National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[E] Optimal methods of assessing the absolute risk of having a pathogenic variant

NICE guideline NG241

Evidence reviews underpinning recommendations 1.6.1 to 1.6.5, bullet point 7 in table 1, the section on risk of developing ovarian cancer in table 3, and research recommendation 3 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.

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Review question

What are the optimal methods of assessing the absolute risk of ovarian cancer?

Introduction

Absolute risk is a way of describing the chance of a disease, it is the number of people with the disease divided by the number of people in the group of interest. So, the number of women who get ovarian cancer out of all the women who carry a pathogenic variant in the *BRCA1* gene would be the absolute risk of ovarian cancer in *BRCA1* pathogenic variant carriers. However, what we do not know currently, is how many women have a *BRCA1* pathogenic variant globally. Nor do we know how many women out of all the women with a *BRCA1* pathogenic variant globally go on to develop ovarian cancer. This is not only unique to *BRCA1*, but to all the pathogenic variants associated with familial ovarian cancer. Moreover, the absolute risk of ovarian cancer will change as a person gets older or if they do things that increase or decrease their general risk of ovarian cancer. This means the absolute risk of ovarian cancer in a woman who carriers a pathogenic variant associated with familial ovarian cancer and is 60 years old is different to someone who is 30 years old. The review aims to determine which methods of estimating the absolute risk of ovarian cancer in high-risk populations are most accurate and can give the most granularity to deliver a personalised absolute risk for an individual.

Summary of the protocol

See Population, Presence or absence of prognostic, risk or predictive factors and outcome (PPO).

Table 1 for a summary of the Population, Presence or absence of prognostic, risk or predictive factors and outcome (PPO).

Table 1: Summary of the protocol (PPO table)

Population	All women

Presence or absence of prognostic, risk or predictive factors	Multivariable prognostic models for lifetime risk of developing ovarian cancer incorporating genetic with other risk factors such as:
	• CanRisk model (Lee 2022)
	
	Prognostic models should include factors linked to risk of ovarian Cancer, such as:
	• Family cancer history
	• Age
	• Genetic factors
	  ○ Pathogenic variants:
	  - such as *BRCA1*
	  ○ Common genetic variants
	  - Polygenetic risk score
	• Lifestyle
	  ○ Height
	  ○ BMI

	○ Alcohol ○ Smoking • Hormonal/reproductive ○ Parity ○ Menarche ○ Menopause ○ HRT ○ Endometriosis ○ Oral contraception • Demographics ○ Country of birth ○ Birth cohort ○ Family ethnicity
Outcomes	**Critical** Accuracy of the prognostic model for incident ovarian cancer: • Lifetime risk • Residual risk (remaining lifetime risk) • 10-year risk • 5-year risk • Annual risk

BMI: body mass index; HRT: hormone replacement therapy

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.

Prognostic evidence

Included studies

One study was included for this review (Lee 2022) which validated an ovarian cancer risk model developed in the UK and validated using a nested case-control design. The study was conducted by the developers of the risk model who validated it using a sample of participants independent of the set used to generate the model.

The included study is 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	Prognostic model	Outcomes
Lee 2022 UK Nested case-control	Validation sample: N=1587 controls (women without ovarian cancer), N=374 cases with ovarian cancer. Cases and controls were women with self-reported European ancestry in the UKCTOCS trial. Age, mean (SD) years: 63 (6.1)	• a risk model for women of European ancestry incorporating: ○ pathogenic variants in *BRCA1, BRCA2, RAD51C, RAD51D* and *BRIP1* ○ Polygenic Risk Score ○ the effects of risk factors (lifestyle, hormonal, reproductive, breast tumour pathology, demographic factors) ○ explicit family history	• Epithelial ovarian cancer risk (within 5 years)

SD: standard deviation; UKCTOCS: UK Collaborative Trial of Ovarian Cancer Screening

See the full evidence tables in appendix D. 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

Only one model was reported that incorporated all the factors in the review protocol. There was moderate quality evidence that the model (available via the CanRisk tool) had poor discrimination (that is, was not a useful test, AUC of 0.61; 95%CI 0.58 to 0.64) between those who do and do not develop ovarian cancer within the next 5 years. The study used a validation sample from UKCTOCS (independent of the set of participants used to develop the model), this was a relatively low risk group and was missing data on pathogenic variants such as *RAD51C*, *RAD51D* and *BRIP1*.

Comparing expected and observed absolute 5-year ovarian cancer risk the CanRisk model (overall E/O 1.05; 95% 0.94 to 1.16) underpredicted risk in the lowest risk quintile (E/O 0.66; 95% 0.52 to 0.91) but otherwise appeared to be well calibrated in all other risk quintiles although the 95% Cis were not reported for the higher quintiles (E/O in 2nd quintile 1.13, 95% CI not reported; E/O in the middle quintile 1.0, 95% CI not reported; E/O in 4th quintile 1.0, 95% CI not reported; E/O in the highest quintile 1.21, 95% CI not reported). This evidence was low to moderate quality.

No evidence was identified for accuracy of models for lifetime risk, residual risk, 10-year risk and annual risk.

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.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The critical outcome was accuracy measured as lifetime risk, residual risk, 10- or 5-year risk and annual risk in prediction of ovarian cancer risk. An accurate estimate of absolute ovarian cancer risk is crucial for decision making because it enables women to properly weigh up risks and benefits. For example, when deciding whether to proceed with risk reducing surgery or deciding at what age to have surgery the beneficial reduction in the absolute risk of ovarian cancer has to be balanced against the harms of the procedure.

The quality of the evidence

The quality of the evidence was assessed using GRADE and was low to moderate. The main issue with the evidence was indirectness of the study population: the validation sample used in the study largely excluded women at high familial risk of ovarian cancer. Also a polygenic risk score (PRS) with 15 variants rather than the 36-variant PRS was included in the model and some other common risk factors were not included in it. Despite this the committee acknowledged the model is likely to be useful in people at risk of familial ovarian cancer because of the way it incorporates published estimates of the association between risk factors such as pathological variants, family history and family ethnicity with ovarian cancer into its algorithm. The quality of the evidence was also downgraded within the reported quintiles due to imprecision.

The evidence review identified only one model that incorporated all the risk factors in the review protocol. For this reason the committee also used their experience and knowledge to agree the recommendations.

Benefits and harms

Assessing the risk of developing ovarian cancer

The committee recommended that the familial ovarian cancer MDT should assess the personal risk of ovarian cancer for women with identified (or otherwise at high risk of) pathogenic variants associated with familial ovarian cancer. This is because a personal risk estimate is key to decision making but the expertise and time to produce this estimate is not available in primary care and so they recommended that this should happen within genetic services.

The committee noted that moderate quality evidence showed that the model (available via the CanRisk tool) was not a useful test to discriminate between those who do and do not develop ovarian cancer within the next 5 years. However, they also discussed that low to moderate evidence showed that the CanRisk tool had reasonable calibration and therefore the committee used it as an example of a tool that could be used in situations where a person has not been tested for genetic pathogenic variants, as well as when it is already known that a person has a genetic pathogenic variant. Such a tool should also take into account age and family history. Whilst no evidence was identified for any other tool, they gave CanRisk as an example of such a tool rather than being prescriptive in case further tools are being developed.

The committee acknowledged that a large part of the person's ovarian cancer risk is accounted for by their age and known pathogenic variants and that some clinicians may use tools and methods based on only such limited information to estimate risks. In these cases the committee thought it was important to prompt clinicians to also consider other risk factors when discussing a personal risk estimate.

Information about risk assessment

The committee acknowledged that people want to know what the next steps are after they have been assessed. They recommended that advice should be given on ovarian cancer risk which should include what their risk is, why they may have to think about taking HRT or oral contraceptives as a primary preventive medicine, lifestyle factors that relate to ovarian cancer and the consequences of ovarian cancer as well as family planning and family size. This advice should help them to make informed choices and to understand what the next steps may be. The committee discussed that it is essential for the person to know about how the risk is assessed, what their personal risk estimate means, and other factors that could increase or decrease the risk and how they can use this information to come to a decision. The healthcare professional can then help them to make choices in a shared decision-making process.

Research recommendation

The committee noted that many validated probability tools exist however the majority of these are only designed to identify those at high risk of carrying a damaging change in the *BRCA* genes. There are other genes that can cause a susceptibility to ovarian cancer alone and the committee decided that more research is needed to incorporate these genes into new probability tools or refine the currently available ones. So, they made a research recommendation to encourage further research in this area.

Cost effectiveness and resource use

There was no existing economic evidence for this review.

The committee discussed the importance of assessing personal ovarian cancer risk in individuals with identified pathogenic variants or those otherwise at high risk of familial ovarian cancer. The current practice incorporates a combination of clinical/family-based criteria and validated tools. The committee explained that using tools may not always be needed, and in some cases, family-based criteria could be more appropriate. Additionally, these tools may not always provide completely accurate results. Adopting a flexible approach will ensure that tools are employed only when beneficial and healthcare professionals time is not wasted.

Personal risk assessment often requires a detailed collection of family cancer history. The duration of this process largely depends on the family history's complexity and information availability. Taking additional factors into account, such as parity, the use of the combined

oral contraceptive pill, and the presence of endometriosis, could slightly extend the process and discussions but the impact of this is likely negligible.

Furthermore, the benefits of assessing a person's risk of developing ovarian cancer will far outweigh any additional costs involved. It is essential to understand an individual's risk in order to make informed decisions. This knowledge may influence the uptake of genetic testing and risk-reducing bilateral salpingo-oophorectomy, which can significantly reduce their cancer risk and the related costs.

Other factors the committee took into account

The committee agreed that there are familial and other risk factors for breast cancer that also increase ovarian cancer risk, and chose to refer to the NICE guideline on familial breast cancer.

The committee agreed that communicating risks and benefits can be a challenge, particularly when there are uncertainties around the estimates. They thought this information should be presented in ways to make it more understandable and so they cross referred to the NICE guideline on shared decision making.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 to 1.6.6 as well as bullet point 7 in Table 1, and the section on ‘risk of developing ovarian cancer’ in Table 3, and research recommendation 3 (on performance characteristics of tools or models to assess the absolute risk of ovarian cancer) in the NICE guideline.

References – included studies

Lee 2022

Lee, A.; Yang, X.; Tyrer, J.; et al. Comprehensive epithelial tubo-ovarian cancer risk prediction model incorporating genetic and epidemiological risk factors.; Journal of medical genetics; vol. 59 (no. 7); 632-643, 2022

Appendices

Appendix A Review protocol

Review protocol for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022340833
1.	Review title	Assessing the absolute risk of ovarian cancer in women with (or at an increased risk of) a pathogenic variant associated with familial ovarian cancer
2.	Review question	What are the optimal methods of assessing the absolute risk of ovarian cancer?
3.	Objective	Estimating a woman's absolute risk of developing ovarian cancer can help her make informed decisions about her care – for example genetic testing and risk reducing treatments. This review aims to compare the accuracy of different ways of estimating the risk of developing ovarian cancer
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Epistemonikos • Embase • MEDLINE, MEDLINE In Process & MEDLINE Epub Ahead of Print

		Searches will be restricted by: • English language • Human Studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved 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: All women
7.	Presence or absence of a prognostic, risk or predictive factor	Multivariable prognostic models for lifetime risk of developing ovarian cancer incorporating genetic with other risk factors such as: • Canrisk model (Lee 2022)

8.	Confounding factors	Prognostic models should include factors linked to risk of ovarian cancer such as:
		• Family cancer history
		• Age
		• Genetic factors
		  ○ Pathogenic variants:
		  – *BRCA1* etc.
		  ○ Common genetic variants
		  – Polygenetic risk score
		• Lifestyle
		  ○ Height
		  ○ BMI

		○ Alcohol ○ Smoking • Hormonal/reproductive ○ Parity ○ Menarche ○ Menopause ○ HRT ○ Endometriosis ○ Oral contraception • Demographics ○ Country of birth ○ Birth cohort ○ Family ethnicity
9.	Types of study to be included	Observational studies (where neither control nor intervention were assigned by the investigator) including: • Systematic reviews of observational studies. • Prospective and retrospective cohort studies • Case control studies • Cross-sectional studies may be included in the absence of other study designs (for example, an ovarian cancer screening study [where outcome & exposures are measured at the same time] may be useful) Study designs where risk factor/exposure data are collected are at the beginning of the study such as prospective cohort studies, nested case-control studies, and record linkage studies will be prioritised over other study designs Population-based studies and multicentre studies will be prioritised

10.	Other exclusion criteria	Inclusion criteria: • Full text papers • Validated prediction tools will be prioritised for inclusion (where the scoring system has been evaluated in a separate population than that used to derive the model) • UK based studies will be prioritised, but publications from other countries will be considered 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 • Studies using qualitative methods only • 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)	Accuracy of the prognostic model for incident ovarian cancer: • Lifetime risk • Residual risk (remaining lifetime risk) • 10 year risk • 5 year risk • Annual risk
13.	Secondary outcomes (important outcomes)	None

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 (or 300 records whichever is smaller); 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. 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. PICOTS will be extracted from each study. For prediction models, development stage and validation status will be extracted.
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: • CHARMS checklist for systematic reviews of prediction models. • QUIPS checklist for prognostic factor 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.
		Data Synthesis
		Where possible meta-analysis to combine the effect estimates across studies for each prognostic tool will be conducted, if studies have comparable populations.
		We will extract either OR or HR; however, we will conduct separate meta-analysis for those studies reporting OR and those reporting HR, as it is inappropriate to pool OR and HR.
		If no meta-analysis is conducted a narrative summary of the available results for each factor will be provided.
		Calibration and discrimination will be assessed for prognostic models and estimates pooled if appropriate.
		Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively.
		In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model.
		Default MIDs will be used for odds and hazard ratios, unless the committee pre-specifies published or other MIDs for specific outcomes
		For odds and hazard ratios: 0.8 and 1.25
		Decision thresholds for classification performance
		• For positive likelihood ratios:
		  ○ Useful test LR ≥ 5.0
		  ○ Not a useful test 1 < LR < 2.0
		• For negative likelihood ratios: 0.2
		  ○ Useful test LR ≤ 0.2
		  ○ Not a useful test 0.5 ≤ LR < 1.0

		Validity 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: https://www.gradeworkinggroup.org/

17.	Analysis of sub-groups	Evidence will be stratified by:
		• Age (<35 vs older)
		• Pre vs post-menopausal
		• High vs low risk settings (general population vs those with family history)
		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		• 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	March 2024		
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	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=340833
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	Female; Humans; Ovarian Neoplasms
33.	Details of existing review of same topic by same authors	

34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☒	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

HR: hazard ratio; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; OR: odds ratio

Appendix B Literature search strategies

Literature search strategies for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer in women with (or at an increased risk of) a pathogenic variant associated with 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.
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
34	Rad51 Recombinase/

#	Searches
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	(CANRISK or (cancer risk adj1 (tool or model*))).ti,ab,kf.
51	Multifactorial Inheritance/
52	((multifactor* or polygenic or polygene* or multigenic or oligogenic) adj2 (inherit* or trait* or character* or disease*)).ti,ab,kf.
53	((complex or heterogene*) adj2 (inherit* or trait*)).ti,ab,kf.
54	((polygenic or polygenetic or genome-wide) adj2 (score or risk or index or indices or study or studies)).ti,ab,kf.
55	Epigenesis, Genetic/
56	(epigene* adj2 (process* or change* or modif* or program* or misprogram*)).ti,ab,kf.
57	Age Factors/ or age groups/ or Life Style/ or Body Height/
58	((age? or birth cohort* or lifestyle or life style or "way* adj1 life" or height or stature) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
59	((lifetime or life time or personal*) adj1 risk).ti,ab.
60	((personal* or lifestyle or life style) adj2 (information or survey* or question*)).ti,ab,kf.
61	body mass index/ or body size/ or body weight/ or Body Composition/ or weight gain/ or overweight/
62	(((body adj2 (mass or weight or size or fat or fatness or composition)) or BMI or quetelet index or skin fold* or skinfold* or (weight adj2 (manag* or gain* or increas* or excess or chang*)) or (fat adj3 (percent* or distribution))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
63	Alcohol Drinking/ or Smoking/ or Smokers/ or "Tobacco Use"/
64	(((alcohol* adj2 (drink* or imbib* or intake or consumption or consum* or binge or abus* or frequenc* or behavio?r* or use* or using or problem*)) or smoking or smoke* or tobacco* or nicotin* or cigar* or cigs or ecig* or e-cig or e-voke* or vape* or vaping) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
65	Parity/ or reproductive history/ or puberty/ or menarche/ or Menopause/
66	((parity or nullipar* or primipar* or primip or multipar* or para or offspring or menarche or menstrua* or menses or menorrhoea or pubert* or menopaus* or perimenopaus* or peri menopaus* or postmenopaus* or post menopaus* or POF or ((reproductive or birth* or pregnanc*) adj2 (histor* or factor*))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
67	Hormone Replacement Therapy/ or ESTROGENS/ or ESTRADIOL/ or contraceptive agents, female/ or contraceptives, oral/ or hormonal contraception/ or ovulation inhibition/
68	(((hormon* adj3 (therap* or substitut* or replacement or exogenous)) or ((oestrogen* or estrogen* or oestradiol or estradiol or estrone or oestrone or progest* or medroxyprogest*) adj3 (therap* or substitut* or replacement or exogenous))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
69	(HRT or HT or MHT).ti,ab,kf.

#	Searches
70	((((oral or hormon*) adj3 contracept*) or (ovulat* adj2 (inhibit* or suppress* or block*))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
71	birth control pill*.ti,ab,kf.
72	Endometriosis/ or Adenomyosis/
73	((endometrios?s or endometrioma* or adenomyos?s or adenomyoma* or adenometrit?s or adenomyosit?s or adenomyometrit?s) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
74	Population Groups/ or Demography/ or "Emigration and Immigration"/
75	exp "health disparity, minority and vulnerable populations"/
76	((ethnic* or nation* or race or racial or minority or minorities or indigenous or demograph* or population or ((countr* or place) adj3 (birth or born or origin*))) adj4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
77	((family or personal) adj2 history).ti,ab,kf.
78	((genetic or environment* or epidemiolog* or hormonal) adj2 risk*).ti,ab,kf.
79	or/50-78
80	exp Mass Screening/
81	((screen* or detect* or test* or diagnos*) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
82	exp Early Diagnosis/
83	(early adj2 (diagnos?s or detect* or identif*) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
84	((assess* or probability or predict* or scor*) adj3 (tool* or model* or system* or test* or threshold*)).ti,ab,kf.
85	risk/ or Epidemiology/
86	(risk adj3 (tool* or assess* or interval* or analys?s or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat* or accuracy or accurate or epidemiolog*)).ti,ab,kf.
87	or/80-86
88	79 and 87
89	49 and 88
90	letter/
91	editorial/
92	news/
93	exp historical article/
94	Anecdotes as Topic/
95	comment/
96	case reports/
97	(letter or comment*).ti.
98	animals/ not humans/
99	exp Animals, Laboratory/
100	exp Animal Experimentation/
101	exp Models, Animal/
102	exp Rodentia/
103	(rat or rats or mouse or mice or rodent*).ti.
104	or/90-103
105	89 not 104
106	limit 105 to English language
107	predict.ti.
108	(validat* or rule*).ti,ab.
109	(predict* and (outcome* or risk* or model*)).ti,ab.
110	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
111	decision*.ti,ab. and Logistic models/
112	(decision* and (model* or clinical*)).ti,ab.
113	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.

#	Searches
114	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
115	ROC curve/
116	risk/
117	or/107-116
118	106 and 117

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/

#	Searches
34	ATM protein/
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	(CANRISK or (cancer risk adj1 (tool or model*))).ti,ab,kf.
52	multifactorial inheritance/
53	((multifactor* or polygenic or polygene* or multigenic or oligogenic) adj2 (inherit* or trait* or character* or disease*)).ti,ab,kf.
54	((complex or heterogene*) adj2 (inherit* or trait*)).ti,ab,kf.
55	((polygenic or polygenetic or genome-wide) adj2 (score or risk or index or indices or study or studies)).ti,ab,kf.
56	genetic epigenesis/
57	(epigene* adj2 (process* or change* or modif* or program* or misprogram*)).ti,ab,kf.
58	age/ or groups by age/ or lifestyle/ or body height/
59	((age? or birth cohort* or lifestyle or life style or "way* adj1 life" or height or stature) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
60	((lifetime or life time or personal*) adj1 risk).ti,ab.
61	((personal* or lifestyle or life style) adj2 (information or survey* or question*)).ti,ab,kf.
62	body mass/ or body size/ or body weight/ or body composition/ or body weight gain/ or obesity/
63	(((body adj2 (mass or weight or size or fat or fatness or composition)) or BMI or quetelet index or skin fold* or skinfold* or (weight adj2 (manag* or gain* or increas* or excess or chang*)) or (fat adj3 (percent* or distribution))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
64	drinking behavior/ or smoking/ or "tobacco use"/
65	(((alcohol* adj2 (drink* or imbib* or intake or consumption or consum* or binge or abus* or frequenc* or behavio?r* or use* or using or problem*)) or smoking or smoke* or tobacco* or nicotin* or cigar* or cigs or ecig* or e-cig or e-voke* or vape* or vaping) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
66	parity/ or reproductive history/ or puberty/ or menarche/ or menopause/
67	((parity or nullipar* or primipar* or primip or multipar* or para or offspring or menarche or menstrua* or menses or menorrhoea or pubert* or menopaus* or perimenopaus* or peri menopaus* or postmenopaus* or post menopaus* or POF or ((reproductive or birth* or pregnanc*) adj2 (histor* or factor*))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
68	hormone substitution/ or estrogen/ or estradiol/ or contraceptive agent/ or oral contraceptive agent/ or hormonal contraception/ or ovulation inhibition/
69	(((hormon* adj3 (therap* or substitut* or replacement or exogenous)) or ((oestrogen* or estrogen* or oestradiol or estradiol or estrone or oestrone or progest* or medroxyprogest*) adj3 (therap* or substitut* or replacement or exogenous))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.

#	Searches
70	(HRT or HT or MHT).ti,ab,kf.
71	((((oral or hormon*) adj3 contracept*) or (ovulat* adj2 (inhibit* or suppress* or block*))) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
72	birth control pill*.ti,ab,kf.
73	endometriosis/ or adenomyosis/
74	((endometrios?s or endometrioma* or adenomyos?s or adenomyoma* or adenometrit?s or adenomyosit?s or adenomyometrit?s) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
75	exp population group/ or demography/ or migration/
76	((ethnic* or nation* or race or racial or minority or minorities or indigenous or demograph* or population or ((countr* or place) adj3 (birth or born or origin*))) adj4 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
77	((family or personal) adj2 history).ti,ab,kf.
78	((genetic or environment* or epidemiolog* or hormonal) adj2 risk*).ti,ab,kf.
79	or/51-78
80	mass screening/
81	((screen* or detect* or test* or diagnos*) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
82	exp Early Diagnosis/
83	(early adj2 (diagnos?s or detect* or identif*) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)).ti,ab,kf.
84	((assess* or probability or predict* or scor*) adj3 (tool* or model* or system* or test* or threshold*)).ti,ab,kf.
85	risk/ or epidemiology/
86	(risk adj3 (tool* or assess* or interval* or analys?s or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat* or accuracy or accurate or epidemiolog*)).ti,ab,kf.
87	or/80-86
88	79 and 87
89	50 and 88
90	letter.pt. or letter/
91	note.pt.
92	editorial.pt.
93	case report/ or case study/
94	(letter or comment*).ti.
95	animal/ not human/
96	nonhuman/
97	exp Animal Experiment/
98	exp Experimental Animal/
99	animal model/
100	exp Rodent/
101	(rat or rats or mouse or mice or rodent*).ti.
102	or/90-101
103	89 not 102
104	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
105	103 not 104
106	limit 105 to English language
107	predict.ti.
108	(validat* or rule*).ti,ab.
109	(predict* and (outcome* or risk* or model*)).ti,ab.
110	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
111	decision*.ti,ab. and Statistical model/
112	(decision* and (model* or clinical*)).ti,ab.
113	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.

#	Searches
114	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
115	Receiver operating characteristic/
116	risk/
117	or/107-116
118	106 and 117

Database: Cochrane Database of Systematic Reviews, Issue 3 of 12, January 2023 & Cochrane Central Register of Controlled Trials, Issue 3 of 12, January 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

#	Searches
#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
#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 cell 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	(CANRISK or ("cancer risk" NEAR/1 (tool or model*))):ti,ab,kw
#51	MeSH descriptor: [Multifactorial Inheritance] this term only
#52	((multifactor* or polygenic or polygene* or multigenic or oligogenic) NEAR/2 (inherit* or trait* or character* or disease*)):ti,ab,kw
#53	((complex or heterogene*) NEAR/2 (inherit* or trait*)):ti,ab,kw
#54	((polygenic or polygenetic or genome-wide) NEAR/2 (score or risk or index or indices or study or studies)):ti,ab,kw
#55	MeSH descriptor: [Epigenesis, Genetic] this term only
#56	(epigene* NEAR/2 (process* or change* or modif* or program* or misprogram*)):ti,ab,kw
#57	MeSH descriptor: [Age Factors] this term only
#58	MeSH descriptor: [Age Groups] this term only
#59	MeSH descriptor: [Life Style] this term only
#60	MeSH descriptor: [Body Height] this term only
#61	((age or ages or birth NEXT cohort* or lifestyle or "life style" or way* NEAR/1 life or height or stature) 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* or risk*)):ti,ab,kw
#62	((lifetime or "life time" or personal*) NEAR/1 risk):ti,ab
#63	((personal* or lifestyle or "life style") NEAR/2 (information or survey* or question*)):ti,ab,kw
#64	MeSH descriptor: [Body Mass Index] this term only
#65	MeSH descriptor: [Body Size] this term only
#66	MeSH descriptor: [Body Weight] this term only
#67	MeSH descriptor: [Body Composition] this term only
#68	MeSH descriptor: [Weight Gain] this term only
#69	MeSH descriptor: [Overweight] this term only
#70	(((body NEAR/2 (mass or weight or size or fat or fatness or composition)) or BMI or "quetelet index" or "skin fold*" or skinfold* or (weight NEAR/2 (manag* or gain* or increas* or excess or chang*)) or (fat NEAR/3 (percent* or distribution))) 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* or risk*)):ti,ab,kw
#71	MeSH descriptor: [Alcohol Drinking] this term only
#72	MeSH descriptor: [Smoking] this term only
#73	MeSH descriptor: [Smokers] this term only

#	Searches
#74	MeSH descriptor: [Tobacco Use] this term only
#75	(((alcohol* NEAR/2 (drink* or imbib* or intake or consumption or consum* or binge or abus* or frequenc* or behavior* or behaviour* or use* or using or problem*)) or smoking or smoke* or tobacco* or nicotin* or cigar* or cigs or ecig* or e-cig or e-voke* or vape* or vaping) 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* or risk*)):ti,ab,kw
#76	MeSH descriptor: [Parity] this term only
#77	MeSH descriptor: [Reproductive History] this term only
#78	MeSH descriptor: [Puberty] this term only
#79	MeSH descriptor: [Menarche] this term only
#80	MeSH descriptor: [Menopause] this term only
#81	((parity or nullipar* or primipar* or primip or multipar* or para or offspring or menarche or menstrua* or menses or menorrhoea or pubert* or menopaus* or perimenopaus* or peri NEXT menopaus* or postmenopaus* or post NEXT menopaus* or POF or ((reproductive or birth* or pregnanc*) NEAR/2 (histor* or factor*))) 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* or risk*)):ti,ab,kw
#82	MeSH descriptor: [Hormone Replacement Therapy] this term only
#83	MeSH descriptor: [Estrogens] this term only
#84	MeSH descriptor: [Estradiol] this term only
#85	MeSH descriptor: [Contraceptive Agents, Female] this term only
#86	MeSH descriptor: [Contraceptives, Oral] this term only
#87	MeSH descriptor: [Hormonal Contraception] this term only
#88	MeSH descriptor: [Ovulation Inhibition] this term only
#89	(((hormon* NEAR/3 (therap* or substitut* or replacement or exogenous)) or ((oestrogen* or estrogen* or oestradiol or estradiol or estrone or oestrone or progest* or medroxyprogest*) NEAR/3 (therap* or substitut* or replacement or exogenous))) 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* or risk*)):ti,ab,kw
#90	(HRT or HT or MHT):ti,ab,kw
#91	((((oral or hormon*) NEAR/3 contracept*) or (ovulat* NEAR/2 (inhibit* or suppress* or block*))) 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* or risk*)):ti,ab,kw
#92	birth control NEXT pill*:ti,ab,kw
#93	MeSH descriptor: [Endometriosis] this term only
#94	MeSH descriptor: [Adenomyosis] this term only
#95	((endometriosis or endometrioses or endometrioma* or adenomyosis or adenomyoses or adenomyoma* or adenometritis or adenometrites or adenomyositis or adenomyosites or adenomyometritis or adenomyometrites) 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* or risk*)):ti,ab,kw
#96	MeSH descriptor: [Population Groups] this term only
#97	MeSH descriptor: [Demography] this term only
#98	MeSH descriptor: [Emigration and Immigration] this term only
#99	MeSH descriptor: [Health Disparate, Minority and Vulnerable Populations] explode all trees
#100	((ethnic* or nation* or race or racial or minority or minorities or indigenous or demograph* or population or ((countr* or place) NEAR/3 (birth or born or origin*))) NEAR/4 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta* or risk*)):ti,ab,kw
#101	((family or personal) NEAR/2 history):ti,ab,kw
#102	((genetic or environment* or epidemiolog* or hormonal) NEAR/2 risk*):ti,ab,kw
#103	{OR #50-#102}
#104	MeSH descriptor: [Mass Screening] explode all trees
#105	((screen* or detect* or test* or diagnos*) 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* or risk*)):ti,ab,kw
#106	MeSH descriptor: [Early Diagnosis] explode all trees
#107	(early NEAR/2 (diagnosis or diagnoses or detect* or identif*) 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* or risk*)):ti,ab,kw
#108	((assess* or probability or predict* or scor*) NEAR/3 (tool* or model* or system* or test* or threshold*)):ti,ab,kw
#109	MeSH descriptor: [Risk] this term only
#110	MeSH descriptor: [Epidemiology] this term only

#	Searches
#111	(risk NEAR/3 (tool* or assess* or interval* or analysis or analyses or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat* or accuracy or accurate or epidemiolog*)):ti,ab,kw
#112	{OR #104-#111}
#113	#103 AND #112
#114	#49 AND #113
#115	predict:ti
#116	(validat* or rule*):ti,ab
#117	(predict* and (outcome* or risk* or model*)):ti,ab
#118	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)):ti,ab
#119	decision*:ti,ab
#120	MeSH descriptor: [Logistic Models] this term only
#121	(decision* and (model* or clinical*)):ti,ab
#122	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)):ti,ab
#123	(stratification or discrimination or discriminate or "c statistic" or "area under the curve" or AUC or calibration or indices or algorithm or multivariable):ti,ab
#124	MeSH descriptor: [ROC Curve] this term only
#125	MeSH descriptor: [Risk] this term only
#126	{OR #115-#125}
#127	#114 AND #126
#128	conference:pt or (clinicaltrials or trialsearch):so
#129	#127 NOT #128

Database: Epistemonikos

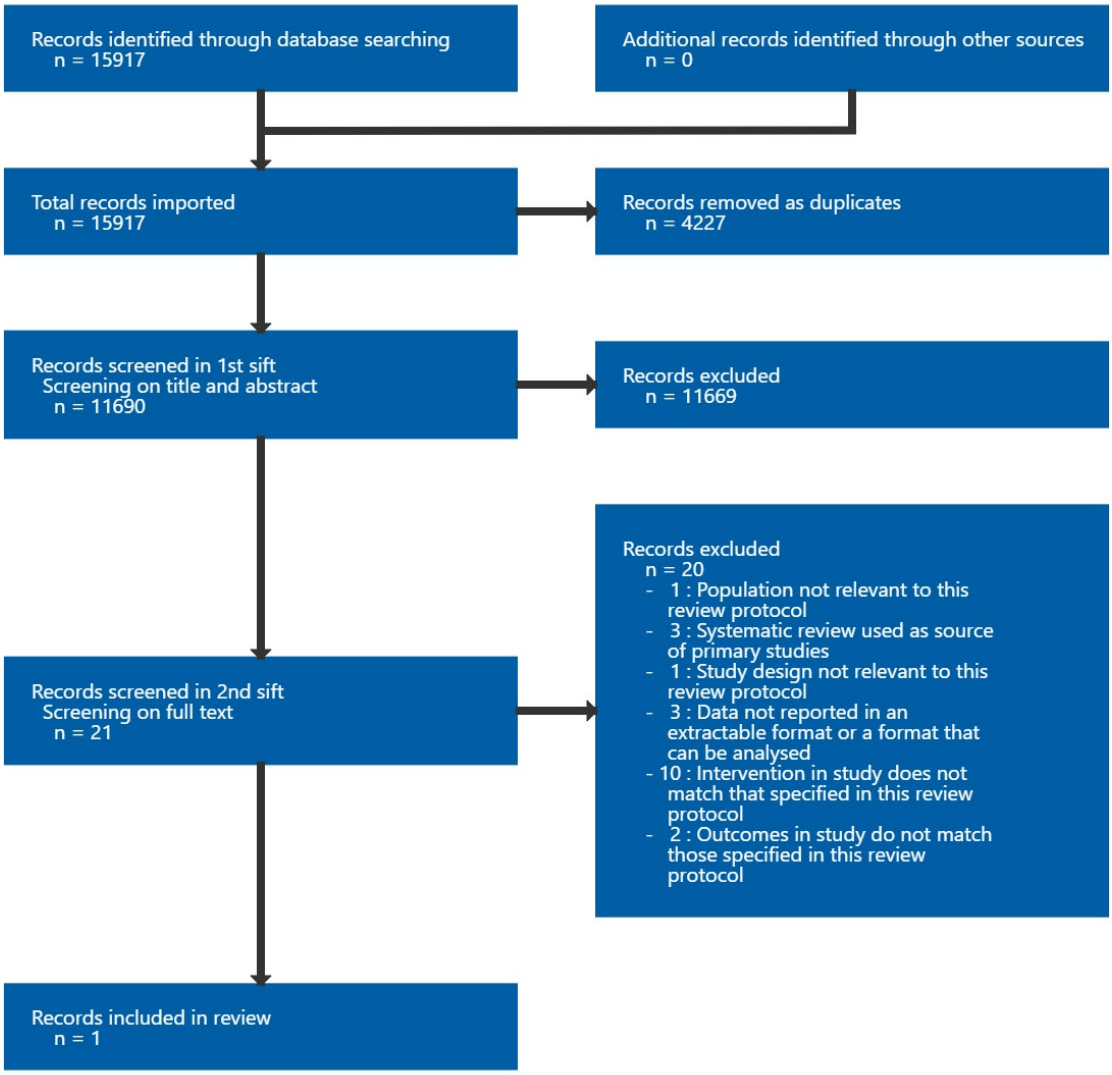
Date of last search: 23/03/2023

#	Searches
1	((advanced_title_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR advanced_abstract_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)))
2	((advanced_title_en:(epigenesis OR polygenic score OR multifactor inheritance OR lifestyle OR age OR alcohol OR weight OR smoking OR height OR parity OR reproductive history OR menarche OR menopause OR hormone replacement therapy OR oral contraception OR family history OR environment OR epidemiology OR genetic) OR advanced_abstract_en:(epigenesis OR polygenic score OR multifactor inheritance OR lifestyle OR age OR alcohol OR weight OR smoking OR height OR parity OR reproductive history OR menarche OR menopause OR hormone replacement therapy OR oral contraception OR family history OR environment OR epidemiology OR genetic))
3	1 AND 2 [Filters: protocol=no]

Appendix C Diagnostic evidence study selection

Study selection for: What are the optimal methods of assessing the absolute risk of ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

Lee, 2022

Bibliographic Reference	Lee, Andrew; Yang, Xin; Tyrer, Jonathan; Gentry-Maharaj, Aleksandra; Ryan, Andy; Mavaddat, Nasim; Cunningham, Alex P; Carver, Tim; Archer, Stephanie; Leslie, Goska; Kalsi, Jatinder; Gaba, Faiza; Manchanda, Ranjit; Gayther, Simon; Ramus, Susan J; Walter, Fiona M; Tischkowitz, Marc; Jacobs, Ian; Menon, Usha; Easton, Douglas F; Pharoah, Paul; Antoniou, Antonis C; Comprehensive epithelial tubo-ovarian cancer risk prediction model incorporating genetic and epidemiological risk factors.; Journal of medical genetics; 2022; vol. 59 (no. 7); 632-643

Study details

Country/ies where study was carried out	UK
Study dates	Validation sample comes from UKCTOCS which recruited from 2001 to 2005.
Inclusion criteria	For model validation: women of self-reported European ancestry participating in the UKCTOCS study. Age 50 to 74 years and postmenopausal status.
Exclusion criteria	Women with a family history of two or more relatives with epithelial ovarian cancer or who were known carriers of *BRCA1/2* pathogenic variants were not eligible to participate in UKCTOCS - so were excluded from the model validation sample. Women with self-reported previous bilateral oophorectomy or ovarian malignancy, or active non-ovarian malignancy. Women older than 74 at study entry were excluded from the calibration and discrimination analysis.
Patient characteristics	N=374 cases with EOC and N=1587 controls. ***Characteristics of controls***: Gender: all female Age at baseline, mean(sd): 63 (6.1) years Non-EOC in 1st and 2nd degree relatives, N(%): 1507 (95%)

	Non-EOC in 1st and 2nd degree relatives, N(%): 1232 (78%) ***Characteristics of cases:*** Gender: all female Age at baseline, mean(sd): 63 (6.0) years Non-EOC (epithelial ovarian cancer) in 1st and 2nd degree relatives, N(%): 344 (92%) Non-EOC in 1st and 2nd degree relatives, N(%): 274 (73%)

Predictors	CanRisk - a multifactorial EOC risk model for women of European ancestry incorporating:
	
	• Family history
	• Sex
	• Age
	• Pathogenic variants in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*
	• Polygenic Risk Score of arbitrary size
	• Lifestyle, hormonal, reproductive factors:
	  ○ Height
	  ○ BMI
	  ○ Endometriosis
	  ○ Use of oral contraception
	  ○ Use of HRT
	  ○ Tubal ligation
	• Breast tumour pathology:
	  ○ Oestrogen
	  ○ Progesterone
	  ○ HER2 receptor
	  ○ CK14, CK5/6 status
	• Demographic factors:
	  ○ Country of origin
	  ○ Birth cohort
	  ○ Family ethnicity

	The study extended the existing CanRisk model to incorporate the explicit effects of pathological variants in *RAD51C*, *RAD51D* and *BRIP1* and up-to-date polygenetic risk scores. The polygenic risk score, pathological variants and risk factors were assumed to act multiplicatively. No large datasets were available that include data on all known genetic and other EOC risk factors. This study used a synthetic approach - to incorporate published estimates of associations of the known risk factors into the model. Thus the model validation sample was not used to develop the model or choose which risk factors to include- it was done to test the performance of the model.
Type of prediction study	Prediction model development (extension of existing model with additional pathological variants) with validation using a sample of patients independent of the development set. Uses a nested case-control design. Model calibration was assessed by partitioning the weighted sample into quintiles of predicted risk. Within each quintile, the weighted mean of predicted risk was compared to the weighted observed incidence using the Hosmer-Lemeshow (HL) $\chi 2$ test.
Duration of follow-up	In the validation sample women were censored at either their age at EOC, their age at other (non-EOC) first cancer diagnosis, their age at death or age 79.
Setting	Validation sample was from UKCTOCS which recruited via primary care trusts.
Sources of funding	Grants from Cancer Research UK (C12292/A20861 and PPRPGM-Nov20\100002). The analysis is part of PROMISE, which was funded through Cancer Research UK PRC Programme Grant A12677 and by The Eve Appeal. National Institute for Health Research University College London Hospitals Biomedical Research Centre and from MRC core funding (MR_UU_12023). UKCTOCS was core funded by the Medical Research Council (G9901012 and G0801228), Cancer Research UK (C1479/A2884) and the Department of Health with additional support from the Eve Appeal. The work received support through the PERSPECTIVE I&I project which is funded by the Government of Canada through Genome Canada (#13529) and the Canadian Institutes of Health Research (#155865), the Ministère de l'Économie et de l'Innovation du Québec through Genome Québec, the Quebec Breast Cancer Foundation, the CHU de Quebec Foundation and the Ontario Research Fund. Cancer Research UK (C8640/A23385). European Union Seventh Framework Programme (2007–2013)/European Research Council (310018).

Study arms

Validation sample (N = 1961)

Outcomes

Study timepoints

- 5 year

Model discrimination

Outcome	**Validation sample, 5 years, N = 1961**
AUC	0.61 [0.58 to 0.64]
Predicted epithelial ovarian cancer (EOC) Nominal	391
Observed EOC Nominal	374
Observed: Expected ratio Ratio (95% CI)	1.05 (0.94 to 1.16)
Predicted and observed 5 years risk of ovarian cancer in lowest risk quintile (%)	Predicted 0.08%, observed 0.12%
Observed: Expected ratio in lowest risk quintile Ratio (95% CI)	0.66 (0.52 to 0.64)
Predicted and observed 5 years risk of ovarian cancer in 2nd risk quintile (%)	Predicted 0.14%, observed 0.14%
Observed: Expected ratio in 2nd risk quintile Ratio (95% CI)	1.13 (NR – but CI includes 1.0)

Outcome	Validation sample, 5 years, N = 1961
Predicted and observed 5 years risk of ovarian cancer in middle risk quintile (%)	Predicted 0.18%, observed 0.16%
Observed: Expected ratio in middle risk quintile Ratio (95% CI)	1.0 (NR – but CI includes 1.0)
Predicted and observed 5 years risk of ovarian cancer in 4th risk quintile (%)	Predicted 0.24%, observed 0.24%
Observed: Expected ratio in 4th risk quintile Ratio (95% CI)	1.0 (NR – but CI includes 1.0)
Predicted and observed 5 years risk of ovarian cancer in highest risk quintile (%)	Predicted 0.41%, observed 0.34%
Observed: Expected ratio in highest risk quintile Ratio (95% CI)	1.21 (NR – but CI includes 1.0)

AUC - Polarity - Higher values are better

Critical appraisal - NGA Critical appraisal - PROBAST tool

Section	Question	Answer
Selection of participants	Risk of bias for selection of participants	Low
Selection of participants	Concerns about applicability of selection of participants	Unclear *(Low risk validation sample - from UKCTOCS; missing data about pathological variants; age restricted to 50-74 years)*
Predictors or their assessment	Risk of bias for predictors or their assessment	Low

Section	Question	Answer
Predictors or their assessment	Concerns about applicability of predictors or their assessment	Low
Outcome or its determination	Risk of bias for outcome or its determination	Low
Outcome or its determination	Concerns about applicability of outcome or its determination	Low
Analysis	Risk of bias for analysis	Low
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns about applicability	Unclear *(Low risk validation sample - from UKCTOCS; missing data about pathological variants; age restricted to 50-74 years)*

Appendix E Forest plots

Forest plots for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F Modified GRADE tables

GRADE tables for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

Table 4: Evidence profile for CanRisk model to discriminate between women who will/will not develop ovarian cancer in 5 years

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
AUC for discrimination between ovarian cancer cases and controls										
Lee 2022	Nested case-control	1961	-	-	AUC 0.61 [0.58–0.64]	Not serious	Not serious	Serious[1]	Not serious	MODERATE

AUC: area under ROC curve; CI, confidence interval
1 Women at increased risk of familial ovarian cancer not included in validation sample. Age restricted to 50-74 years. Data on pathological variants was not available to input into the risk model

Table 5: Evidence profile for calibration of CanRisk model 5 year ovarian cancer risk predictions

No. of studies	Study design	Sample size	Expected (predicted by model)	Observed	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Predicted and observed cases of ovarian cancer over 5 years follow-up										
Lee 2022	Nested case-control	1961	391	374	E/O 1.05 (0.94 to 1.16); HL test P=0.08	Not serious	Not serious	Serious[1]	Not serious	MODERATE
Predicted and observed 5 years risk of ovarian cancer in lowest risk quintile										
Lee 2022	Nested case-control	392	0.08%	0.12%	E/O 0.66 (0.52 to 0.91)	Not serious	Not serious	Serious[1]	serious imprecision[2]	LOW
Predicted and observed absolute 5 years risk of ovarian cancer in 2nd risk quintile										
Lee 2022	Nested case-control	392	0.14%	0.14%	E/O 1.13 (CI NR)	Not serious	Not serious	Serious[1]	serious imprecision[2]	LOW
Predicted and observed absolute 5 years risk of ovarian cancer in middle risk quintile										
Lee 2022	Nested case-control	392	0.18%	0.16%	E/O 1.0 (CI NR)	Not serious	Not serious	Serious[1]	serious imprecision[2]	LOW
Predicted and observed absolute 5 years risk of ovarian cancer in 4th risk quintile										
Lee 2022	Nested case-control	392	0.24%	0.24%	E/O 1.0 (CI NR)	Not serious	Not serious	Serious[1]	serious imprecision[2]	LOW
Predicted and observed absolute 5 years risk of ovarian cancer in highest risk quintile										
Lee 2022	Nested case-control	392	0.41%	0.34%	E/O 1.21 (CI NR)	Not serious	Not serious	Serious[1]	serious imprecision[2]	LOW

CI, confidence interval; E: expected; HL: Hosmer-Lemeshow; O: observed; NR: not reported

1 Women at increased risk of familial ovarian cancer not included in validation sample. Age restricted to 50-74 years. Data on pathological variants likely not available. Data on pathological variants was not available to input into the risk model
2 Sample size of N = 200-400

Appendix G Economic evidence study selection

Study selection for: What are the optimal methods of assessing the absolute risk of 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: What are the optimal methods of assessing the absolute risk of ovarian cancer?

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

Appendix I Economic model

Economic model for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the optimal methods of assessing the absolute risk of ovarian cancer?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Antoniou, A C, Gayther, S A, Stratton, J F et al. (2000) Risk models for familial ovarian and breast cancer. Genetic epidemiology 18(2): 173-90	- Intervention in study does not match that specified in this review protocol *Models designed to estimate the effect of rare genetic variants of BRCA1, BRCA2 and potential 3rd gene*
Blackford, Amanda L, Childs, Erica J, Porter, Nancy et al. (2021) A risk prediction tool for individuals with a family history of breast, ovarian, or pancreatic cancer: BRCAPANCPRO. British journal of cancer 125(12): 1712-1717	- Data not reported in an extractable format or a format that can be analysed
Carver, Tim, Hartley, Simon, Lee, Andrew et al. (2021) CanRisk Tool-A Web Interface for the Prediction of Breast and Ovarian Cancer Risk and the Likelihood of Carrying Genetic Pathogenic Variants. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 30(3): 469-473	- Study design in study does not match that specified in this review protocol *No study data, just describing a web interface*
Dareng, Eileen O, Tyrer, Jonathan P, Barnes, Daniel R et al. (2022) Polygenic risk modeling for prediction of epithelial ovarian cancer risk. European journal of human genetics : EJHG 30(3): 349-362	- Intervention in study does not match that specified in this review protocol *Risk model based on common genetic variants (polygenic risk score), does not incorporate other known risk factors or rare genetic variants*
Friebel, Tara M; Domchek, Susan M; Rebbeck, Timothy R (2014) Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. Journal of the National Cancer Institute 106(6): dju091	- Systematic review used as source of primary studies
Gaba, Faiza, Blyuss, Oleg, Liu, Xinting et al. (2020) Population Study of Ovarian Cancer Risk Prediction for Targeted Screening and Prevention. Cancers 12(5)	- Outcomes in study do not match those specified in this review protocol *Does not evaluate the accuracy of the ovarian cancer risk prediction model*
Giannakeas, Vasily, Sopik, Victoria, Shestopaloff, Konstantin et al. (2015) A model for estimating ovarian cancer risk: application for preventive oophorectomy. Gynecologic oncology 139(2): 242-7	- Population in study does not match that specified in this review protocol *Simulation study only - model not validated with real data*
Guo, J.-Z., Xiao, Q., Gao, S. et al. (2021) Review of Mendelian Randomization Studies on Ovarian Cancer. Frontiers in Oncology 11: 681396	- Systematic review used as source of primary studies *No comprehensive models of ovarian cancer risk reported*
Hart, Gregory R, Nartowt, Bradley J, Muhammad, Wazir et al. (2019) Stratifying Ovarian Cancer Risk Using Personal Health Data. Frontiers in big data 2: 24	- Intervention in study does not match that specified in this review protocol

Study	Code [Reason]
	Risk model does not incorporate genetic variants (rare or common)
Jervis, Sarah, Song, Honglin, Lee, Andrew et al. (2015) A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. Journal of medical genetics 52(7): 465-75	- Data not reported in an extractable format or a format that can be analysed *Earlier version of CanRisk model (see Lee 2021)*
Kachuri, L., Graff, R.E., Smith-Byrne, K. et al. (2020) Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction. Nature Communications 11(1): 6084	- Intervention in study does not match that specified in this review protocol *Model does not include rare pathogenic genetic variants*.
Kazerouni, Neely, Greene, Mark H, Lacey, James V Jr et al. (2006) Family history of breast cancer as a risk factor for ovarian cancer in a prospective study. Cancer 107(5): 1075-83	- Data not reported in an extractable format or a format that can be analysed *No genetic factors included in the prognostic model*
Lee, Andrew, Mavaddat, Nasim, Cunningham, Alex et al. (2022) Enhancing the BOADICEA cancer risk prediction model to incorporate new data on RAD51C, RAD51D, BARD1 updates to tumour pathology and cancer incidence. Journal of medical genetics 59(12): 1206-1218	- Outcomes in study do not match those specified in this review protocol *Study reports an update of the models underlying CanRisk, but does not report validation data*
Marroni, F., Aretini, P., D'Andre, E. et al. (2004) Penetrances of breast and ovarian cancer in a large series of families tested for BRCA1/2 mutations. European Journal of Human Genetics 12(11): 899-906	- Intervention in study does not match that specified in this review protocol *Model includes BRCA1/2 pathogenic variants only - does not include common genetic variants or non-genetic risk factors*
Mavaddat, Nasim, Peock, Susan, Frost, Debra et al. (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. Journal of the National Cancer Institute 105(11): 812-22	- Intervention in study does not match that specified in this review protocol *Does not take into account known non-genetic risk factors*
Pearce, Celeste Leigh, Stram, Daniel O, Ness, Roberta B et al. (2015) Population distribution of lifetime risk of ovarian cancer in the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 24(4): 671-676	- Intervention in study does not match that specified in this review protocol *Model does not account for pathogenic variants such as BRCA1/2*
Sutcliffe, S, Pharoah, P D, Easton, D F et al. (2000) Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. International journal of cancer 87(1): 110-7	- Intervention in study does not match that specified in this review protocol *Reports ovarian cancer risks in BRCA1/2 positive families - does not report a risk prediction model*
Tanha, Kiarash, Mottaghi, Azadeh, Nojomi, Marzieh et al. (2021) Investigation on factors associated with ovarian cancer: an umbrella review of systematic review and meta-analyses. Journal of ovarian research 14(1): 153	- Systematic review used as source of primary studies *Focuses on any kind of risk factors on ovarian cancer among all women and not specifically women with (or at an increased risk of) a pathogenic variant associated with familial ovarian cancer*
Weiderpass, Elisabete, Sandin, Sven, Inoue, Manami et al. (2012) Risk factors for epithelial ovarian cancer in Japan - results from the Japan Public Health Center-based	- Intervention in study does not match that specified in this review protocol *Risk model does not incorporate genetic variants (rare or common)*

Study	Code [Reason]
Prospective Study cohort. International journal of oncology 40(1): 21-30	
Yarmolinsky, James, Relton, Caroline L, Lophatananon, Artitaya et al. (2019) Appraising the role of previously reported risk factors in epithelial ovarian cancer risk: A Mendelian randomization analysis. PLoS medicine 16(8): e1002893	- Intervention in study does not match that specified in this review protocol *Does not report a model for ovarian cancer risk, does not include rare genetic variants*

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: What are the optimal methods of assessing the absolute risk of ovarian cancer?

K 1.1 Research recommendation

What are the performance characteristics of tools or models to assess the absolute risk of ovarian cancer?

Why this is important

Those who carry ovarian cancer susceptibility genes are at an increased lifetime risk of developing ovarian cancer; this cancer has a poor prognosis, and its treatment is resource intensive. Those found to be carriers of ovarian cancer susceptibility genes can be offered risk reduction strategies, such as prophylactic surgery, which greatly reduces their risk of developing ovarian cancer. Therefore, there is innate benefit to identifying carriers before they develop ovarian cancer for both the individuals and healthcare systems.

Probability tools are one such way to identify a population so that it contains a high number of women who are ovarian cancer susceptibility gene carriers. Their use reduces the chance of detecting variants of unknown significance. Therefore, their use decreases the number of women who undergo testing which enables a more judicious use of resources. In addition, they help reduce non-beneficial interventions. To date, many validated probability tools exist however the majority of these are only designed to identify those at high risk of carrying a damaging change in the BRCA genes. As our understanding of other genes that can cause a susceptibility to ovarian cancer increases, research is needed to incorporate these genes into probability tools and refine the currently available ones.

Rationale for research recommendation

Table 7: Research recommendation rationale

Importance to 'patients' or the population	Importance to people at risk of ovarian cancer is through the more accurate identification of those women at an inherited risk of ovarian cancer. This would enable these women to make informed decisions about how they could reduce their personal cancer risk.
Relevance to NICE guidance	The relative absence of evidence regarding this topic currently restricts NICE guidance from making recommendations regarding the use of probability tools that are not restricted to *BRCA1* and *BRCA2*. The outcome of this research would allow such recommendations to be developed and become part of NICE guidance .
Relevance to the NHS	Importance to the NHS is through a reduction in the number of genetic tests that would need to be performed which would free up genomic medicine resources.
National priorities	High - Cancer survival is a key priority for patients and the government, as stated in documents such as the NHS long term plan for cancer and NHS Clinically-led review of NHS cancer standards: models of care and management.
Current evidence base	Current evidence is limited regarding the utility and accuracy of probability tools in identifying high risk populations for carrying ovarian cancer susceptibility genes; this is most marked when

	looking to find those who carry such gene changes that are not in either BRCA1 or BRCA2.
Equality considerations	Different ovarian cancer susceptibility genes will be seen more commonly in certain populations of women. Therefore, including lesser studied genes in probability tools will ensure a greater degree of benefit across a wider range of women.
Feasibility	Large biobanks with associated clinical data are available. In addition, prospective validation studies are possible and have been carried out previously.
Other comments	None

Modified PICO table

Table 8: Research recommendation modified PICO table

Population	Women at risk of ovarian cancer The committee agreed that research would be particularly welcome in groups of people with characteristics under the Equality 2010 Act (for example trans and non-binary people or people from different ethnic backgrounds).
Intervention	Mutation carrier probability tools
Comparator	Unselected populations
Outcome	The accurate identification of ovarian cancer susceptibility, including • Sensitivity • Specificity
Study design	Prospective cohort studies
Timeframe	3 years
Additional information	Retrospective studies are also possible with the use of the large established biobanks with linked clinical information