National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[O] Pathology protocol

NICE guideline NG241

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

NICE accredited
www.nice.org.uk/accreditation

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 All NICE guidance is subject to regular review and may be updated or withdrawn.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

© NICE 2024. All rights reserved. Subject to Notice of rights.

ISBN: 978-1-4731-5835-1

Contents

Pathology protocol **6**
Introduction 6
Summary of the protocol 6
Methods and process 7
Diagnostic evidence 7
Summary of included studies 7
Summary of the evidence 10
Economic evidence 10
Summary of included economic evidence 11
Economic model 11
Evidence statements 11
The committee's discussion and interpretation of the evidence 11
Recommendations supported by this evidence review 12
References – included studies 13
Appendices **14**
Appendix A Review protocols **14**
Review protocol for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 14
Appendix B Literature search strategies **22**
Literature search strategies for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 22
Appendix C Diagnostic evidence study selection **29**
Study selection for: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 29
Appendix D Evidence tables **30**
Evidence tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 30
Appendix E Forest plots **45**
Forest plots for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 45
Appendix F Modified GRADE tables **54**
GRADE tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-

reducing surgery for women at increased risk of familial ovarian cancer? 54

Appendix G Economic evidence study selection 56

Study selection for: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 56

Appendix H Economic evidence tables 57

Economic evidence tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 57

Appendix I Economic model 58

Economic model for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 58

Appendix J Excluded studies 59

Excluded studies for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 59

Appendix K Research recommendations – full details 63

Research recommendations for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer? 63

Appendix L Outcome data used in meta-analysis and meta-regression 64

Pathology protocol

What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Introduction

Women with familial ovarian cancer risk are offered risk reducing surgery to help mitigate their lifetime risk of developing ovarian cancer. This typically involves removing the tubes and the ovaries in their entirety. These tissues are sent to pathologists, doctors who diagnose abnormalities in tissues, for analysis. Before these tissues are examined by the pathologist, they must be fixed and areas are selected to be made into slides for the pathologist to look at. The number of areas sampled and made into slides depends on the degree of risk of there being something abnormal within the specimen. It is not possible to examine the whole sample as this would take too much time.

Women who have had risk reducing surgery due to having a familial ovarian cancer risk are at an increased risk of having an undiagnosed pre-cancerous or cancerous lesion at the time of their surgery. It is important to diagnose these occult lesions, if they exist, as if a woman has a cancer she may need more treatment. Therefore, the way in which samples from risk reducing surgery in women with a familial ovarian cancer risk are processed needs to be agreed to ensure lesions are not missed but also the workload is manageable. This review aims to investigate the best protocol to be used when processing pathology specimens taken from risk reducing surgery in women with a familial ovarian cancer risk.

Summary of the protocol

See Table 1 for a summary of the Population, Index test, Reference Standard and Target condition (PIRT) characteristics of this review.

Table 1: Summary of the protocol

Population	Women at increased risk of familial ovarian cancer who had a risk-reducing surgery
Index test	Pathology protocol for handling specimens from risk-reducing surgeries for women at increased risk of ovarian cancer
Reference standard	Protocol for sectioning and extensively examining the fimbriated end (SEE-FIM) of the fallopian tube specified in the study

Target condition	**Critical**
	• Ovarian/tubal cancer incidence
	• Serous tubal intraepithelial carcinoma (STIC) incidence
	• Diagnostic accuracy, for example:
	  ○ sensitivity
	  ○ specificity
	  ○ likelihood ratios (positive and negative)
	  ○ area under the ROC curve
	Important
	• None

ROC: receiver operating characteristic; SEE-FIM: sectioning and extensively examining the fimbriated end; STIC: serous tubal intraepithelial carcinoma

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

Six studies were included for this review, 2 systematic reviews (Bogaerts 2022, Cheng 2020), 2 retrospective cohort studies (Pross 2021, Rhiem 2011) and 2 cross-sectional studies (Rabban 2011, Samimi 2018).

Four studies (Bogaerts 2022, Cheng 2020, Pross 2021, Samimi 2018) reported the prevalence of serous tubal intraepithelial carcinoma (STIC) at risk-reducing salpingo-oophorectomy (RRSO) and 4 studies reported the prevalence of occult ovarian cancer at RRSO (Cheng 2020, Pross 2021, Rabban 2011, Rhiem 2011). All studies included women undergoing RRSO due to germline *BRCA* mutations.

There was considerable overlap between the studies included in the systematic reviews so the Bogaerts 2022 review was used for the STIC outcome and the Cheng 2020 review for the ovarian cancer outcome as that optimised the data available for these two outcomes.

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	Test	Reference standard	Outcomes
Bogaerts 2022 Systematic review Primary studies conducted in various international countries	N=6833 participants who underwent RRSO from 39 studies published between 2004 and 2020 n=3642 with known *BRCA1* pathogenic variant n=2695 with known *BRCA2* pathogenic variant	Characteristics of the pathology protocol: • SEE-FIM • Immunohistochemistry • Dedicated gynaecopathologist	NA[1]	• STIC incidence

Study	Population	Test	Reference standard	Outcomes
	n=35 with both variants n=461 with no specified variant Age at RSSO (mean (SD) years): overall mean (SD) not reported but study means ranged from 43 to 54 years (SDs not reported)			
Cheng 2020 Systematic review Primary studies conducted in various international countries	N=4039 participants who underwent RRSO from 34 studies published between 2000 and 2018 n=2345 with known *BRCA1* pathogenic variant n=1654 with known *BRCA2* pathogenic variant n=14 with both variants n=426 with no specified variant Age at RSSO (mean (SD) years): overall mean not reported but study means ranged from 43 to 53 years (SD not reported)	Characteristics of the pathology protocol: • SEE-FIM	NA[1]	• STIC incidence • Ovarian cancer incidence
Pross 2021 Retrospective cohort Germany	N=191 women who underwent RRSO n=123 with known *BRCA1* pathogenic variant n=53 with known *BRCA2* pathogenic variant n=35 with both variants	Characteristics of the pathology protocol: • SEE-FIM • Experienced gynaecopathologist	NA[1]	• STIC incidence • Ovarian cancer incidence

Study	Population	Test	Reference standard	Outcomes
	n=1 with *HNPCC* variant n=1 with *PALB2* variant n=8 with no specified variant n=5 with no variant Age at RSSO (mean (SD) years): 48.34 (9.19)			
Rabban 2011 USA Cross-sectional	N=134 women with a documented *BRCA* germline mutation undergoing RRSO n=74 with known *BRCA1* pathogenic variant n=60 with known *BRCA2* pathogenic variant Age at RSSO (mean (SD) years): Not reported but median (range), years: 46 (32-69)	Characteristics of the pathology protocol: • Gynecopathologist (gross (macroscopic) pathology) • Specialized pathologic evaluation protocol	NA[1]	• STIC incidence • Ovarian cancer incidence
Rhiem 2011 Germany Retrospective cohort	N=175 *BRCA* mutation carriers who had at least one ovary in situ, were free of ovarian cancer at the time of genetic testing and underwent RRSO n=92 with known *BRCA1* pathogenic variant n=83 with known *BRCA2* pathogenic variant Age at RSSO (mean (SD) years): Not reported but (median, (range), years): 47 (range not reported)	Characteristics of the pathology protocol: • Routine method of examining pathological sections	NA[1]	• Ovarian cancer incidence •

Study	Population	Test	Reference standard	Outcomes
Samimi 2018 Cross-sectional Canada	N=354 *BRCA* mutation carriers who underwent RRSO n=354 with known *BRCA1* or *BRCA2* pathogenic variant Age at RSSO (mean (SD), years): 45.9 (13)	Characteristics of the pathology protocol: • SEE-FIM • Dedicated gynaecopathologist	NA[1]	• STIC incidence

H&E: haematoxylin and eosin; NA: not applicable; RRSO: risk-reducing salpingo oophorectomy; SEE-FIM: protocol for sectioning and extensively examining the fimbriated end of the fallopian tube; SD: standard deviation; STIC: serous tubal intraepithelial carcinoma
1. Histopathological examination of the surgical specimen from RRSO was effectively the reference standard in these studies

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

There was a lack of evidence from studies directly comparing pathology protocols and no evidence on diagnostic accuracy outcomes. Instead, there was low to moderate quality evidence from studies reporting the prevalence of occult ovarian cancer and STIC at risk reducing salpingo-oophorectomy (RRSO). The overall prevalence of ovarian cancer in surgical specimens from RRSO was 3.56% (95% CI 2.98 to 4.25%). The overall prevalence of STIC in surgical specimens from RRSO was 3.11% (95% CI 2.43 to 3.96).

Similar prevalence rates were seen when the analyses were restricted to studies using the SEE-FIM protocol, studies that reported having a dedicated gynaecopathologist and studies reporting the use of immunohistochemistry. However it was invalid to compare for example studies reporting use of SEE-FIM with studies that did not mention its use because according to the committee's experience some of these studies were likely to have used SEE-FIM but did not mention it because it was not the focus of the study.

The committee thought that age at surgery may contribute to this inconsistency with women tending to have surgery at younger ages in more recent studies. However, in meta-regression mean age at surgery was not a significant predictor of the effect size and the residual heterogeneity remained serious (see Appendix L for the meta-regression analyses).

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

Ovarian/tubal cancer incidence and serous tubal intraepithelial carcinoma incidence were chosen as critical outcomes because it is critical for the pathology protocol to detect these occult lesions if they exist. When such lesions are detected then the woman may need additional staging or treatment. If any characteristics of the pathological protocol are associated with a higher incidence then this suggests these characteristics make the protocol more sensitive.

Diagnostic accuracy was also identified as a critical outcome because it measures the ability of the pathology protocol to differentiate benign from malignant occult lesions: false positives could lead to unnecessary further staging or treatment. False negatives would mean ovarian cancer was missed and the person could be undertreated. The committee did not include any further (important) outcomes because they agreed that the critical outcomes would provide sufficient information to base recommendations on.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated low to moderate. This was due to a serious risk of bias (reported in the included systematic reviews) and very serious imprecision due to low event rates for all outcomes. For some outcomes there was also serious inconsistency. The committee thought that age at surgery may contribute to this inconsistency with women tending to have surgery at younger ages in more recent studies. However, in meta-regression mean age at surgery was not a significant predictor of the effect size and the residual heterogeneity remained serious.

No evidence was found for diagnostic accuracy outcomes, because the pathological examination of the surgical specimen was generally considered the reference standard and by definition its results could not be false positive or false negative. The committee considered the prevalence of ovarian/tubal cancers and serous tubal intraepithelial carcinoma detected in the surgical specimens were related to the sensitivity of the pathological examination technique – as more sensitive protocols would detect more cancers.

Although there was a lack of evidence directly comparing pathology protocols the committee agreed to make recommendations based on their experience as certain pathology protocols have become a standard of care and they were aware of evidence from earlier cohort papers that suggested cancers could be missed if they are not used.

Benefits and harms

Despite the low to moderate quality evidence the committee decided to make strong recommendations on this topic because having a clearly defined detailed pathology protocol can save lives. Although there was a lack of evidence comparing it to other protocols, the committee agreed, based on their knowledge and experience, that people undergoing risk-reducing surgery are at increased risk of having occult pre-cancerous or malignant lesions, so intensive pathological investigation by a dedicated pathologist is needed even if the evidence suggested that detection rates were similar without one. The committee recommended that Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) should be used when carrying out risk reducing surgery. Compared to older pathology protocols the SEE-FIM protocol examines a greater amount of tissue, with multiple sagittal sections of fimbriae combined with 2 mm-thick sections of the remainder. Based on their expertise they noted that this type of sectioning is necessary to maximise the detection of early cancers, to allow for further staging or treatment if needed.

Based on expertise the committee noted that immunohistochemistry is a relatively cheap, yet informative, investigation that is available in all NHS pathology laboratories. Immunohistochemistry for p53 and ki67 helps in the identification of serous tubal intraepithelial carcinoma (STIC) and high-grade serous ovarian carcinomas. The committee agreed that investigations of these markers are only necessary if a pre-malignant or malignant lesion is suspected on morphological examination. They should not be performed in morphologically normal fallopian tubes because immunohistochemistry would not provide any additional information or would even lead to false positives as p53 signatures are found in normal tissue.

The committee noted once the adnexa have been removed from the body, it is impossible to determine their laterality. They recommended that surgeons should ensure adnexal specimens are submitted in 2 separate containers and labelled as either originating from the left or right adnexa. This will enable pathologists to issue accurate reports.

The committee also agreed that peritoneal cytology is needed to correctly stage any pre-cancerous or cancerous lesions and to detect occult primary peritoneal cancers which could otherwise be missed.

Although the evidence review did not cover endometrial cancer the committee acknowledged that risk reducing surgery for women with Lynch syndrome typically also involves hysterectomy. Due to the increased risk of endometrial cancer in this group they recommended that the entire endometrium should be submitted for pathological examination to ensure that such cancers are identified and treated.

Cost effectiveness and resource use

The committee noted that there were no relevant published economic evaluations that had been identified in this area. Therefore, they based their recommendations on the clinical evidence, their knowledge and experience. They recognised that pathological investigations are being carried out but that there is variation in the techniques that are being used. The committee agreed that using the SEE-FIM pathology protocol would be the most effective way to identify occult pre-cancerous or malignant lesion. This could lead to timelier interventions and better outcomes. The recommendations in this area are standardising practice and where practices will have to change it would not require significant additional NHS resources to implement.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.9.1 to 1.9.5 of the NICE guideline.

References – included studies

Bogaerts 2022

Bogaerts, J.M.A., Steenbeek, M.P., van Bommel, M.H.D. et al. Recommendations for diagnosing STIC: a systematic review and meta-analysis. Virchows Archiv 480(4): 725-737, 2022

Cheng 2020

Cheng, Aoshuang, Li, Lei, Wu, Ming et al. Pathological findings following risk-reducing salpingo-oophorectomy in BRCA mutation carriers: A systematic review and meta-analysis. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 46(1): 139-147, 2020

Pross 2021

Pross, T., Karsten, M.M., Blohmer, J.-U. et al. Role of Routine Peritoneal Biopsies during Risk Reducing Salpingo-Oophorectomy (RRSO). Geburtshilfe und Frauenheilkunde 81(9): 1031-1038, 2021

Rabban 2011

Rabban, J.T., MacKey, A., Powell, C.B. et al. Correlation of macroscopic and microscopic pathology in risk reducing salpingo-oophorectomy: Implications for intraoperative specimen evaluation. Gynecologic Oncology 121(3): 466-471, 2011

Rhiem 2011

Rhiem, K., Foth, D., Wappenschmidt, B. et al. Risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers. Archives of Gynecology and Obstetrics 283(3): 623-627, 2011

Samimi 2018

Samimi, G., Trabert, B., Geczik, A.M. et al. Population Frequency of Serous Tubal Intraepithelial Carcinoma (STIC) in Clinical Practice Using SEE-Fim Protocol. JNCI Cancer Spectrum 2(4): pky061, 2018

Appendices

Appendix A Review protocols

Review protocol for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	42022360536
1.	Review title	Effectiveness of pathology protocols for handling specimens from risk-reducing surgery for women at increased risk of familial ovarian cancer in the diagnosis of ovarian cancer
2.	Review question	What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?
3.	Objective	To establish the effectiveness of pathology protocols for handling specimens from risk-reducing surgery for women at increased risk of familial ovarian cancer in the diagnosis of 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, MEDLINE in Process & MEDLINE Epub Ahead of Print Epistemonikos Searches will be restricted by: English language studies Human studies

ID	Field	Content
		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: Women at increased risk of familial ovarian cancer who had a risk-reducing surgery Exclusion: none
7.	Test	• Pathology protocol for handling specimens from risk-reducing surgeries for women at increased risk of ovarian cancer
8.	Reference standard	• Protocol for sectioning and extensively examining the fimbriated end (SEE-FIM) of the fallopian tube specified in the study
9.	Types of studies to be included	Cross sectional diagnostic accuracy studies or systematic reviews of such studies
10.	Other exclusion criteria	Inclusion criteria: • Full text papers 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	Pathology protocol to assess histological samples removed during risk-reducing surgery in women at increased risk of familiar ovarian cancer in primary, secondary or tertiary care
12.	Primary outcomes (critical outcomes)	• Ovarian/tubal cancer incidence • Serous tubal intraepithelial carcinoma (STIC) incidence • Diagnostic accuracy, for example: ○ sensitivity

ID	Field	Content
		○ specificity ○ likelihood ratios (positive and negative) ○ area under the ROC curve
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. 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	Quality assessment of individual studies will be performed using the following checklist: QUADAS-2 for diagnostic accuracy studies 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 appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi and midas applications in STATA or WinBugs and Cochrane Review Manager. Sensitivity and specificity with 95% CIs will be used as the outcome for diagnostic test usefulness. Diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. Validity

ID	Field	Content
		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/ The risk of bias and indirectness GRADE domains will be based on the corresponding items in the QUADAS 2 checklist. Inconsistency will be based on visual inspection of forest plots and using statistical measures of heterogeneity (if meta-analysis has been done at a specified threshold). The GRADE imprecision domain will be judged using 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 These thresholds will be used to determine whether imprecision is not serious, serious or very serious depending on whether confidence intervals cross zero, one or two thresholds.
17.	Analysis of sub-groups	Evidence will be stratified by: • In situ lesions • Invasive lesions 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

<table>
<tr><th>ID</th><th>Field</th><th>Content</th></tr>
<tr><td></td><td></td><td>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.</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td>☐ Intervention
☒ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td>English</td></tr>
<tr><td>20.</td><td>Country</td><td>England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td>January 2022</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td>13 March 2024</td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td><table><tr><th>Review stage</th><th>Started</th><th>Completed</th></tr><tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr></table></td></tr>
</table>

ID	Field	Content		
		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 **5e Organisational affiliation of the review** NICE		
25.	Review team members	From the Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) • Senior Systematic Reviewer • Systematic Reviewer		
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		

ID	Field	Content
		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?RecordID=360536
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	None
34.	Current review status	☐ Ongoing ☐ Completed but not published

ID	Field	Content
		☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B Literature search strategies

Literature search strategies for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Database: Ovid MEDLINE(R) ALL

Date of last search: 21/12/2023

#	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*)).ti,ab,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*)).ti,ab,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*)).ti,ab,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).ti,ab,kf.
14	HNPCC.ti,ab,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).ti,ab,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).ti,ab,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)).ti,ab,kf.
18	gardner* syndrome*.ti,ab,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).ti,ab,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*)).ti,ab,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).ti,ab,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*)).ti,ab,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).ti,ab,kf.
25	((carrier* or gene*) adj3 mutat*).ti,ab,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*))).ti,ab,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).ti,ab,kf.
30	or/9-29
31	8 and 30
32	exp Fanconi Anemia Complementation Group Proteins/
33	(Fanconi An?emia adj3 protein*).ti,ab,kf.
34	(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,kf.

#	Searches
35	("breast cancer gene 1" or "breast cancer gene 2").ti,ab.
36	Rad51 Recombinase/
37	Ataxia Telangiectasia Mutated Proteins/
38	((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).ti,ab,kf.
39	Checkpoint Kinase 2/
40	(((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).ti,ab,kf.
41	Carcinoma, Small Cell/ge [Genetics]
42	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
43	(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.
44	exp Sertoli-Leydig Cell Tumor/
45	(((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.
46	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
47	Epithelial Cell Adhesion Molecule/
48	Epithelial cell adhesion molecule*.tw,kf.
49	(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.
50	(serous tubal intraepithelial carcinoma* or STIC).tw,kf.
51	or/32-50
52	31 or 51
53	exp Salpingectomy/
54	exp Ovariectomy/
55	(oophorectom* or salping* or ovar??ctom* or ovar??tom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO).tw,kf.
56	(((fallopian* or ovar* or tubal) adj4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*).tw,kf.
57	Hysterectomy, Vaginal/ or Hysterectomy/
58	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*).tw,kf.
59	((supervaginal or supravaginal or uterus* or uteri*) adj3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)).tw,kf.
60	(gyn?ecolog* adj2 surg*).tw,kf.
61	exp Prophylactic Surgical Procedures/
62	(((risk adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
63	risk reduction behavior/
64	(risk adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
65	or/53-64
66	52 and 65
67	exp Histology/
68	exp Pathology/
69	exp Cells/pa [Pathology]
70	exp Tissues/pa [Pathology]
71	exp Cytodiagnosis/
72	(cytolog* or cytodiag* or cytomorph* or cytopatholog*).tw,kf.
73	(immunohistochem* or immunocytochem*).tw,kf.
74	((specimen* or tissue* or cell* or sample* or smear* or scrap*) adj5 (identif* or examin* or evaluat* or analys* or histolog* or histopath* or pathol* or diagnos* or remov* or collect* or protocol* or standard* or guide* or plan* or practice* or process* or dissect* or pathog*)).tw,kf.
75	((tubal or fallopian* or fimbria*) adj4 (brush* or cytobrush* or scrap* or smear*)).tw,kf.
76	or/67-75
77	66 and 76
78	letter/
79	editorial/
80	news/
81	exp historical article/

#	Searches
82	Anecdotes as Topic/
83	comment/
84	case report/
85	(letter or comment*).ti.
86	or/78-85
87	randomized controlled trial/ or random*.ti,ab.
88	86 not 87
89	animals/ not humans/
90	exp Animals, Laboratory/
91	exp Animal Experimentation/
92	exp Models, Animal/
93	exp Rodentia/
94	(rat or rats or mouse or mice or rodent*).ti.
95	or/88-94
96	77 not 95
97	limit 96 to English language

Database: Embase

Date of last search: 21/12/2022

#	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/

#	Searches
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	or/8-28
30	7 and 29
31	Fanconi anemia protein/
32	(Fanconi An?emia adj3 protein*).tw,kf.
33	(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.
34	("breast cancer gene 1" or "breast cancer gene 2").tw.
35	Rad51 protein/
36	ATM protein/
37	((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.
38	checkpoint kinase 2/
39	(((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.
40	small cell carcinoma/
41	genetics/
42	40 and 41
43	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
44	(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.
45	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
46	(((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.
47	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
48	epithelial cell adhesion molecule/
49	Epithelial cell adhesion molecule*.tw,kf.
50	(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.
51	(serous tubal intraepithelial carcinoma* or STIC).tw,kf.
52	or/31-39,42-51
53	30 or 52
54	salpingectomy/
55	exp ovariectomy/
56	(oophorectom* or salping* or ovar??ctom* or ovar??tom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO).tw,kf.
57	(((fallopian* or ovar* or tubal) adj4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*).tw,kf.
58	exp hysterectomy/
59	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*).tw,kf.
60	((supervaginal or supravaginal or uterus* or uteri*) adj3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)).tw,kf.
61	(gyn?ecolog* adj2 surg*).tw,kf.
62	prophylactic surgical procedure/
63	(((risk* adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
64	risk reduction/
65	(risk* adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
66	or/54-65
67	53 and 66
68	exp histology/
69	exp pathology/
70	exp cells/

#	Searches
71	exp tissues/
72	70 or 71
73	exp pathology/
74	72 and 73
75	exp cytodiagnosis/
76	(cytolog* or cytodiag* or cytomorph* or cytopatholog*).tw,kf.
77	(immunohistochem* or immunocytochem*).tw,kf.
78	((specimen* or tissue* or cell* or sample* or smear* or scrap*) adj5 (identif* or examin* or evaluat* or analys* or histolog* or histopath* or pathol* or diagnos* or remov* or collect* or protocol* or standard* or guide* or plan* or practice* or process* or dissect* or pathog*)).tw,kf.
79	((tubal or fallopian* or fimbria*) adj4 (brush* or cytobrush* or scrap* or smear*)).tw,kf.
80	or/68-69,74-79
81	67 and 80
82	letter.pt. or letter/
83	note.pt.
84	editorial.pt.
85	case report/ or case study/
86	(letter or comment*).ti.
87	or/82-86
88	randomized controlled trial/ or random*.ti,ab.
89	87 not 88
90	animal/ not human/
91	nonhuman/
92	exp Animal Experiment/
93	exp Experimental Animal/
94	animal model/
95	exp Rodent/
96	(rat or rats or mouse or mice or rodent*).ti.
97	or/89-96
98	81 not 97
99	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
100	98 not 99
101	limit 100 to English language

Database: Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2022 and Cochrane Central Register of Controlled Trials, Issue 11 of 12, November 2022

Date of last search: 21/12/2022

#	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

#	Searches
#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 tumuor* 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	{OR #9-#29}
#31	#8 AND #30
#32	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#33	(Fanconi NEXT Anemia NEAR/3 protein*):ti,ab,kw
#34	(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
#35	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#36	MeSH descriptor: [Rad51 Recombinase] this term only
#37	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#38	("Ataxia telangiectasia" NEAR/1 mutated NEXT (protein* or kinase*)):ti,ab,kw
#39	(ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#40	MeSH descriptor: [Checkpoint Kinase 2] this term only
#41	((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)):ti,ab,kw
#42	(CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#43	MeSH descriptor: [Carcinoma, Small Cell] explode all trees and with qualifier(s): [genetics - GE]
#44	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#45	(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
#46	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#47	(((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
#48	(DICER or DICER1 or DICER1e or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H4.8 LIKE"):ti,ab,kw
#49	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#50	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#51	(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
#52	(serous NEXT tubal NEXT intraepithelial NEXT carcinoma* or STIC):ti,ab,kw
#53	{OR #32-#52}

#	Searches
#54	#31 OR #53
#55	MeSH descriptor: [Salpingectomy] explode all trees
#56	MeSH descriptor: [Ovariectomy] explode all trees
#57	(oophorectom* or salping* or ovariectom* or ovarectom* or ovariotom* or ovarotom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO):ti,ab,kw
#58	(((fallopian* or ovar* or tubal) NEAR/4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*):ti,ab,kw
#59	MeSH descriptor: [Hysterectomy, Vaginal] this term only
#60	MeSH descriptor: [Hysterectomy] this term only
#61	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*):ti,ab,kw
#62	((supervaginal or supravaginal or uterus* or uteri*) NEAR/3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)):ti,ab,kw
#63	((gynecolog* or gynaecolog*) NEAR/2 surg*):ti,ab,kw
#64	MeSH descriptor: [Prophylactic Surgical Procedures] explode all trees
#65	(((risk* NEAR/2 reduc*) or prevent* or prophyla*) NEAR/2 surg*):ti,ab,kw
#66	MeSH descriptor: [Risk Reduction Behavior] this term only
#67	(risk* NEAR/2 reduc* NEAR/2 (behavior* or behaviour* or choice* or strateg* or decision*)):ti,ab,kw
#68	{OR #55-#67}
#69	#54 AND #68
#70	MeSH descriptor: [Histology] explode all trees
#71	MeSH descriptor: [Pathology] explode all trees
#72	MeSH descriptor: [Cells] explode all trees and with qualifier(s): [pathology - PA]
#73	MeSH descriptor: [Tissues] explode all trees and with qualifier(s): [pathology - PA]
#74	MeSH descriptor: [Cytodiagnosis] explode all trees
#75	(cytolog* or cytodiag* or cytomorph* or cytopatholog*):ti,ab,kw
#76	(immunohistochem* or immunocytochem*):ti,ab,kw
#77	((specimen* or tissue* or cell* or sample* or smear* or scrap*) NEAR/5 (identif* or examin* or evaluat* or analys* or histolog* or histopath* or pathol* or diagnos* or remov* or collect* or protocol* or standard* or guide* or plan* or practice* or process* or dissect* or pathog*)):ti,ab,kw
#78	((tubal or fallopian* or fimbria*) NEAR/4 (brush* or cytobrush* or scrap* or smear*)):ti,ab,kw
#79	{OR #70-#78}
#80	#69 AND #79
#81	conference:pt or (clinicaltrials or trialsearch):so
#82	#80 NOT #81

Database: Epistemonikos

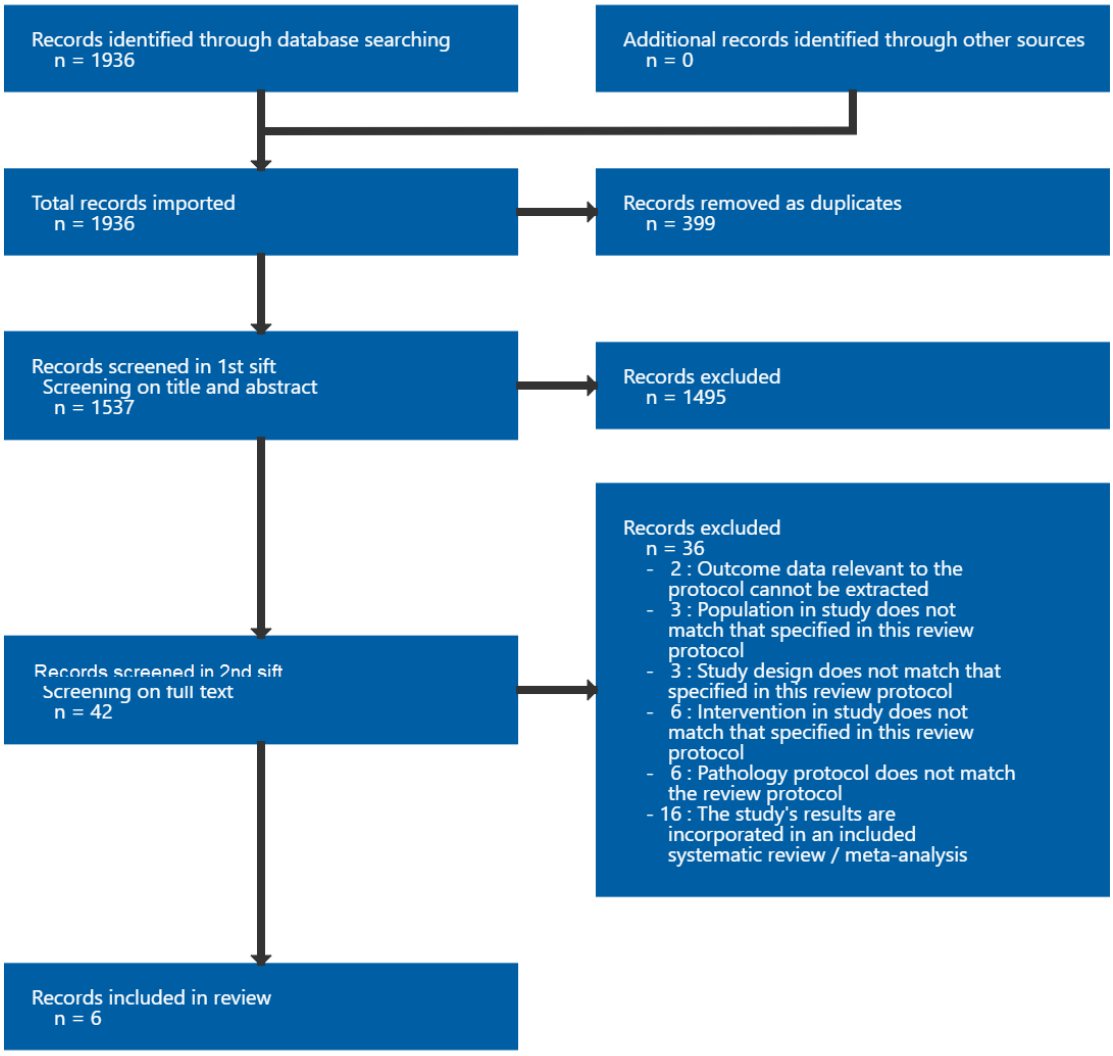
Date of last search: 21/12/2022

#	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:((oophorectom* OR salping* OR ovariectom* OR ovariotom* OR BSO OR RRSO* OR RRBSO OR RRSDO OR RRESDO OR colpohysterectom* OR panhysterectom* OR hysterocolpectom* OR hysterectom*)) OR advanced_abstract_en:((oophorectom* OR salping* OR ovariectom* OR ovariotom* OR BSO OR RRSO* OR RRBSO OR RRSDO OR RRESDO OR colpohysterectom* OR panhysterectom* OR hysterocolpectom* OR hysterectom*)))
3	(advanced_title_en:(((specimen* OR tissue* OR cell* OR sample* OR smear* OR scrap*) AND (identif* OR examin* OR evaluat* OR analys* OR histolog* OR histopath* OR pathol* OR diagnos* OR remov* OR collect* OR protocol* OR standard* OR guide* OR plan* OR practice* OR process* OR dissect* OR pathog*))) OR advanced_abstract_en:(((specimen* OR tissue* OR cell* OR sample* OR smear* OR scrap*) AND (identif* OR examin* OR evaluat* OR analys* OR histolog* OR histopath* OR pathol* OR diagnos* OR remov* OR collect* OR protocol* OR standard* OR guide* OR plan* OR practice* OR process* OR dissect* OR pathog*))))
4	2 AND 3
5	1 AND 4

Appendix C Diagnostic evidence study selection

Study selection for: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Table 4: Evidence tables

Bogaerts, 2022

Bibliographic Reference	Bogaerts, J.M.A.; Steenbeek, M.P.; van Bommel, M.H.D.; Bulten, J.; van der Laak, J.A.W.M.; de Hullu, J.A.; Simons, M.; Recommendations for diagnosing STIC: a systematic review and meta-analysis; Virchows Archiv; 2022; vol. 480 (no. 4); 725-737

Study details

Country/ies where study was carried out	Primary studies conducted in various international countries
Study type	Systematic review
Study dates	Studies published between 2004 and 2020
Inclusion criteria	• studies describing the pathology results of a risk-reducing salpingo-oophorectomy (RRSO), performed among *BRCA1/2* pathogenic variant carriers, aimed at defining the incidence or describing the histopathological characteristics of ovaries and fallopian tubes
Exclusion criteria	• where subgroup data for summarized *BRAC1/2* results was not available • articles written in another language than English or Dutch • conference abstracts • case reports • review articles
Patient characteristics	N=6833 cases from 39 studies (10 prospective, 29 retrospective studies) n=3642 with known *BRCA1* pathogenic variant

	n=2695 with known *BRCA2* pathogenic variant n=35 with both variants n=461 with no specified *BRCA* variant Age at RSSO (mean (SD) years): overall mean (SD) not reported but study means ranged from 43 to 54 years (SDs not reported)
Pathology protocol(s)	Immunohistochemistry (IHC): The use of IHC in diagnosing STIC was described by 21 studies SEE-FIM: consistently used in 20 studies Dedicated gynaecopathologist: Pathology specimens were assessed in 25 studies
Target conditions	STIC (serous tubal intraepithelial carcinoma)
Reference standard(s)	Histopathological examination of the surgical specimen from RRSO (as described above in pathology protocols)
Duration of follow-up	Not reported
Sources of funding	Not reported
Outcomes	See Appendix L
Other information	The methodological quality of each study was assessed using the quality assessment tool for observational cohort and cross-sectional studies of the National Heart, Lung and Blood institute (NIH). Overall there were concerns about length of follow-up (37% of studies), definition of outcome measures (56% of studies), description of intervention (47% of studies), comparability of control groups (41% of studies) and inclusion of consecutive cases (36% of studies). For this reason evidence from this review is at serious risk of bias

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Serious (*biases in primary studies were significant and not addressed in the synthesis*)
Overall study ratings	Overall risk of bias	Serious (*due to risk of bias in primary studies)*
Overall study ratings	Applicability as a source of data	Fully applicable

Cheng, 2020

Bibliographic Reference	Cheng, Aoshuang; Li, Lei; Wu, Ming; Lang, Jinghe; Pathological findings following risk-reducing salpingo-oophorectomy in BRCA mutation carriers: A systematic review and meta-analysis.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2020; vol. 46 (no. 1); 139-147

Study details

Country/ies where study was carried out	Primary studies conducted in various international countries
Study type	Systematic review

Study dates	Included studies were published between 2000 and 2018
Inclusion criteria	• Studies published in English • reporting on patients with a deleterious germline *BRCA1/2* mutation who underwent a prophylactic oophorectomy
Exclusion criteria	• studies with overlapping data and case reports with fewer than 5 cases
Patient characteristics	N=4039 cases from 34 studies n=2345 with known *BRCA1* pathogenic variant n=1654 with known *BRCA2* pathogenic variant n=14 with both variants n=426 with no specified variant Age at RSSO (mean (SD) years): overall mean not reported but study means ranged from 43 to 53 years (SD not reported)
Pathology protocol(s)	Protocols using SEE-FIM Protocols not using SEE-FIM
Target conditions	Ovarian cancer STIC (serous tubal intraepithelial carcinoma)
Reference standard(s)	Histopathological examination of the surgical specimen from RRSO (as described above in pathology protocols)
Duration of follow-up	Not reported
Sources of funding	Supported by the Chinese Academy of Medical Sciences Initiative for Innovative Medicine (CAMS-2017-I2M-1- 002) and by the National Science-Technology Support Plan Projects (2015BAI13B04)
Outcomes	See Appendix L

Other information	The methodological quality of each study was assessed using the criteria of the Agency for Healthcare Research and Quality (AHRQ). Studies ranged from low to medium quality (exact numbers not reported)..For this reason evidence from this review is at serious risk of bias. There is also overlap of the included studies with the studies reported in Bogaerts 2022 – which also concluded a serious risk of bias.

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Serious (*biases in primary studies were significant and not addressed in the synthesis*)
Overall study ratings	Overall risk of bias	Serious (*due to risk of bias in primary studies)*
Overall study ratings	Applicability as a source of data	Fully applicable

Pross, 2021

Bibliographic Reference	Pross, T.; Karsten, M.M.; Blohmer, J.-U.; Speiser, D.; Role of Routine Peritoneal Biopsies during Risk Reducing Salpingo-Oophorectomy (RRSO); Geburtshilfe und Frauenheilkunde; 2021; vol. 81 (no. 9); 1031-1038

Study details	
Country/ies where study was carried out	Germany
Study type	Retrospective cohort study
Study dates	2014-2020
Inclusion criteria	• Women who underwent (risk reducing salpingo-oophorectomy) RRSO
Exclusion criteria	• If RRSO was combined with any other operation (such as enucleation of myoma, mastectomy, hysteroscopy)
Patient characteristics	N=191 n=123 with known *BRCA1* pathogenic variant n=53 with known *BRCA2* pathogenic variant n=35 with both variants n=1 with *HNPCC* variant n=1 with *PALB2* variant n=8 with no specified variant n=5 with no variant **Age at RSSO (mean (SD):** 48.34 (9.19)
Pathology protocol(s)	All specimen collected during RRSO were analysed using the protocol for Sectioning and Extensively Examining the FIMbria (SEE-FIM) by experienced pathologists trained in gynaecologic pathology. Immunohistochemistry staining not reported
Target conditions	Ovarian cancer

	STIC (serous tubal intraepithelial carcinoma)
Reference standard(s)	Histopathological examination of the surgical specimen from RRSO (as described above in pathology protocols)
Duration of follow-up	None
Sources of funding	No funding from agencies in the public, commercial, or not-for-profit sectors.
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?	High *(Unclear how participants were sampled)*
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?	High *(Not all patients included in analysis. Pathology protocol was the reference standard – there was no way to evaluate the accuracy of the pathology protocol)*

Rabban, 2011

Bibliographic Reference	Rabban, J.T.; MacKey, A.; Powell, C.B.; Crawford, B.; Zaloudek, C.J.; Chen, L.-M.; Correlation of macroscopic and microscopic pathology in risk reducing salpingo-oophorectomy: Implications for intraoperative specimen evaluation; Gynecologic Oncology; 2011; vol. 121 (no. 3); 466-471

Study details

Country/ies where study was carried out	USA
Study type	Cross-sectional study
Study dates	1998-2009
Inclusion criteria	• women with a documented *BRCA1/2* germline mutation undergoing bilateral risk reducing salpingo-oophorectomy (RRSO)
Exclusion criteria	Not reported

Patient characteristics	N=134 n=74 with known *BRCA1* pathogenic variant n=60 with known *BRCA2* pathogenic variant **Age at RSSO (mean (SD) years):** Not reported but median (range), years: 46 (32-69)
Pathology protocol(s)	• Gynecopathologist (gross (macroscopic) pathology) The method of intraoperative evaluation was determined on an ad hoc basis by the pathologist and consisted of either 1) gross inspection only; 2) specimen dissection with gross inspection only; or 3) specimen dissection with frozen section evaluation. All diagnoses of malignancy were independently verified by a second gynaecologic pathologist. • Specialized pathologic evaluation protocol A specialized pathologic evaluation protocol was used to maximize visualization of the tissues most at risk for harbouring microscopic foci of carcinoma, the mucosa of the fallopian tube fimbriae and the ovarian surface epithelium. The default practice was to use the specialized protocol unless the surgeon had a strong suspicion for tumour based on the intraoperative macroscopic finding.
Target conditions	Ovarian cancer STIC (serous tubal intraepithelial carcinoma)
Reference standard(s)	Histopathological examination of the surgical specimen from RRSO (as described above in pathology protocols)
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?	Unclear (*unclear how patients were sampled*)
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?	Serious (*use of the specialized protocol reference standard depended on the intraoperative macroscopic findings. Pathology protocol was the reference standard – there was no way to evaluate the accuracy of the pathology protocol)*

Rhiem, 2011

Bibliographic Reference	Rhiem, K.; Foth, D.; Wappenschmidt, B.; Gevensleben, H.; Buttner, R.; Ulrich, U.; Schmutzler, R.K.; Risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers; Archives of Gynecology and Obstetrics; 2011; vol. 283 (no. 3); 623-627

Study details

Country/ies where study was carried out	Germany
Study type	Retrospective cohort study
Study dates	1996-2009
Inclusion criteria	• *BRCA* mutation carriers who had at least one ovary in situ and who were free of ovarian cancer at the time of genetic testing undergoing risk-reducing salpingo-oophorectomy (RRSO)
Exclusion criteria	Not reported
Patient characteristics	N=175 n=92 with known *BRCA1* pathogenic variant n=83 with known *BRCA2* pathogenic variant **Age at RSSO (mean (SD) years):** Not reported but median age at RRSO (years): 47
Pathology protocol(s)	Histopathologic evaluation of RRSO specimens from carriers of BRCA mutations included careful macroscopic examination by a pathologist. Tissue specimens were subsequently fixed in 4% buffered formaldehyde and entirely embedded in paraffin. After fixation, systematic pathologic microsectioning and histopathologic examination of hematoxylin–eosinstained cross sections of the complete ovarian and fallopian tube tissue were performed.
Target conditions	Ovarian cancer

Reference standard(s)	Histopathologic evaluation of RRSO specimens as described above
Duration of follow-up	Median time of follow-up (months): 47.8 (range 1–372). Participants were followed from the date of first counselling until, (1) the development of ovarian, peritoneal or fallopian tube cancer, (2) the last visitation in the Centre, or (3) the death of the proband.
Sources of funding	Grant from the German Cancer Aid to RKS
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?	High (*Pathology protocol was the reference standard – there was no way to evaluate the accuracy of the pathology protocol*)

Samimi, 2018

Bibliographic Reference	Samimi, G.; Trabert, B.; Geczik, A.M.; Duggan, M.A.; Sherman, M.E.; Population Frequency of Serous Tubal Intraepithelial Carcinoma (STIC) in Clinical Practice Using SEE-Fim Protocol; JNCI Cancer Spectrum; 2018; vol. 2 (no. 4); pky061

Study details

Country/ies where study was carried out	Canada
Study type	Cross-sectional study
Study dates	2014-2016
Inclusion criteria	• population-based data from Calgary Laboratory Services (CLS) in Alberta, Canada, which performs total or modified SEE-FIM processing on all fallopian tubes, including histologic examination of all tubal segments and the entire fimbria, where most STIC arises
Exclusion criteria	Not reported
Patient characteristics	N=354 *BRCA1/2* mutations carriers had risk-reducing surgery (risk-reducing includes: risk reducing, prophylactic, *BRCA* positive, *BRCA* test pending, family history of cancer (breast/ovarian/uterine), and family history of *BRCA* positive) **Age (mean (SD), years):** 45.9 (13)

Pathology protocol(s)	Total or modified SEE-FIM Haematoxylin and eosin-stained glass slides of formalin-fixed paraffin-embedded tissue sections are reviewed for morphologic changes indicative of STIC, and these were usually confirmed by p53 immunohistochemical staining. Diagnostically challenging cases were reviewed by the laboratory's gynaecological pathologists.
Target conditions	STIC (serous tubal intraepithelial carcinoma)
Reference standard(s)	• Histopathological examination of the surgical specimen from RRSO (as described above in pathology protocols)
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
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

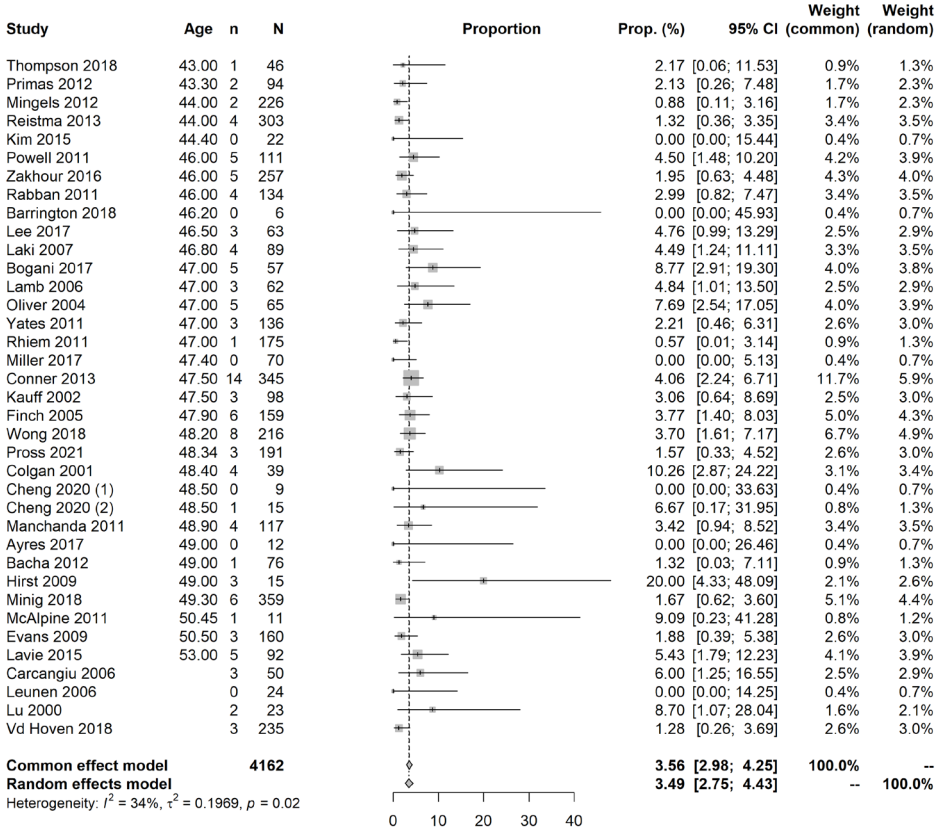
Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High (*Pathology protocol was the reference standard – there was no way to evaluate the accuracy of the pathology protocol)*

Appendix E Forest plots

Forest plots for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

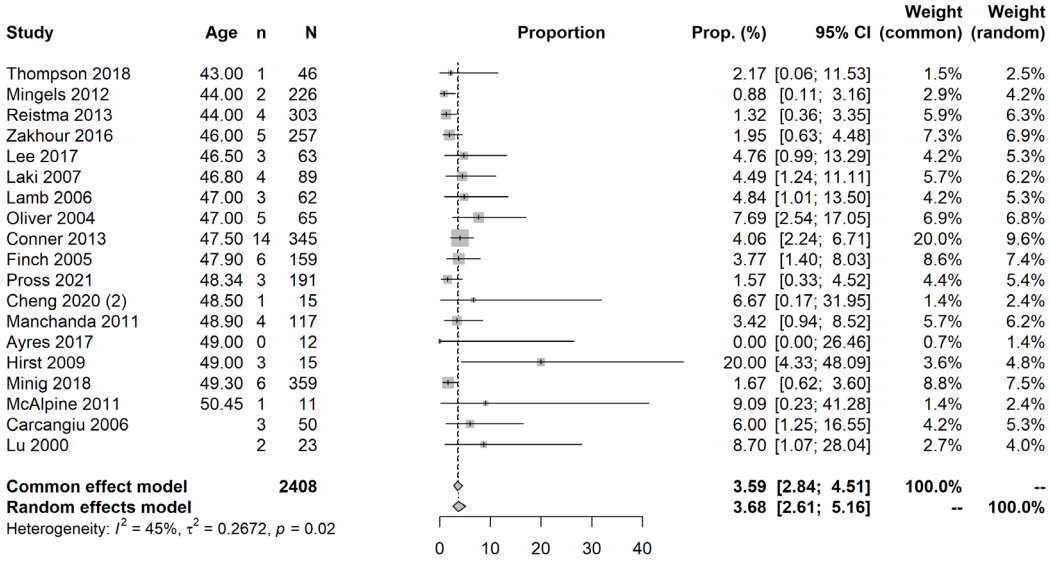
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Prevalence of ovarian cancer in risk reducing salpingo-oophorectomy specimens



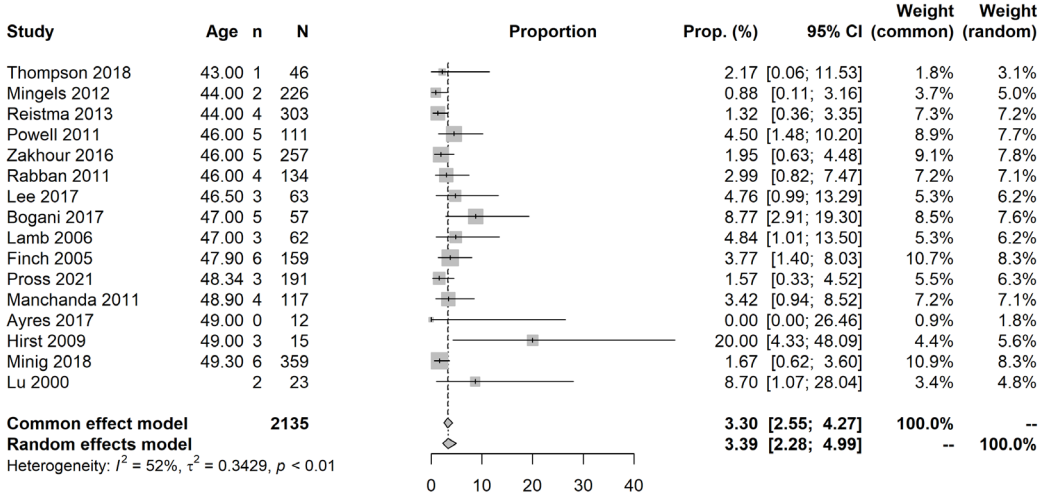
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews, except for Pross 2021, Rabban 2011, Rhiem 2011

Figure 3: Prevalence of ovarian cancer in risk reducing salpingo-oophorectomy specimens studies using the SEE-FIM protocol



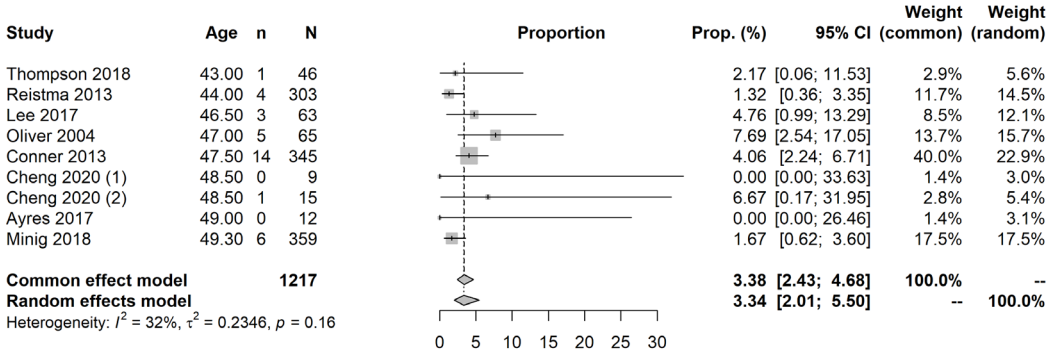
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews, except for Pross 2021

Figure 4: Prevalence of ovarian cancer in risk reducing salpingo-oophorectomy specimens in studies reporting a dedicated gynaecopathologist



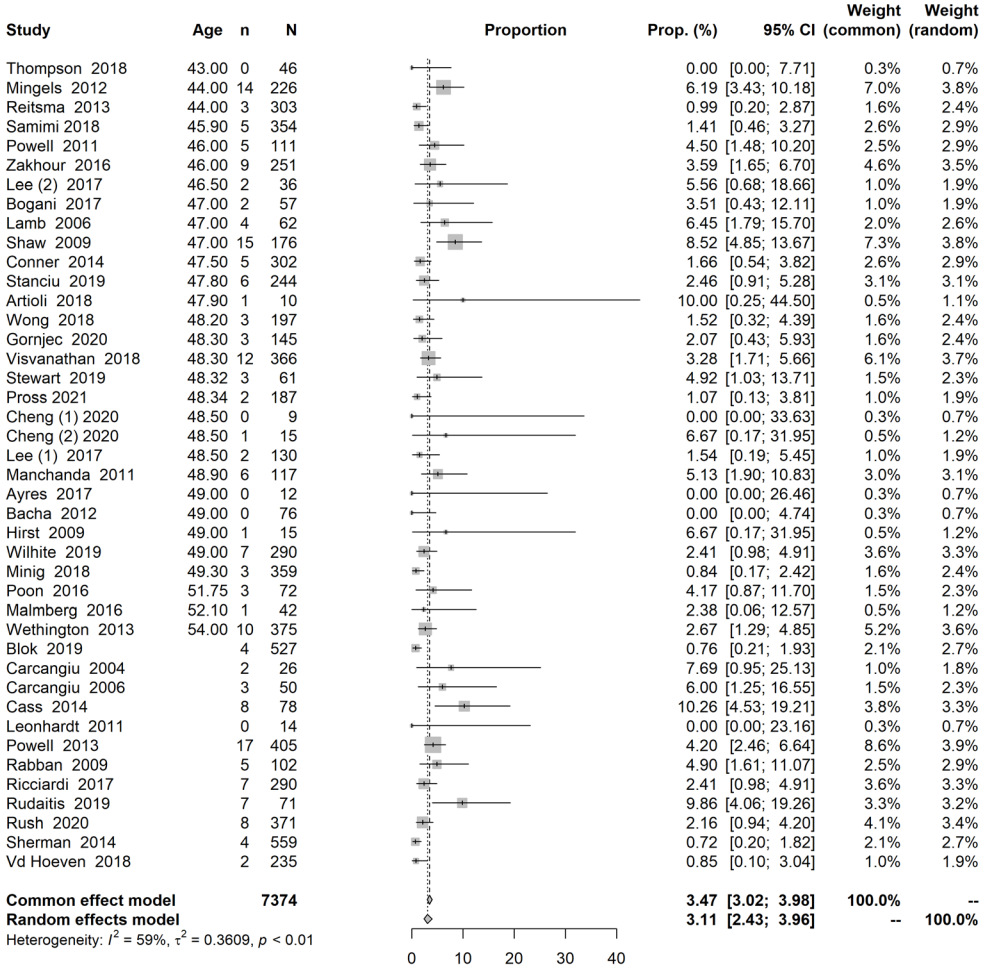
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews, except for Pross 2021, Rabban 2011

Figure 5: Prevalence of ovarian cancer in risk reducing salpingo-oophorectomy specimens in studies which reported using immunohistochemistry



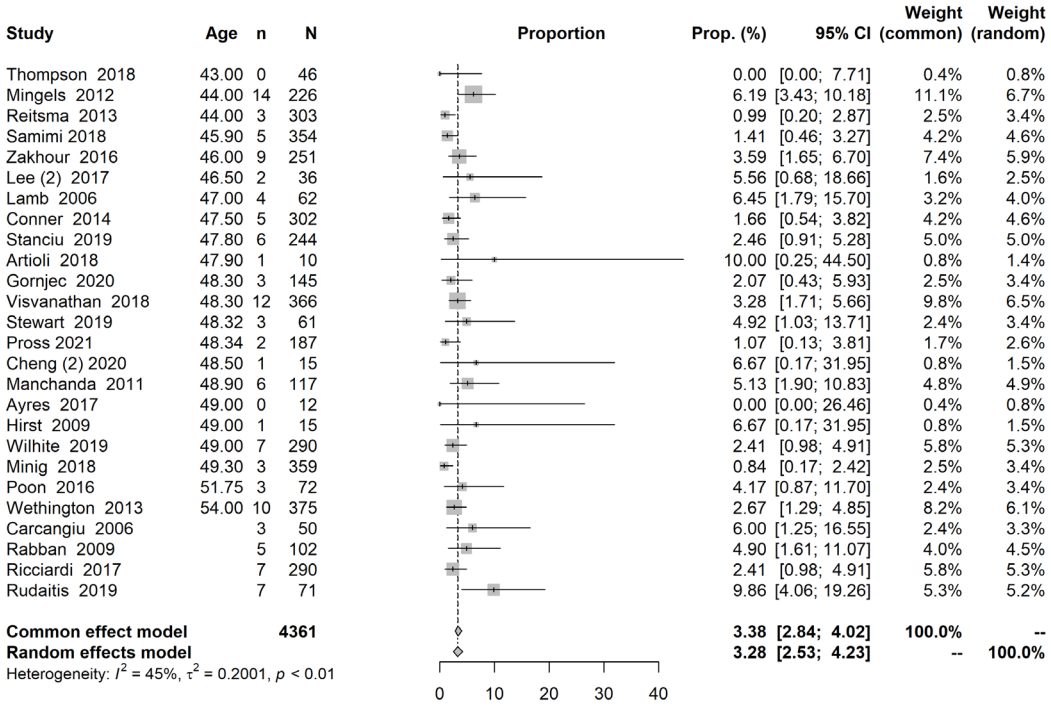
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews

Figure 6: Prevalence of STIC in risk reducing salpingo-oophorectomy specimens



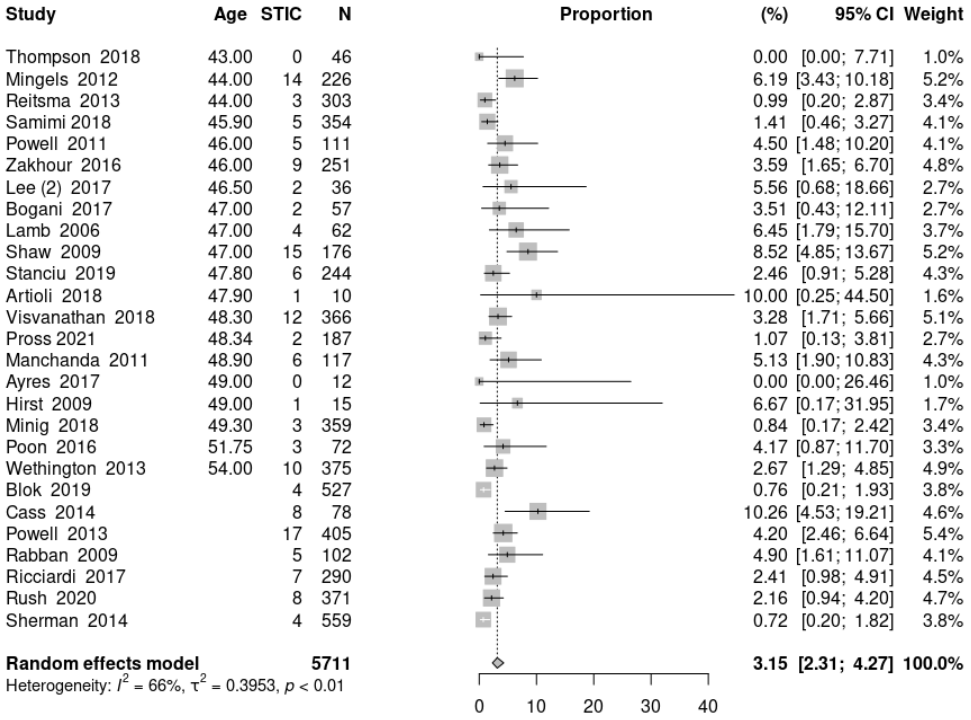
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews, except for Pross 2021, Samimi 2018

Figure 7: Prevalence of STIC in risk reducing salpingo-oophorectomy specimens studies using the SEE-FIM protocol



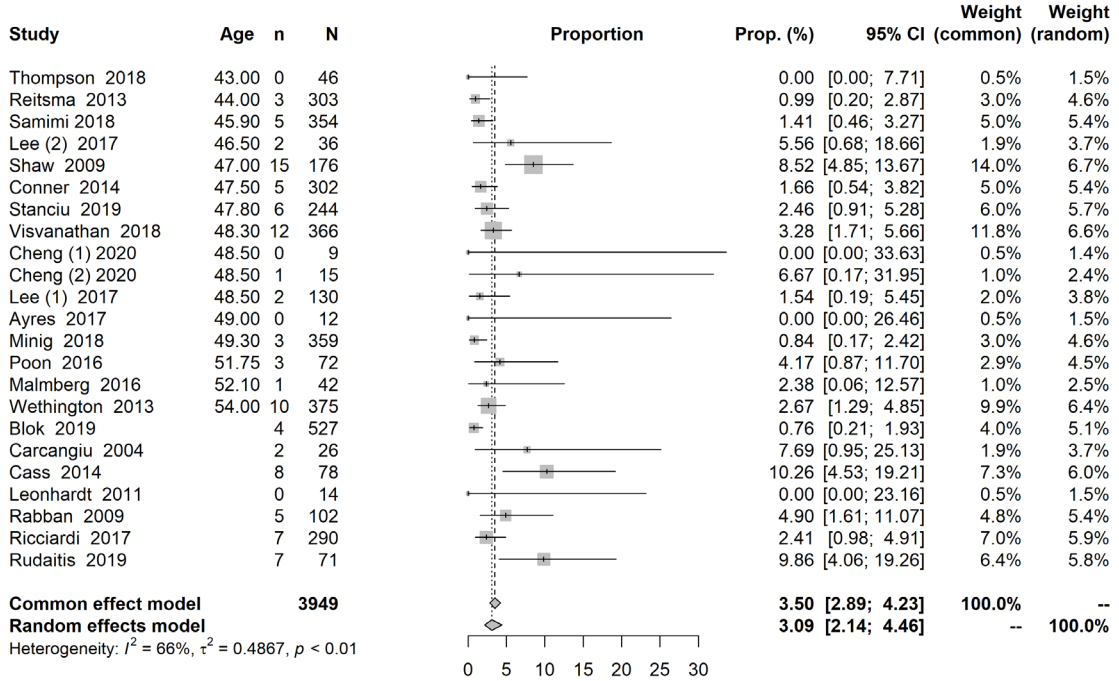
Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews, except for Pross 2021, Samimi 2018

Figure 8: Prevalence of STIC in risk reducing salpingo-oophorectomy specimens in studies reporting a dedicated gynaecopathologist



Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews except for Samimi 2018

Figure 9: Prevalence of STIC in risk reducing salpingo-oophorectomy specimens in studies which reported using immunohistochemistry



Age refers to the mean (or median if mean not reported) age at RRSO in the study (where reported)
Studies come from the Cheng 2020 & Bogaerts 2022 systematic reviews except for Samimi 2018

Appendix F Modified GRADE tables

GRADE tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Table 5: Evidence profile for prevalence of ovarian cancer according to characteristics of the pathology protocol

No. of studies	Study design	No of OC / Total no of patients	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence of ovarian cancer at RRSO								
37[1]	Cohort studies	117/4162	3.56% (2.98 to 4.25)	Serious[2]	Not serious	Not serious	Not serious	MODERATE
Prevalence of ovarian cancer at RRSO in studies using the SEE-FIM protocol								
19[4]	Cohort studies	70/2408	3.59% (2.84 to 4.51)	Serious[2]	Not serious	Not serious	Not serious	MODERATE
Prevalence of ovarian cancer at RRSO in studies with a dedicated gynaecopathologist								
16[5]	Cohort studies	56/2135	3.39% (2.28 to 4.99)	Serious[2]	Serious[3]	Not serious	Not serious	LOW
Prevalence of ovarian cancer at RRSO in studies reporting use of IHC								
9[6]	Cohort studies	34/1217	3.38% (2.43 to 4.68)	Serious[2]	Not serious	Not serious	Not serious	MODERATE

CI: confidence interval; IHC: immunohistochemistry; OC: ovarian cancer; RRSO: risk reducing salpingo-oophorectomy; SEE-FIM: sectioning and extensively examining the fimbriated end

1. Cheng 2020 & Bogaerts 2022 systematic reviews, Pross 2021, Rabban 2011, Rhiem 2011

2. Serious risk of bias according to the quality assessment reported in Cheng 2020 (using the criteria of the Agency for Healthcare Research and Quality)

3. Serious heterogeneity not explained by meta-regression with mean age in study as a predictor. No other subgroup analysis (as per protocol) was possible

4. Cheng 2020 & Bogaerts 2022 systematic reviews , Pross 2021

5. Cheng 2020 & Bogaerts 2022 systematic reviews, Pross 2021, Rabban 2011

6. Cheng 2020 & Bogaerts 2022 systematic reviews

Table 6: Evidence profile for prevalence of STIC according to characteristics of the pathology protocol

No. of studies	Study design	No of STIC / Total no of patients	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence of STIC at RRSO								
42[1]	Cohort studies	195/7374	3.11% (2.43 to 3.96)	Serious[2]	Serious[3]	Not serious	Not serious	LOW
Prevalence of STIC at RRSO in studies using the SEE-FIM protocol								
26[1]	Cohort studies	122/4361	3.38% (2.84 to 4.02)	Serious[2]	Not serious	Not serious	Not serious	MODERATE
Prevalence of STIC at RRSO in studies with a dedicated gynaecopathologist								
27[4]	Cohort studies	156/5711	3.15% (2.31 to 4.27)	Serious[2]	Serious[3]	Not serious	Not serious	LOW
Prevalence of STIC at RRSO in studies reporting IHC								
23[4]	Cohort studies	101/3949	3.09% (2.14 to 4.46)	Serious[2]	Serious[3]	Not serious	Not serious	LOW

CI: confidence interval; IHC: immunohistochemistry; RRSO: risk reducing salpingo-oophorectomy; SEE-FIM: sectioning and extensively examining the fimbriated end ; STIC: serous tubal intraepithelial carcinoma

1. Cheng 2020 & Bogaerts 2022 systematic reviews , Pross 2021, Samimi 2018

2. Serious risk of bias according to the quality assessment tool for observational cohort and cross-sectional studies of the National Heart, Lung and Blood Institute (NIH; reported in Bogaerts 2022)

3. Serious heterogeneity not explained by meta-regression with mean age in study as a predictor. No other subgroup analysis (as per protocol) was possible

4. Cheng 2020 & Bogaerts 2022 systematic reviews, Samimi 2018

Appendix G Economic evidence study selection

Study selection for: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

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

Appendix I Economic model

Economic model for review question: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery 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: What pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

Excluded diagnostic studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Blok, F., Roes, E.M., van Leenders, G.J.L.H. et al. (2016) The lack of clinical value of peritoneal washing cytology in high risk patients undergoing risk-reducing salpingo-oophorectomy: A retrospective study and review. BMC Cancer 16(1): 18	- Pathology protocol does not match the review protocol *Cytology study*
Carr, C.E., Chambers, L., Jernigan, A.M. et al. (2021) Short- And long-term outcomes for single-port risk-reducing salpingo-oophorectomy with and without hysterectomy for women at risk for gynecologic cancer. International Journal of Gynecological Cancer 31(2): 215-221	- Intervention in study does not match that specified in this review protocol *No details about the pathology protocol*
Colgan, T.J., Murphy, J., Cole, D.E.C. et al. (2001) Occult carcinoma in prophylactic oophorectomy specimens: Prevalence and association with BRCA germline mutation status. American Journal of Surgical Pathology 25(10): 1283-1289	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Cheng 2020*
Cowan, R., Nobre, S.P., Pradhan, N. et al. (2021) Outcomes of incidentally detected ovarian cancers diagnosed at time of risk-reducing salpingo-oophorectomy in BRCA mutation carriers. Gynecologic Oncology 161(2): 521-526	- The study's results are incorporated in an included systematic review / meta-analysis *Pathology protocol not reported*
Deligdisch, L., Gil, J., Kerner, H. et al. (1999) Ovarian dysplasia in prophylactic oophorectomy specimens. Cytogenetic and morphometric correlations. Cancer 86(8): 1544-1550	- Intervention in study does not match that specified in this review protocol *No details about the pathology protocol*
Domchek, S.M., Friebel, T.M., Garber, J.E. et al. (2010) Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. Breast Cancer Research and Treatment 124(1): 195-203	- Intervention in study does not match that specified in this review protocol *No details about the pathology protocol*
Finch, A., Shaw, P., Rosen, B. et al. (2006) Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecologic Oncology 100(1): 58-64	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Cheng 2020 systematic review*
Goldenberg, M., Revivo, P.E., Gurevitch, S. et al. (2022) Risk-reducing bilateral salpingo-oopherectomy for BRCA mutation carriers via the transvaginal natural orifice transluminal endoscopic surgery approach. International Journal of Gynecology and Obstetrics 158(3): 764-765	- Intervention in study does not match that specified in this review protocol *Pathology protocol not reported*
Gornjec, A., Merlo, S., Novakovic, S. et al. (2020) The prevalence of occult ovarian cancer in the series of 155 consequently operated	- The study's results are incorporated in an included

Study	Reason for exclusion
high risk asymptomatic patients - Slovenian population based study. Radiology and Oncology 54(2): 180-186	systematic review / meta-analysis *Included in Bogaerts 2022*
Haldar, K; Giamougiannis, P; Crawford, R (2011) Utility of peritoneal lavage cytology during laparoscopic salpingo-oophorectomy: a retrospective analysis. BJOG : an international journal of obstetrics and gynaecology 118(1): 28-33	- Pathology protocol does not match the review protocol *Cytology study*
Kotsopoulos, J., Karlan, B., Gronwald, J. et al. (2020) Long-term outcomes following a diagnosis of ovarian cancer at the time of preventive oophorectomy among BRCA1 and BRCA2 mutation carriers. International Journal of Gynecological Cancer 30(6): 825-830	- Intervention in study does not match that specified in this review protocol *Pathology protocol not reported*
Landon, G, Stewart, J, Deavers, M et al. (2012) Peritoneal washing cytology in patients with BRCA1 or BRCA2 mutations undergoing risk-reducing salpingo-oophorectomies: a 10-year experience and reappraisal of its clinical utility. Gynecologic oncology 125(3): 683-6	- Pathology protocol does not match the review protocol *Cytology study*
Laokulrath, N., Warnnissorn, M., Chuangsuwanich, T. et al. (2019) Sectioning and extensively examining the fimbriated end (SEE-FIM) of the fallopian tube in routine practices, is it worth the effort?. Journal of Obstetrics and Gynaecology Research 45(3): 665-670	- Population does not match the review protocol *Not just RRSO*
Lee, Y.-J., Lee, S.-W., Kim, K.-R. et al. (2017) Pathologic findings at risk-reducing salpingo-oophorectomy (RRSO) in germline BRCA mutation carriers with breast cancer: Significance of bilateral RRSO at the optimal age in germline BRCA mutation carriers. Journal of Gynecologic Oncology 28(1): e3	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022*
Leeper, K., Garcia, R., Swisher, E. et al. (2002) Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecologic Oncology 87(1): 52-56	- Study design does not match that specified in this review protocol *Case review*
Lu, K.H., Garber, J.E., Cramer, D.W. et al. (2000) Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. Journal of Clinical Oncology 18(14): 2728-2732	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Cheng 2020*
Mahe, E., Tang, S., Deb, P. et al. (2013) Do deeper sections increase the frequency of detection of serous tubal intraepithelial carcinoma (stic) in the sectioning and extensively examining the fimbriated end (see-fim) protocol?. International Journal of Gynecological Pathology 32(4): 353-357	- Population in study does not match that specified in this review protocol *Not RRSO*
Menkiszak, J., Chudecka-Glaz, A., Bedner, R. et al. (2012) Genital malignant tumors and precancerous conditions in female carriers of constitutional BRCA1 gene mutations undergoing prophylactic adnexectomy. Current Gynecologic Oncology 10(4): 270-285	- Outcome data relevant to the protocol cannot be extracted
Menkiszak, J., Chudecka-Glaz, A., Gronwald, J. et al. (2016) Prophylactic salpingo-oophorectomy in BRCA1 mutation carriers and postoperative incidence of peritoneal and breast cancers. Journal of Ovarian Research 9(1): 220	- Study design does not match that specified in this review protocol *Not concerned with pathological findings of RRSO*
Miller, H., Pipkin, L.S., Tung, C. et al. (2017) The Role of Routine Peritoneal and Omental Biopsies at Risk-Reducing Salpingo-Oophorectomy. Journal of Minimally Invasive Gynecology 24(5): 772-776	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Cheng 2020*

Study	Reason for exclusion
Morice, P., Pautier, P., Mercier, S. et al. (1999) Laparoscopic prophylactic oophorectomy in women with inherited risk of ovarian cancer. European Journal of Gynaecological Oncology 20(3): 202-204	- Outcome data relevant to the protocol cannot be extracted
Nomura, H., Ikki, A., Fusegi, A. et al. (2021) Clinical and pathological outcomes of risk-reducing salpingo-oophorectomy for Japanese women with hereditary breast and ovarian cancer. International Journal of Clinical Oncology 26(12): 2331-2337	- Population does not match the review protocol *Not RRSO* *Adnexectomy*
Olivier, R.I., Van Beurden, M., Lubsen, M.A.C. et al. (2004) Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. British Journal of Cancer 90(8): 1492-1497	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Cheng 2020*
Piek, J M, van Diest, P J, Zweemer, R P et al. (2001) Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. The Journal of pathology 195(4): 451-6	- Pathology protocol does not match the review protocol *Not SEE-FIM*
Powell, B.C., Kenley, E., Chen, L.-M. et al. (2005) Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: Role of serial sectioning in the detection of occult malignancy. Journal of Clinical Oncology 23(1): 127-132	- The study's results are incorporated in an included systematic review / meta-analysis *Cohort included in Cheng systematic review (as Powell 2011 study)*
Powell, C.B., Littell, R.D., Landen, C.N. et al. (2020) Cytological sampling of fallopian tubes using a hysteroscopic catheter: A multi-center study. Gynecologic Oncology 156(3): 636-640	- Pathology protocol does not match the review protocol *Cytology study*
Pramanik, Sharmila; Yang, Eric; Wu, Wendy (2020) Cytologic studies of in vivo fallopian tube specimens in patients undergoing salpingo-oophorectomy. CytoJournal 17: 19	- Pathology protocol does not match the review protocol *Cytology study*
Reitsma, W., De Bock, G.H., Oosterwijk, J.C. et al. (2013) Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. European Journal of Cancer 49(1): 132-141	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022*
Ricciardi, E., Tomao, F., Aletti, G. et al. (2017) Risk-reducing salpingo-oophorectomy in women at higher risk of ovarian and breast cancer: A single institution prospective series. Anticancer Research 37(9): 5241-5248	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022*
Rudaitis, V., Mikliusas, V., Januska, G. et al. (2020) The incidence of occult ovarian neoplasia and cancer in BRCA1/2 mutation carriers after the bilateral prophylactic salpingo-oophorectomy (PBSO): A single-center prospective study. European Journal of Obstetrics and Gynecology and Reproductive Biology 247: 26-31	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022*
Sherman, M.E., Piedmonte, M., Mai, P.L. et al. (2014) Pathologic findings at risk-reducing salpingo-oophorectomy: Primary results from Gynecologic Oncology Group trial GOG-0199. Journal of Clinical Oncology 32(29): 3275-3283	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022*
Stuckey, A., Dizon, D., Scalia Wilbur, J. et al. (2010) Clinical characteristics and choices regarding risk-reducing surgery in	- Intervention in study does not match that specified in this review protocol

Study	Reason for exclusion
BRCA mutation carriers. Gynecologic and Obstetric Investigation 69(4): 270-273	*Pathology protocol not reported*
Tait, D.L. (2005) Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: Role of serial sectioning in the detection of occult malignancy. Women's Oncology Review 5(2): 101-102	- Study design does not match that specified in this review protocol *Commentary on another article (Powell 2005)*
Thompson, C., McCormick, C., Kamran, W. et al. (2018) Risk reduction surgery (RRS) for tubo-ovarian cancer in an Irish gynaecological practice: an analysis of indications and outcomes. Irish Journal of Medical Science 187(3): 789-794	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022 and Cheng 2020*
Wethington, S.L., Park, K.J., Soslow, R.A. et al. (2013) Clinical outcome of isolated Serous tubal intraepithelial carcinomas (STIC). International Journal of Gynecological Cancer 23(9): 1603-1611	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022 and Cheng 2020*
Wong, S.; Ratner, E.; Buza, N. (2018) Intra-operative evaluation of prophylactic hysterectomy and salpingo-oophorectomy specimens in hereditary gynaecological cancer syndromes. Histopathology 73(1): 109-123	- The study's results are incorporated in an included systematic review / meta-analysis *Included in Bogaerts 2022 and Cheng 2020*

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 pathology protocol for handling specimens from risk reducing surgery should be followed for risk-reducing surgery for women at increased risk of familial ovarian cancer?

No research recommendations were made for this review question.

Appendix L Outcome data used in meta-analysis and meta-regression

Key to variables in Table 8 and Table 9:

- study_id – study identification variable
- source – source of the study
- age - mean age at surgery (median if mean was not reported)
- oc - number of ovarian carcinomas detected at RRSO
- stic - number of serous tubal intraepithelial carcinomas detected at RRSO
- brca_total - total number of women with *BRCA* mutation who underwent RRSO
- see_fim – whether the study reported the SEE-FIM protocol was used
- gynaecopath - whether the study reported a dedicated gynaecopathologist
- IHC – whether the study reported that immunohistochemistry was used

Table 8: Raw data used for the meta-analysis of ovarian cancer prevalence at RRSO

study_id	source	age	oc	brca_total	see_fim	gynaecopath	IHC	
Ayres 2017	Cheng 2020/ Bogaerts 2022	49.00	0	12	y	y	y	
Bacha 2012	Cheng 2020/ Bogaerts 2022	49	1	76	n	nr	nr	
Barrington 2018	Cheng 2020/ Bogaerts 2022	46.2	0	6	n	nr	nr	
Bogani 2017	Cheng 2020/ Bogaerts 2022	47	5	57	n	y	nr	
Carcangiu 2006	Cheng 2020/ Bogaerts 2022	na	3	50	y	nr	nr	
Cheng 2020 (1)	Cheng 2020/ Bogaerts 2022	48.5	0	9	n	nr	y	
Cheng 2020 (2)	Cheng 2020/ Bogaerts 2022	48.5	1	15	y	nr	y	
Colgan 2001	Cheng 2020/ Bogaerts 2022	48.4	4	39	n	nr	nr	
Conner 2013	Cheng 2020/ Bogaerts 2022	47.5	14	345	y	nr	y	
Evans 2009	Cheng 2020/ Bogaerts 2022	50.5	3	160	n	nr	nr	
Finch 2005	Cheng 2020/ Bogaerts 2022	47.9	6	159	y	y	nr	
Hirst 2009	Cheng 2020/ Bogaerts 2022	49	3	15	y	y	nr	
Kauff 2002	Cheng 2020/ Bogaerts 2022	47.5	3	98	n	nr	nr	
Kim 2015	Cheng 2020/ Bogaerts 2022	44.4	0	22	na	na	na	
Laki 2007	Cheng 2020/ Bogaerts 2022	46.8	4	89	y	nr	nr	
Lamb 2006	Cheng 2020/ Bogaerts 2022	47	3	62	y	y	nr	

study_id	source	age	oc	brca_total	see_fim	gynaecopath	IHC	
Lavie 2015	Cheng 2020/ Bogaerts 2022	53	5	92	na	na	na	
Lee 2017	Cheng 2020/ Bogaerts 2022	46.5	3	63	y	y	y	
Leunen 2006	Cheng 2020/ Bogaerts 2022	na	0	24	na	na	na	
Lu 2000	Cheng 2020/ Bogaerts 2022	na	2	23	y	y	nr	
Manchanda 2011	Cheng 2020/ Bogaerts 2022	48.9	4	117	y	y	nr	
McAlpine 2011	Cheng 2020/ Bogaerts 2022	50.45	1	11	y	na	na	
Miller 2017	Cheng 2020/ Bogaerts 2022	47.4	0	70	na	na	na	
Mingels 2012	Cheng 2020/ Bogaerts 2022	44	2	226	y	y	nr	
Minig 2018	Cheng 2020/ Bogaerts 2022	49.3	6	359	y	y	y	
Oliver 2004	Cheng 2020/ Bogaerts 2022	47.00	5	65	y	nr	y	
Powell 2011	Cheng 2020/ Bogaerts 2022	46	5	111	n	y	nr	
Primas 2012	Cheng 2020/ Bogaerts 2022	43.3	2	94	na	na	na	
Reistma 2013	Cheng 2020/ Bogaerts 2022	44.00	4	303	y	y	y	
Thompson 2018	Cheng 2020/ Bogaerts 2022	43	1	46	y	y	y	
Vd Hoven 2018	Cheng 2020/ Bogaerts 2022	na	3	235	n	nr	nr	
Wong 2018	Cheng 2020/ Bogaerts 2022	48.2	8	216	na	nr	nr	
Yates 2011	Cheng 2020/ Bogaerts 2022	47	3	136	n	na	na	
Zakhour 2016	Cheng 2020/ Bogaerts 2022	46	5	257	y	y	nr	
Pross 2021	Lit search	48.34	3	191	y	y	nr	
Rabban 2011	Lit search	46	4	134	n	y	nr	
Rhiem 2011	Lit search	47	1	175	n	nr	nr	

na: missing value; nr: not reported; RRSO: risk-reducing salpingo oophorectomy; SEE-FIM: protocol for sectioning and extensively examining the fimbriated end of the fallopian tube

Table 9: Raw data used for the meta-analysis of serous tubal intraepithelial carcinoma prevalence at RRSO

study_id	source	age	see_fim	gynaecopath	IHC	stic	brca_total
Artioli 2018	Cheng 2020/ Bogaerts 2022	47.9	y	y	nr	1	10

study_id	source	age	see_fim	gynae copath	IHC	stic	brca_total
Ayres 2017	Cheng 2020/ Bogaerts 2022	49	y	y	y	0	12
Bacha 2012	Cheng 2020/ Bogaerts 2022	49	n	n	nr	0	76
Blok 2019	Bogaerts 2022	na	n	y	y	4	527
Bogani 2017	Cheng 2020/ Bogaerts 2022	47	n	y	nr	2	57
Carcangiu 2004	Cheng 2020/ Bogaerts 2022	na	n	n	y	2	26
Carcangiu 2006	Cheng 2020/ Bogaerts 2022	na	y	n	nr	3	50
Cass 2014	Cheng 2020/ Bogaerts 2022	na	na	y	y	8	78
Cheng (1) 2020	Bogaerts 2022	48.5	n	n	y	0	9
Cheng (2) 2020	Bogaerts 2022	48.5	y	n	y	1	24
Conner 2014	Cheng 2020/ Bogaerts 2022	47.5	y	n	y	5	302
Gornjec 2020	Bogaerts 2022	48.3	y	n	nr	3	145
Hirst 2009	Cheng 2020/ Bogaerts 2022	49	y	y	nr	1	15
Lamb 2006	Cheng 2020/ Bogaerts 2022	47	y	y	nr	4	62
Lee (1) 2017	Cheng 2020/ Bogaerts 2022	48.5	n	n	y	2	130
Lee (2) 2017	Cheng 2020/ Bogaerts 2022	46.5	y	y	y	2	36
Leonhardt 2011	Cheng 2020/ Bogaerts 2022	na	na	n	y	0	14
Malmberg 2016	Cheng 2020/ Bogaerts 2022	52.1	n	n	y	1	42
Manchanda 2011	Cheng 2020/ Bogaerts 2022	48.9	y	y	nr	6	117
Mingels 2012	Cheng 2020/ Bogaerts 2022	44	y	y	nr	14	226
Minig 2018	Cheng 2020/ Bogaerts 2022	49.3	y	y	y	3	359
Poon 2016	Cheng 2020/ Bogaerts 2022	51.75	y	y	y	3	72
Powell 2011	Cheng 2020/ Bogaerts 2022	46	n	y	nr	5	111
Powell 2013	Cheng 2020/ Bogaerts 2022	na	na	y	nr	17	405
Rabban 2009	Cheng 2020/ Bogaerts 2022	na	y	y	y	5	102
Reitsma 2013	Cheng 2020/ Bogaerts 2022	44	y	y	y	3	303
Ricciardi 2017	Cheng 2020/ Bogaerts 2022	na	y	y	y	7	290

study_id	source	age	see_fim	gynae copath	IHC	stic	brca_total
Rudaitis 2019	Bogaerts 2022	na	y	n	y	7	71
Rush 2020	Bogaerts 2022	na	na	y	nr	8	371
Shaw 2009	Cheng 2020/ Bogaerts 2022	47	n	y	y	15	176
Sherman 2014	Cheng 2020/ Bogaerts 2022	na	n	y	nr	4	559
Stanciu 2019	Bogaerts 2022	47.8	y	y	y	6	244
Stewart 2019	Bogaerts 2022	48.32	y	n	nr	3	61
Thompson 2018	Cheng 2020/ Bogaerts 2022	43	y	y	y	0	46
Vd Hoeven 2018	Cheng 2020/ Bogaerts 2022	na	n	n	nr	2	235
Visvanathan 2018	Cheng 2020/ Bogaerts 2022	48.3	y	y	y	12	366
Wethington 2013	Cheng 2020/ Bogaerts 2022	54	y	y	y	10	375
Wilhite 2019	Bogaerts 2022	49	y	n	nr	7	290
Wong 2018	Cheng 2020/ Bogaerts 2022	48.2	na	n	nr	3	197
Zakhour 2016	Cheng 2020/ Bogaerts 2022	46	y	y	nr	9	251
Pross 2021	Lit search	48.34	y	y	nr	2	187
Samimi 2018	Lit search	45.9	y	y	y	5	354

na: missing value; nr: not reported; RRSO: risk-reducing salpingo oophorectomy; SEE-FIM: protocol for sectioning and extensively examining the fimbriated end of the fallopian tube

Meta-analytic and meta-regression analysis output from R-studio

[1] "*********oc--overall*********"

Review: oc – overall

	events	95%-CI	%W(common)	%W(random)
Ayres 2017	0.0000	[0.0000; 26.4648]	0.4	0.7
Bacha 2012	1.3158	[0.0333; 7.1144]	0.9	1.3
Barrington 2018	0.0000	[0.0000; 45.9258]	0.4	0.7
Bogani 2017	8.7719	[2.9099; 19.2957]	4.0	3.8
Carcangiu 2006	6.0000	[1.2549; 16.5482]	2.5	2.9
Cheng 2020 (1)	0.0000	[0.0000; 33.6267]	0.4	0.7
Cheng 2020 (2)	6.6667	[0.1686; 31.9485]	0.8	1.3
Colgan 2001	10.2564	[2.8660; 24.2210]	3.1	3.4
Conner 2013	4.0580	[2.2360; 6.7149]	11.7	5.9
Evans 2009	1.8750	[0.3884; 5.3816]	2.6	3.0
Finch 2005	3.7736	[1.3972; 8.0323]	5.0	4.3

Hirst 2009	20.0000	[4.3312; 48.0891]	2.1		2.6
Kauff 2002	3.0612	[0.6358; 8.6863]	2.5		3.0
Kim 2015	0.0000	[0.0000; 15.4373]	0.4		0.7
Laki 2007	4.4944	[1.2380; 11.1092]	3.3		3.5
Lamb 2006	4.8387	[1.0092; 13.4962]	2.5		2.9
Lavie 2015	5.4348	[1.7880; 12.2287]	4.1		3.9
Lee 2017	4.7619	[0.9930; 13.2918]	2.5		2.9
Leunen 2006	0.0000	[0.0000; 14.2474]	0.4		0.7
Lu 2000	8.6957	[1.0710; 28.0379]	1.6		2.1
Manchanda 2011	3.4188	[0.9392; 8.5224]	3.4		3.5
McAlpine 2011	9.0909	[0.2299; 41.2780]	0.8		1.2
Miller 2017	0.0000	[0.0000; 5.1334]	0.4		0.7
Mingels 2012	0.8850	[0.1074; 3.1600]	1.7		2.3
Minig 2018	1.6713	[0.6157; 3.6021]	5.1		4.4
Oliver 2004	7.6923	[2.5448; 17.0456]	4.0		3.9
Powell 2011	4.5045	[1.4786; 10.1993]	4.2		3.9
Primas 2012	2.1277	[0.2587; 7.4752]	1.7		2.3
Reistma 2013	1.3201	[0.3608; 3.3454]	3.4		3.5
Thompson 2018	2.1739	[0.0550; 11.5272]	0.9		1.3
Vd Hoven 2018	1.2766	[0.2640; 3.6852]	2.6		3.0
Wong 2018	3.7037	[1.6123; 7.1671]	6.7	4.9	
Yates 2011	2.2059	[0.4572; 6.3111]	2.6		3.0
Zakhour 2016	1.9455	[0.6347; 4.4816]	4.3		4.0
Pross 2021	1.5707	[0.3251; 4.5213]	2.6		3.0
Rabban 2011	2.9851	[0.8192; 7.4665]	3.4		3.5
Rhiem 2011	0.5714	[0.0145; 3.1425]	0.9		1.3

Number of studies combined: k = 37

Number of observations: o = 4162

Number of events: e = 117

events 95%-CI

Common effect model	3.5633	[2.9849; 4.2489]
Random effects model	3.4938	[2.7481; 4.4325]

Quantifying heterogeneity:

tau^2 = 0.1969 [0.0029; 0.5946]; tau = 0.4437 [0.0540; 0.7711]

I^2 = 34.5% [1.9%; 56.2%]; H = 1.24 [1.01; 1.51]

Test of heterogeneity:

Q	d.f.	p-value
54.93	36	0.0225

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 33; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-36.8964	73.7927	79.7927	84.0947	80.6816

tau^2 (estimated amount of residual heterogeneity): 0.1714 (SE = 0.1252)

tau (square root of estimated tau^2 value): 0.4140

I^2 (residual heterogeneity / unaccounted variability): 35.03%

H^2 (unaccounted variability / sampling variability): 1.54

R^2 (amount of heterogeneity accounted for): 8.34%

Test for Residual Heterogeneity:

QE(df = 31) = 45.2882, p-val = 0.0470

Test of Moderators (coefficient 2):
QM(df = 1) = 2.9481, p-val = 0.0860

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-8.4930	3.0161	-2.8159	0.0049	-14.4044	-2.5816	**
age	0.1090	0.0635	1.7170	0.0860	-0.0154	0.2334	.

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

[1] "*********oc--IHC*********"
Review: oc -- IHC

	events	95%-CI	%W(common)	%W(random)
Ayres 2017	0.0000	[0.0000; 26.4648]	1.4	3.1
Cheng 2020 (1)	0.0000	[0.0000; 33.6267]	1.4	3.0
Cheng 2020 (2)	6.6667	[0.1686; 31.9485]	2.8	5.4
Conner 2013	4.0580	[2.2360; 6.7149]	40.0	22.9
Lee 2017	4.7619	[0.9930; 13.2918]	8.5	12.1
Minig 2018	1.6713	[0.6157; 3.6021]	17.5	17.5
Oliver 2004	7.6923	[2.5448; 17.0456]	13.7	15.7
Reistma 2013	1.3201	[0.3608; 3.3454]	11.7	14.5
Thompson 2018	2.1739	[0.0550; 11.5272]	2.9	5.6

Number of studies combined: k = 9
Number of observations: o = 1217
Number of events: e = 34

	events	95%-CI
Common effect model	3.3805	[2.4345; 4.6765]
Random effects model	3.3364	[2.0072; 5.4966]

Quantifying heterogeneity:

tau^2 = 0.2346 [0.0000; 1.0952]; tau = 0.4844 [0.0000; 1.0465]

I^2 = 32.3% [0.0%; 68.7%]; H = 1.22 [1.00; 1.79]

Test of heterogeneity:

Q	d.f.	p-value
11.81	8	0.1598

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 9; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-8.4923	16.9846	22.9846	22.8223	30.9846

tau^2 (estimated amount of residual heterogeneity): 0.2968 (SE = 0.3595)

tau (square root of estimated tau^2 value): 0.5448

I^2 (residual heterogeneity / unaccounted variability): 48.12%

H^2 (unaccounted variability / sampling variability): 1.93

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:

QE(df = 7) = 11.4715, p-val = 0.1193

Test of Moderators (coefficient 2):

QM(df = 1) = 0.3876, p-val = 0.5336

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-7.7158	6.9960	-1.1029	0.2701	-21.4276	5.9961
age	0.0927	0.1488	0.6226	0.5336	-0.1991	0.3844

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

[1] "*********oc--see_fim*********"

Review: oc -- see_fim

	events	95%-CI	%W(common)	%W(random)
Ayres 2017	0.0000	[0.0000; 26.4648]	0.7	1.4
Carcangiu 2006	6.0000	[1.2549; 16.5482]	4.2	5.3
Cheng 2020 (2)	6.6667	[0.1686; 31.9485]	1.4	2.4
Conner 2013	4.0580	[2.2360; 6.7149]	20.0	9.6
Finch 2005	3.7736	[1.3972; 8.0323]	8.6	7.4
Hirst 2009	20.0000	[4.3312; 48.0891]	3.6	4.8
Laki 2007	4.4944	[1.2380; 11.1092]	5.7	6.2
Lamb 2006	4.8387	[1.0092; 13.4962]	4.2	5.3
Lee 2017	4.7619	[0.9930; 13.2918]	4.2	5.3
Lu 2000	8.6957	[1.0710; 28.0379]	2.7	4.0
Manchanda 2011	3.4188	[0.9392; 8.5224]	5.7	6.2
McAlpine 2011	9.0909	[0.2299; 41.2780]	1.4	2.4
Mingels 2012	0.8850	[0.1074; 3.1600]	2.9	4.2

Minig 2018	1.6713	[0.6157; 3.6021]	8.8	7.5
Oliver 2004	7.6923	[2.5448; 17.0456]	6.9	6.8
Reistma 2013	1.3201	[0.3608; 3.3454]	5.9	6.3
Thompson 2018	2.1739	[0.0550; 11.5272]	1.5	2.5
Zakhour 2016	1.9455	[0.6347; 4.4816]	7.3	6.9
Pross 2021	1.5707	[0.3251; 4.5213]	4.4	5.4

Number of studies combined: k = 19

Number of observations: o = 2408

Number of events: e = 70

	events	95%-CI
Common effect model	3.5854	[2.8449; 4.5098]
Random effects model	3.6793	[2.6096; 5.1642]

Quantifying heterogeneity:

tau^2 = 0.2672 [0.0095; 1.0327]; tau = 0.5169 [0.0977; 1.0162]

I^2 = 44.7% [5.1%; 67.7%]; H = 1.34 [1.03; 1.76]

Test of heterogeneity:

Q	d.f.	p-value
32.52	18	0.0191

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 17; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-17.2995	34.5991	40.5991	42.7232	42.7809

tau^2 (estimated amount of residual heterogeneity): 0.2364 (SE = 0.1973)
tau (square root of estimated tau^2 value): 0.4862
I^2 (residual heterogeneity / unaccounted variability): 45.61%
H^2 (unaccounted variability / sampling variability): 1.84
R^2 (amount of heterogeneity accounted for): 15.34%

Test for Residual Heterogeneity:
QE(df = 15) = 25.4562, p-val = 0.0441

Test of Moderators (coefficient 2):
QM(df = 1) = 3.6160, p-val = 0.0572

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-12.8373	4.9995	-2.5677	0.0102	-22.6362	-3.0385	*
age	0.2012	0.1058	1.9016	0.0572	-0.0062	0.4086	.

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

[1] "*********oc--gynaecopath*********"
Review: oc -- gynaecopath

	events	95%-CI	%W(common)	%W(random)
Ayres 2017	0.0000	[0.0000; 26.4648]	0.9	1.8
Bogani 2017	8.7719	[2.9099; 19.2957]	8.5	7.6

Finch 2005	3.7736	[1.3972; 8.0323]	10.7	8.3
Hirst 2009	20.0000	[4.3312; 48.0891]	4.4	5.6
Lamb 2006	4.8387	[1.0092; 13.4962]	5.3	6.2
Lee 2017	4.7619	[0.9930; 13.2918]	5.3	6.2
Lu 2000	8.6957	[1.0710; 28.0379]	3.4	4.8
Manchanda 2011	3.4188	[0.9392; 8.5224]	7.2	7.1
Mingels 2012	0.8850	[0.1074; 3.1600]	3.7	5.0
Minig 2018	1.6713	[0.6157; 3.6021]	10.9	8.3
Powell 2011	4.5045	[1.4786; 10.1993]	8.9	7.7
Reistma 2013	1.3201	[0.3608; 3.3454]	7.3	7.2
Thompson 2018	2.1739	[0.0550; 11.5272]	1.8	3.1
Zakhour 2016	1.9455	[0.6347; 4.4816]	9.1	7.8
Pross 2021	1.5707	[0.3251; 4.5213]	5.5	6.3
Rabban 2011	2.9851	[0.8192; 7.4665]	7.2	7.1

Number of studies combined: k = 16

Number of observations: o = 2135

Number of events: e = 56

	events	95%-CI
Common effect model	3.2990	[2.5459; 4.2650]
Random effects model	3.3853	[2.2838; 4.9909]

Quantifying heterogeneity:

tau^2 = 0.3429 [0.0398; 1.3301]; tau = 0.5856 [0.1995; 1.1533]

I^2 = 51.8% [14.6%; 72.8%]; H = 1.44 [1.08; 1.92]

Test of heterogeneity:

Q	d.f.	p-value
31.10	15	0.0085

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 15; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-15.6543	31.3087	37.3087	39.0035	39.9753

tau^2 (estimated amount of residual heterogeneity): 0.3200 (SE = 0.2459)
tau (square root of estimated tau^2 value): 0.5657
I^2 (residual heterogeneity / unaccounted variability): 52.11%
H^2 (unaccounted variability / sampling variability): 2.09
R^2 (amount of heterogeneity accounted for): 4.59%

Test for Residual Heterogeneity:
QE(df = 13) = 26.4592, p-val = 0.0147

Test of Moderators (coefficient 2):
QM(df = 1) = 2.1173, p-val = 0.1456

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-11.4069	5.5053	-2.0720	0.0383	-22.1972	-0.6167	*
age	0.1708	0.1173	1.4551	0.1456	-0.0592	0.4007	

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

[1] "*********stic--overall*********"

Review: stic -- overall

	events	95%-CI	%W(common)	%W(random)
Artioli 2018	10.0000	[0.2529; 44.5016]	0.5	1.1
Ayres 2017	0.0000	[0.0000; 26.4648]	0.3	0.7
Bacha 2012	0.0000	[0.0000; 4.7379]	0.3	0.7
Blok 2019	0.7590	[0.2072; 1.9319]	2.1	2.7
Bogani 2017	3.5088	[0.4278; 12.1071]	1.0	1.9
Carcangiu 2004	7.6923	[0.9455; 25.1303]	1.0	1.8
Carcangiu 2006	6.0000	[1.2549; 16.5482]	1.5	2.3
Cass 2014	10.2564	[4.5331; 19.2127]	3.8	3.3
Cheng (1) 2020	0.0000	[0.0000; 33.6267]	0.3	0.7
Cheng (2) 2020	6.6667	[0.1686; 31.9485]	0.5	1.2
Conner 2014	1.6556	[0.5397; 3.8212]	2.6	2.9
Gornjec 2020	2.0690	[0.4287; 5.9272]	1.6	2.4
Hirst 2009	6.6667	[0.1686; 31.9485]	0.5	1.2
Lamb 2006	6.4516	[1.7857; 15.7028]	2.0	2.6
Lee (1) 2017	1.5385	[0.1869; 5.4469]	1.0	1.9
Lee (2) 2017	5.5556	[0.6800; 18.6637]	1.0	1.9
Leonhardt 2011	0.0000	[0.0000; 23.1636]	0.3	0.7
Malmberg 2016	2.3810	[0.0603; 12.5659]	0.5	1.2
Manchanda 2011	5.1282	[1.9050; 10.8280]	3.0	3.1
Mingels 2012	6.1947	[3.4277; 10.1753]	7.0	3.8
Minig 2018	0.8357	[0.1727; 2.4226]	1.6	2.4
Poon 2016	4.1667	[0.8676; 11.6975]	1.5	2.3
Powell 2011	4.5045	[1.4786; 10.1993]	2.5	2.9
Powell 2013	4.1975	[2.4639; 6.6357]	8.6	3.9
Rabban 2009	4.9020	[1.6106; 11.0696]	2.5	2.9
Reitsma 2013	0.9901	[0.2046; 2.8661]	1.6	2.4

Ricciardi 2017	2.4138	[0.9759; 4.9099]	3.6	3.3
Rudaitis 2019	9.8592	[4.0566; 19.2644]	3.3	3.2
Rush 2020	2.1563	[0.9354; 4.2045]	4.1	3.4
Shaw 2009	8.5227	[4.8487; 13.6673]	7.3	3.8
Sherman 2014	0.7156	[0.1953; 1.8219]	2.1	2.7
Stanciu 2019	2.4590	[0.9076; 5.2751]	3.1	3.1
Stewart 2019	4.9180	[1.0259; 13.7069]	1.5	2.3
Thompson 2018	0.0000	[0.0000; 7.7062]	0.3	0.7
Vd Hoeven 2018	0.8511	[0.1032; 3.0403]	1.0	1.9
Visvanathan 2018	3.2787	[1.7054; 5.6571]	6.1	3.7
Wethington 2013	2.6667	[1.2860; 4.8493]	5.2	3.6
Wilhite 2019	2.4138	[0.9759; 4.9099]	3.6	3.3
Wong 2018	1.5228	[0.3152; 4.3857]	1.6	2.4
Zakhour 2016	3.5857	[1.6525; 6.6973]	4.6	3.5
Pross 2021	1.0695	[0.1298; 3.8099]	1.0	1.9
Samimi 2018	1.4124	[0.4602; 3.2652]	2.6	2.9

Number of studies combined: k = 42

Number of observations: o = 7374

Number of events: e = 195

	events	95%-CI
Common effect model	3.4684	[3.0213; 3.9788]
Random effects model	3.1087	[2.4338; 3.9630]

Quantifying heterogeneity:

tau^2 = 0.3609 [0.1299; 0.6860]; tau = 0.6008 [0.3604; 0.8283]

I^2 = 59.3% [42.9%; 71.0%]; H = 1.57 [1.32; 1.86]

Test of heterogeneity:

Q	d.f.	p-value
100.85	41	< 0.0001

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 30; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-32.6497	65.2994	71.2994	75.2960	72.2994

tau^2 (estimated amount of residual heterogeneity):	0.2242 (SE = 0.1372)
tau (square root of estimated tau^2 value):	0.4735
I^2 (residual heterogeneity / unaccounted variability):	46.40%
H^2 (unaccounted variability / sampling variability):	1.87
R^2 (amount of heterogeneity accounted for):	0.00%

Test for Residual Heterogeneity:

QE(df = 28) = 50.5537, p-val = 0.0056

Test of Moderators (coefficient 2):

QM(df = 1) = 0.2482, p-val = 0.6183

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-2.0536	2.8006	-0.7333	0.4634	-7.5427	3.4355
age	-0.0291	0.0584	-0.4982	0.6183	-0.1437	0.0854

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

[1] "*********stic--IHC*********"

Review: stic -- IHC

	events	95%-CI	%W(common)	%W(random)
Ayres 2017	0.0000	[0.0000; 26.4648]	0.5	1.5
Blok 2019	0.7590	[0.2072; 1.9319]	4.0	5.1
Carcangiu 2004	7.6923	[0.9455; 25.1303]	1.9	3.7
Cass 2014	10.2564	[4.5331; 19.2127]	7.3	6.0
Cheng (1) 2020	0.0000	[0.0000; 33.6267]	0.5	1.4
Cheng (2) 2020	6.6667	[0.1686; 31.9485]	1.0	2.4
Conner 2014	1.6556	[0.5397; 3.8212]	5.0	5.4
Lee (1) 2017	1.5385	[0.1869; 5.4469]	2.0	3.8
Lee (2) 2017	5.5556	[0.6800; 18.6637]	1.9	3.7
Leonhardt 2011	0.0000	[0.0000; 23.1636]	0.5	1.5
Malmberg 2016	2.3810	[0.0603; 12.5659]	1.0	2.5
Minig 2018	0.8357	[0.1727; 2.4226]	3.0	4.6
Poon 2016	4.1667	[0.8676; 11.6975]	2.9	4.5
Rabban 2009	4.9020	[1.6106; 11.0696]	4.8	5.4
Reitsma 2013	0.9901	[0.2046; 2.8661]	3.0	4.6
Ricciardi 2017	2.4138	[0.9759; 4.9099]	7.0	5.9
Rudaitis 2019	9.8592	[4.0566; 19.2644]	6.4	5.8
Shaw 2009	8.5227	[4.8487; 13.6673]	14.0	6.7
Stanciu 2019	2.4590	[0.9076; 5.2751]	6.0	5.7
Thompson 2018	0.0000	[0.0000; 7.7062]	0.5	1.5
Visvanathan 2018	3.2787	[1.7054; 5.6571]	11.8	6.6
Wethington 2013	2.6667	[1.2860; 4.8493]	9.9	6.4
Samimi 2018	1.4124	[0.4602; 3.2652]	5.0	5.4

Number of studies combined: k = 23

Number of observations: o = 3949

Number of events: e = 101

	events	95%-CI
Common effect model	3.5006	[2.8905; 4.2339]
Random effects model	3.0914	[2.1353; 4.4562]

Quantifying heterogeneity:

tau^2 = 0.4867 [0.1363; 1.0083]; tau = 0.6976 [0.3692; 1.0041]

I^2 = 66.2% [47.7%; 78.2%]; H = 1.72 [1.38; 2.14]

Test of heterogeneity:

Q	d.f.	p-value
65.17	22	< 0.0001

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 16; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-17.2770	34.5540	40.5540	42.4712	42.9540

tau^2 (estimated amount of residual heterogeneity): 0.3480 (SE = 0.2598)

tau (square root of estimated tau^2 value): 0.5899

I^2 (residual heterogeneity / unaccounted variability): 55.95%

H^2 (unaccounted variability / sampling variability): 2.27

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:

QE(df = 14) = 34.1658, p-val = 0.0020

Test of Moderators (coefficient 2):

QM(df = 1) = 0.3194, p-val = 0.5720

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-5.7843	3.8332	-1.5090	0.1313	-13.2972	1.7287
age	0.0447	0.0791	0.5652	0.5720	-0.1103	0.1997

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

[1] "*********stic--see_fim*********"

Review: stic -- see_fim

	events	95%-CI	%W(common)	%W(random)
Artioli 2018	10.0000	[0.2529; 44.5016]	0.8	1.4
Ayres 2017	0.0000	[0.0000; 26.4648]	0.4	0.8
Carcangiu 2006	6.0000	[1.2549; 16.5482]	2.4	3.3
Cheng (2) 2020	6.6667	[0.1686; 31.9485]	0.8	1.5
Conner 2014	1.6556	[0.5397; 3.8212]	4.2	4.6
Gornjec 2020	2.0690	[0.4287; 5.9272]	2.5	3.4
Hirst 2009	6.6667	[0.1686; 31.9485]	0.8	1.5
Lamb 2006	6.4516	[1.7857; 15.7028]	3.2	4.0
Lee (2) 2017	5.5556	[0.6800; 18.6637]	1.6	2.5

Manchanda 2011	5.1282	[1.9050; 10.8280]	4.8	4.9
Mingels 2012	6.1947	[3.4277; 10.1753]	11.1	6.7
Minig 2018	0.8357	[0.1727; 2.4226]	2.5	3.4
Poon 2016	4.1667	[0.8676; 11.6975]	2.4	3.4
Rabban 2009	4.9020	[1.6106; 11.0696]	4.0	4.5
Reitsma 2013	0.9901	[0.2046; 2.8661]	2.5	3.4
Ricciardi 2017	2.4138	[0.9759; 4.9099]	5.8	5.3
Rudaitis 2019	9.8592	[4.0566; 19.2644]	5.3	5.2
Stanciu 2019	2.4590	[0.9076; 5.2751]	5.0	5.0
Stewart 2019	4.9180	[1.0259; 13.7069]	2.4	3.4
Thompson 2018	0.0000	[0.0000; 7.7062]	0.4	0.8
Visvanathan 2018	3.2787	[1.7054; 5.6571]	9.8	6.5
Wethington 2013	2.6667	[1.2860; 4.8493]	8.2	6.1
Wilhite 2019	2.4138	[0.9759; 4.9099]	5.8	5.3
Zakhour 2016	3.5857	[1.6525; 6.6973]	7.4	5.9
Pross 2021	1.0695	[0.1298; 3.8099]	1.7	2.6
Samimi 2018	1.4124	[0.4602; 3.2652]	4.2	4.6

Number of studies combined: k = 26

Number of observations: o = 4361

Number of events: e = 122

	events	95%-CI
Common effect model	3.3813	[2.8390; 4.0228]
Random effects model	3.2759	[2.5288; 4.2341]

Quantifying heterogeneity:

tau^2 = 0.2001 [0.0243; 0.6315]; tau = 0.4473 [0.1558; 0.7947]

I^2 = 45.2% [12.9%; 65.4%]; H = 1.35 [1.07; 1.70]

Test of heterogeneity:

Q	d.f.	p-value

45.58 25 0.0072

Details on meta-analytical method:
- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 22; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc
-22.5076	45.0151	51.0151	54.0023	52.5151

tau^2 (estimated amount of residual heterogeneity):	0.1766 (SE = 0.1383)
tau (square root of estimated tau^2 value):	0.4202
I^2 (residual heterogeneity / unaccounted variability):	41.63%
H^2 (unaccounted variability / sampling variability):	1.71
R^2 (amount of heterogeneity accounted for):	0.00%

Test for Residual Heterogeneity:
QE(df = 20) = 33.0778, p-val = 0.0331

Test of Moderators (coefficient 2):
QM(df = 1) = 0.0150, p-val = 0.9025

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-3.1495	2.7532	-1.1439	0.2526	-8.5457	2.2467

age -0.0070 0.0574 -0.1225 0.9025 -0.1195 0.1054

Signif. Codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

[1] "*********stic–gynaecopath*********"

Review: stic – gynaecopath

	events	95%-CI	%W(common)	%W(random)
Artioli 2018	10.0000	[0.2529; 44.5016]	0.6	1.6
Ayres 2017	0.0000	[0.0000; 26.4648]	0.3	1.0
Blok 2019	0.7590	[0.2072; 1.9319]	2.6	3.8
Bogani 2017	3.5088	[0.4278; 12.1071]	1.3	2.7
Cass 2014	10.2564	[4.5331; 19.2127]	4.8	4.6
Hirst 2009	6.6667	[0.1686; 31.9485]	0.6	1.7
Lamb 2006	6.4516	[1.7857; 15.7028]	2.5	3.7
Lee (2) 2017	5.5556	[0.6800; 18.6637]	1.3	2.7
Manchanda 2011	5.1282	[1.9050; 10.8280]	3.8	4.3
Mingels 2012	6.1947	[3.4277; 10.1753]	8.7	5.2
Minig 2018	0.8357	[0.1727; 2.4226]	2.0	3.4
Poon 2016	4.1667	[0.8676; 11.6975]	1.9	3.3
Powell 2011	4.5045	[1.4786; 10.1993]	3.2	4.1
Powell 2013	4.1975	[2.4639; 6.6357]	10.8	5.4
Rabban 2009	4.9020	[1.6106; 11.0696]	3.2	4.1
Reitsma 2013	0.9901	[0.2046; 2.8661]	2.0	3.4
Ricciardi 2017	2.4138	[0.9759; 4.9099]	4.6	4.5
Rush 2020	2.1563	[0.9354; 4.2045]	5.2	4.7
Shaw 2009	8.5227	[4.8487; 13.6673]	9.1	5.2
Sherman 2014	0.7156	[0.1953; 1.8219]	2.6	3.8
Stanciu 2019	2.4590	[0.9076; 5.2751]	3.9	4.3
Thompson 2018	0.0000	[0.0000; 7.7062]	0.3	1.0
Visvanathan 2018	3.2787	[1.7054; 5.6571]	7.7	5.1
Wethington 2013	2.6667	[1.2860; 4.8493]	6.5	4.9

Zakhour 2016	3.5857	[1.6525; 6.6973]	5.8	4.8
Pross 2021	1.0695	[0.1298; 3.8099]	1.3	2.7
Samimi 2018	1.4124	[0.4602; 3.2652]	3.3	4.1

Number of studies combined: k = 27

Number of observations: o = 5711

Number of events: e = 156

	events	95%-CI
Common effect model	3.5585	[3.0485; 4.1503]
Random effects model	3.1479	[2.3350; 4.2314]

Quantifying heterogeneity:

tau^2 = 0.3953 [0.1465; 0.9402]; tau = 0.6287 [0.3828; 0.9696]

I^2 = 65.8% [48.7%; 77.2%]; H = 1.71 [1.40; 2.09]

Test of heterogeneity:

Q	d.f.	p-value
76.07	26	< 0.0001

Details on meta-analytical method:

- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies
- Events per 100 observations

Mixed-Effects Model (k = 20; tau^2 estimator: REML)

logLik	deviance	AIC	BIC	AICc

-21.5603 43.1206 49.1206 51.7918 50.8349

Tau^2 (estimated amount of residual heterogeneity):	0.2882 (SE = 0.1842)
tau (square root of estimated tau^2 value):	0.5368
I^2 (residual heterogeneity / unaccounted variability):	56.68%
H^2 (unaccounted variability / sampling variability):	2.31
R^2 (amount of heterogeneity accounted for):	0.00%

Test for Residual Heterogeneity:
QE(df = 18) = 39.9332, p-val = 0.0021

Test of Moderators (coefficient 2):
QM(df = 1) = 0.0498, p-val = 0.8233

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-2.6451	3.1375	-0.8431	0.3992	-8.7945	3.5043
age	-0.0147	0.0658	-0.2233	0.8233	-0.1437	0.1143

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1