review on Cost-effectiveness Studies Evaluating Ovarian Cancer Early Detection and Prevention Strategies. Cancer prevention research (Philadelphia, Pa.) 13(5): 429-442	- Systematic review used as source of primary studies
Stewart, M.E., Knisely, A.T., Sullivan, M.W. et al. (2019) Evaluation of screening and risk-reducing surgery for women followed in a high-risk breast/ovarian cancer clinic: it is all about the tubes in BRCA mutation carriers. Gynecologic Oncology Reports 28: 18-22	- Intervention in study does not match that specified in this review protocol *Outcomes reported for RRSO group only*
Tailor, A, Bourne, TH, Campbell, S et al. (2003) Results from an ultrasound-based familial ovarian cancer screening clinic: a 10-year observational study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 21(4): 378-85	- Study design does not match that specified in this review protocol *Outcomes reported for screening group only*
Tschernichovsky, Roi and Goodman, Annekathryn (2017) Risk-Reducing Strategies for Ovarian Cancer in BRCA Mutation Carriers: A Balancing Act. The oncologist 22(4): 450-459	- Systematic review used as source of primary studies
Tzortzatos, Gerasimos, Andersson, Emil, Soller, Maria et al. (2015) The gynecological surveillance of women with Lynch syndrome in Sweden. Gynecologic oncology 138(3): 717-22	- Intervention in study does not match that specified in this review protocol *Outcomes reported for screening group only*
van Driel, Catheleine M G, de Bock, Geertruida H, Arts, Henriette J G et al. (2015) Stopping ovarian cancer screening in BRCA1/2 mutation carriers: effects on risk management decisions & outcome of risk-reducing salpingo-oophorectomy specimens. Maturitas 80(3): 318-22	- Outcomes in study do not match those specified in this review protocol *Interval cancers (not detected by screening) not reported*

Study	Reason for exclusion
Vasen, H F A, Tesfay, E, Boonstra, H et al. (2005) Early detection of breast and ovarian cancer in families with BRCA mutations. European journal of cancer (Oxford, England: 1990) 41(4): 549-54	- Outcomes in study do not match those specified in this review protocol
Wainberg, Sara and Husted, Janice (2004) Utilization of screening and preventive surgery among unaffected carriers of a BRCA1 or BRCA2 gene mutation. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 13(12): 1989-95	- Systematic review used as source of primary studies
Yang, Kathleen Y, Caughey, Aaron B, Little, Sarah E et al. (2011) A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. Familial cancer 10(3): 535-43	- Study design does not match that specified in this review protocol *A theoretical population of women with Lynch Syndrome at age 30 was used for the analysis*

Excluded economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: How effective are different methods of surveillance for women at increased risk of familial ovarian cancer?

No research recommendations were made for this review question.

Appendix L Outcome data tables

Key to variables

- study: study identifier
- population: study population (*BRCA1/2* carriers or other increased risk groups)
- tests: surveillance tests
- screeningpoint: point during surveillance from which the results come (incidence screen, prevalence screen or both)
- TP, FP, FN, TN: true positive, false positive, false negative, true negative

Table 8: Diagnostic accuracy data

study	population	tests	screening_point	TP	FP	FN	TN
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Prevalent	9	12	1	3541
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Prevalent	6	4	1	527
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Incident	13	38	4	3466
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Incident	10	4	3	509
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Incident + prevalent	13	149	6	4180
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident + prevalent	9	16	5	779
Skates 2017	20% carrier probability	The ROCA Test + TVUS	Incident + prevalent	9	186	10	3243
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Incident + prevalent	7	52	3	558
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125	Incident + prevalent	7	66	3	544
Cortesi 2017	increased familial/genetic ovarian cancer risk	TVUS	Incident + prevalent	5	33	5	577
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Incident + prevalent	8	1	3	115
Hermsen 2007	BRCA1/2 carriers	CA125 + TVUS	Incident + prevalent	5	16	7	431
Karlan 2014	increased familial/genetic ovarian cancer risk	CA125 + HE4 + TVUS	Incident + prevalent	2	10	6	1161
Lentz 2020	BRCA1/2 carriers	The ROCA Test + the HE4 ROCA Test	Incident + prevalent	0	23	2	124
Nanez 2021	BRCA1/2 carriers	CA125 + TVUS	Incident + prevalent	2	7	2	97
Oei 2006	High Risk	CA125 + TVUS	Incident + prevalent	1	23	1	487
Stirling 2005	increased familial/genetic ovarian cancer risk	TVUS	Incident + prevalent	6	29	7	1006
Stirling 2005	increased familial/genetic ovarian cancer risk	CA125	Incident + prevalent	9	5	2	744

study	population	tests	screening_point	TP	FP	FN	TN
Stirling 2005	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Incident + prevalent	10	29	3	964
Woodward 2007	>=10% Lifetime risk	TVUS	Incident + prevalent	1	27	2	149
Woodward 2007	>=10% Lifetime risk	CA125	Incident + prevalent	2	3	2	172
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Incident + prevalent	2	30	2	145
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Incident + prevalent	6	13	2	746
Phillpott 2023	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Incident + prevalent	6	13	2	746

ROCA: Risk of Ovarian Cancer Algorithm; TVUS: transvaginal ultrasound

Key to variables

- study: study identifier
- population: study population (*BRCA1/2* carriers or other increased risk groups)
- tests: surveillance tests
- time_point: route by which the cancers were detected
- n_cancers: total number of cancers detected
- stage_i, stage_ii, stage_iiia, stage_iiibc, stage_iv: number of cancers detected at stage I, II, IIIa, IIIb-c or IV respectively
- low_stage: number of cancers detected at stage IIIa or lower

Table 9: Stage at diagnosis data

study	population	tests	time_point	n_cancers	stage_i	stage_ii	stage_iiia	stage_iiibc	stage_iv	low_stage
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	9	5	1	1	2	0	7
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	6	2	1	1	2	0	4
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	13	2	2	1	8	0	5
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	10	1	1	1	7	0	3
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Screen negative (interval cancers)	8	1	0	0	5	2	1
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Screen negative (interval cancers)	8	1	0	0	5	2	1
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Prevalence screen detected	1	0	0	0	1	0	0
Rosenthal 2017	BRCA1/2 carriers		Prevalence screen detected	1	0	0	0	1	0	0
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Incident screen detected	12	2	3	1	6	0	6
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	10	1	3	0	6	0	4

study	population	tests	time_point	n_cancers	stage_i	stage_ii	stage_iiia	stage_iiibc	stage_iv	low_stage
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	6	4	1	1	0	0	6
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	6	4	1	1	0	0	6
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	> 1 year post screening	18	1	0	0	14	3	1
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	> 1 year post screening	17	1	0	0	13	3	1
Skates 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Prevalence screen detected	4	0	0	0	3	1	0
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	4	0	0	0	3	1	0
Skates 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Incident screen detected	6	0	2	0	4	0	2
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	4	0	2	0	2	0	2
Skates 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	9	6	0	1	2	0	7
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	7	5	0	0	2	0	5
Cortesi 2017	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	2	0	1	0	1	0	1
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	2	0	1	0	1	0	1
Cortesi 2017	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	7	1	3	0	2	1	4
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	6	1	2	0	2	1	3
Cortesi 2017	>=10% Lifetime risk	CA125 + TVUS	Screen negative (interval cancers)	3	0	0	0	2	1	0
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Screen negative (interval cancers)	3	0	0	0	2	1	0
Oei 2006	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	1	0	0	0	1	0	0
Oei 2006	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	1	0	0	0	1	0	0
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	2	1	1	0	0	0	2
Stirling 2005	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	3	2	1	0	0	0	3
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	3	0	1	0	2	0	1
Stirling 2005	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	7	1	1	0	4	1	2
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Screen negative (interval cancers)	2	0	0	0	1	1	0
Stirling 2005	>=10% Lifetime risk	CA125 + TVUS	Screen negative (interval cancers)	2	0	0	0	1	1	0
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	1	0	0	0	0	1	0
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Screen negative (occult OC at RRSO)	1	0	0	1	0	1	1

study	population	tests	time_point	n_cancers	stage_i	stage_ii	stage_iiia	stage_iiibc	stage_iv	low_stage
Stirling 2005	>=10% Lifetime risk	CA125 + TVUS	Screen negative (occult OC at RRSO)	1	0	0	1	0	1	1
Evans 2009	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	26	7	2	0	17	0	9
Evans 2009	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	21	2	2	0	17	0	4
Evans 2009	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	27	8	5	0	14	0	13
Evans 2009	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	19	5	5	0	9	0	10
Evans 2009	>=10% Lifetime risk	CA125 + TVUS	Screen negative (interval cancers)	11	1	0	0	10	0	1
Evans 2009	BRCA1/2 carriers	CA125 + TVUS	Screen negative (interval cancers)	9	1	0	0	8	0	1
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	3	0	1	1	1	0	2
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	3	1	0	0	1	1	1
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	2	2	0	0	0	0	2
Phillpott 2023	>=10% Lifetime risk	The ROCA Test + TVUS	Prevalence screen detected	3	0	1	1	1	0	2
Phillpott 2023	>=10% Lifetime risk	The ROCA Test + TVUS	Incident screen detected	3	1	0	0	1	1	1
Phillpott 2023	>=10% Lifetime risk	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	2	2	0	0	0	0	2
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Screen negative (occult OC at RRSO)	4	2	1	0	1	0	3
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Screen negative (occult OC at RRSO)	4	2	1	0	1	0	3
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	> 1 year post screening	10	1	1	0	6	2	2

OC: ovarian cancer; ROCA: Risk of Ovarian Cancer Algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Key to variables

- study: study identifier
- population: study population (*BRCA1/2* carriers or other increased risk groups)
- tests: surveillance tests
- time_point: route by which the cancers were detected
- n_cancers: total number of cancers detected
- low_grade: number of low grade cancers detected
- high_grade: number of high grade cancers detected

Table 10: Grade data

study	population	tests	time_point	n_cancers	low_grade	high_grade
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	9	1	8
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	6	1	5
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	13	5	8
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	10	3	7
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Screen negative	8	1	7
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Prevalence screen detected	1	0	1
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	1	0	1
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Incident screen detected	12	1	11
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	10	1	9
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	6	1	5
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	1 year post screening	18	0	18
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	1 year post screening	17	0	17
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Prevalence screen detected	4	1	3
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	4	1	3
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Incident screen detected	6	0	6
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	4	0	4
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	9	5	4
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Incident screen detected	7	0	7
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	6	0	6
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Screen negative	3	0	3
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	5	1	4
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	5	1	4
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Screen negative	5	1	4
Lentz 2020	BRCA1/2 carriers	CA125 + TVUS	Screen negative	1	0	1
Lentz 2020	BRCA1/2 carriers	The ROCA Test + the HE4 ROCA Test	Screen negative	2	0	2
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	1	0	1
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Screen negative	2	0	2
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	3	0	3
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	3	0	3
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	2	0	2

OC: ovarian cancer; ROCA: Risk of Ovarian Cancer Algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound

Key to variables

- study: study identifier
- population: study population (*BRCA1/2* carriers or other increased risk groups)
- tests: surveillance tests
- time_point: route by which the cancers were detected
- n_cancers: total number of cancers detected
- clear_cell, serous, endometrioid, small_cell, serous_endometrioid, mucinous, other: number of cancers detected with clear cell, serous, endometrioid, small-cell, serous/endometrioid, mucinous or other histological type respectively

Table 11: Histological type data

study	population	tests	time_point	n_cancers	clear_cell	serous	endometrioid	small_cell	serous_endometriod	mucinous	other
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Prevalence screen detected	9	2	7	0	0	0	0	0
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	6	0	6	0	0	0	0	0
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	13	0	7	3	0	1	0	2
Rosenthal 2013	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	10	0	5	2	0	1	0	2
Rosenthal 2013	>=10% Lifetime risk	CA125 + TVUS	Screen negative	8	0	6	0	1	1	0	0
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Prevalence screen detected	1	0	0	0	0	1	0	0
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	1	0	0	0	0	1	0	0
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	Incident screen detected	12	1	9	1	0	1	0	0
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	10	0	8	1	0	1	0	0
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	5	0	4	1	0	0	0	0
Rosenthal 2017	>=10% Lifetime risk	The ROCA Test + TVUS	1 year post screening	18	0	18	0	0	0	0	0
Rosenthal 2017	BRCA1/2 carriers	The ROCA Test + TVUS	1 year post screening	17	0	17	0	0	0	0	0
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Prevalence screen detected	4	0	4	0	0	0	0	0

study	population	tests	time_point	n_cancers	clear_cell	serous	endometrioid	small_cell	serous_endometriod	mucinous	other
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	4	0	4	0	0	0	0	0
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Incident screen detected	6	0	4	0	0	1	0	1
Skates 2017	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	4	0	2	0	0	1	0	1
Skates 2017	increased familial/genetic ovarian cancer risk	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	9	0	6	1	0	0	0	2
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Incident screen detected	7	0	7	0	0	0	0	0
Cortesi 2017	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	6	0	6	0	0	0	0	0
Cortesi 2017	increased familial/genetic ovarian cancer risk	CA125 + TVUS	Screen negative	3	0	3	0	0	0	0	0
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	5	0	4	1	0	0	0	0
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	5	0	2	1	0	0	2	0
Hemsen 2007	BRCA1/2 carriers	CA125 + TVUS	Screen negative	5	0	3	2	0	0	0	0
Lentz 2020	BRCA1/2 carriers	CA125 + TVUS	Screen negative	1	0	1	0	0	0	0	0
Lentz 2020	BRCA1/2 carriers	The ROCA Test + the HE4 ROCA Test	Screen negative	2	0	2	0	0	0	0	0
Stirling 2005	High Risk	CA125 + TVUS	Prevalence screen detected	3	0	2	0	0	0	0	1
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Prevalence screen detected	2	0	1	0	0	0	0	1
Stirling 2005	High Risk	CA125 + TVUS	Incident screen detected	7	0	4	1	0	2	0	3
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Incident screen detected	3	0	2	0	0	1	0	2
Stirling 2005	High Risk	CA125 + TVUS	Screen negative	3	1	2	0	0	0	0	0
Stirling 2005	BRCA1/2 carriers	CA125 + TVUS	Screen negative	2	0	2	0	0	0	0	0
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Incident screen detected	1	0	1	0	0	0	0	0

study	population	tests	time_point	n_cancers	clear_cell	serous	endometrioid	small_cell	serous_endometriod	mucinous	other
Woodward 2007	>=10% Lifetime risk	CA125 + TVUS	Screen negative	2	0	1	1	0	0	0	0
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Prevalence screen detected	3	0	3	0	0	0	0	0
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Incident screen detected	3	0	3	0	0	0	0	0
Phillpott 2023	BRCA1/2 carriers	The ROCA Test + TVUS	Screen negative (occult OC at RRSO)	2	0	2	0	0	0	0	0

OC: ovarian cancer; ROCA: Risk of Ovarian Cancer Algorithm; RRSO: risk reducing salpingo-oophorectomy; TVUS: transvaginal ultrasound