National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[M] Preventive medicines

NICE guideline NG241

Evidence review underpinning recommendations 1.7.1 to 1.7.4 and research recommendation 6 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

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Preventive medicines

Review question

How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Introduction

Women with a familial ovarian cancer risk are motivated to take steps to reduce their risk of developing ovarian cancer. These women are offered surgery to remove their tubes and ovaries to mitigate this risk; however, surgery comes with its own inherent risk which may be unacceptable to some. Other women with familial ovarian cancer do not wish to have surgery due to its impact on fertility. Finally, others are not well enough to have the risk reducing surgery. In addition, surgery cannot reduce the risk of developing ovarian cancer completely. Therefore, other ways to reduce an individual's risk of familial ovarian cancer are a priority to those with an inherited risk and their clinicians. It is known that certain medications can reduce the risk of ovarian cancer in all or specific inherited ovarian cancer syndromes. The evidence review will consider those medications, the evidence that supports them, their side effects and the effective doses needed to reduce ovarian cancer in those with a familial ovarian cancer risk.

Summary of the protocol

See **Table 1** for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women at increased risk of familial ovarian cancer
Intervention	Medicines: • oral contraceptives • NSAIDs
Comparison	In comparison with: • each other • placebo
Outcome	**Critical** • ovarian cancer incidence • health related quality of life (measured using a validated scale) **Important** • treatment related adverse effects • overall survival

NSAIDS: non-steroidal anti-inflammatory drugs

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.

Effectiveness evidence

Included studies

Eight studies were included for this review, 1 systematic review of case-control and cohort studies (van Bommel 2023), 3 individual patient data meta-analyses (Hurwitz 2021, Hurwitz 2022, Hurwitz 2023), 1 cohort study (Michels 2018) and 3 case-control studies (Gross 1992, McLaughlin 2007, Vicus 2009).

Three individual patient data meta-analyses (Hurwitz 2021, Hurwitz 2022, Hurwitz 2023) compared frequent/daily aspirin use to infrequent/no aspirin use. Although there was some overlap in the study participants included in these studies, the studies focused on, and analysed different populations, namely women with a history of ovarian cancer only (Hurwitz 2021), women with a history of both ovarian cancer or breast cancer (Hurwitz 2022) and women with genetic data available (Hurwitz 2023). One systematic review compared oral contraceptive use to no oral contraceptive use among *BRCA1/2* carriers (van Bommel 2023). One cohort study (Michels 2018) compared oral contraceptive use to no oral contraceptive use. Three case-controls studies compared oral contraceptive use to no oral contraceptive use (Gross 1992, McLaughlin 2007, Vicus 2009).

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

The landmark CAPP2 trial (Burn 2020) comparing aspirin to placebo for cancer prevention in people with Lynch syndrome could not be included as results were not reported separately for women.

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	Intervention	Comparison	Outcomes
Gross 1992 Case-control USA	N total=130 women with a family history of ovarian cancer n=31 women with epithelial ovarian cancer, n=16 used oral contraceptive and n=15 did not use it Age reported for all cases of ovarian cancer in the cohort (n=283): age mean (SD): not reported. Age by	Oral contraceptive use	No oral contraceptive use	• Epithelian ovarian cancer incidence

Study	Population	Intervention	Comparison	Outcomes
	category (years): 20-29=7%, 30-39=11%, 40-49=40%, 50-54=42% n=99 controls, n=52 used oral contraceptive and n=47did not use it Age reported for all controls in the cohort (n=1929): age mean (SD): not reported. Age by category (years): 20-29=5%, 30-39=12%, 40-49=43%, 50-54=40%			
Hurwitz 2021 IPD meta-analysis USA	N=7074 women with a family history of ovarian cancer n=1446 daily aspirin use n=5628 no daily aspirin use Age by category of aspirin use for the whole cohort reported (mean (SD), years): aspirin use = 63.4 (5.3), no aspirin use = 62.21 (5.39)	Daily aspirin use	No daily aspirin use	• Ovarian cancer incidence
Hurwitz 2022 IPD meta-analysis USA	N=505404 Participants identified from 9 cohort studies and 8 case-control studies. Age mean (SD): ranged from 46 to 68.2 years in the cohort studies (SD not reported) and the median ranged from 56.2 to 60.7 years in the cases in the	Frequent aspirin use (aspirin use for ≥6 days/week or ≥28 days/month and for a duration of ≥6 months)	Non-frequent aspirin use (no less frequent use than intervention group)	• Ovarian cancer incidence

Study	Population	Intervention	Comparison	Outcomes
	case-control studies. Not reported for the controls.			
Hurwitz 2023 IPD meta-analysis USA	N=11135 Participants identified from 8 case-control studies Age mean (SD): not reported. Age, median (IQR): 58 (50-66) years for cases and 57 (49-65) years for controls	Frequent aspirin use (daily or almost daily use of aspirin for ≥6 months)	Non-frequent aspirin use (less frequent use than intervention group)	• Ovarian cancer incidence
McLaughlin 2007 Case-control Multinational, Canada	N total=3223 women with *BRCA1*/2 mutation n=799 women with invasive ovarian cancer Age at questionnaire* (median (range), years): 53 (27-81) n=2424 controls Age at questionnaire* (median (range), years): 53 (33-82) *age at questionnaire and not cancer diagnosis because the latter is not applicable here for the control group	Oral contraceptive use	No oral contraceptive use	• Ovarian cancer risk
Michels 2018 Cohort USA	N total=5062 women with a family history of ovarian cancer n=51 women with ovarian cancer n=5011 controls	Oral contraceptive use	No or <1 year oral contraceptive use	• Ovarian cancer incidence

Study	Population	Intervention	Comparison	Outcomes
	Age by category of oral contraceptive use duration for the whole cohort reported (median (range), years): 1-4 years=59 (55-64), 5-9 years=59 (55-64), >=10 years=60 (56-64)			
Van Bommel 2023 Systematic review of observational studies Netherlands	N=21,425 in 10 studies Women with *BRCA1* or *BRCA2* pathogenic mutations Age mean (SD): not reported. Age range: 20 to 93 years	Oral contraception pill	No oral contraception	• Ovarian cancer incidence
Vicus 2009 Case-control Multinational	N total=714 women with *BRCA1* mutation n=154 women with ovarian cancer and a previous history of breast cancer Age at diagnosis of ovarian cancer (mean (range), years): 51.4 (35-75) n=560 controls (women with a history of breast cancer) Age at diagnosis of ovarian cancer (mean (range), years): not applicable; age at diagnosis of breast cancer (mean (range), years):43 (26-68)	Oral contraceptive use	No oral contraceptive use	• Ovarian cancer risk

IPD: individual patient data; SD: standard deviation.

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

Summary of the evidence

Frequent aspirin use versus infrequent or no aspirin use

The evidence showed no important differences from frequent aspirin use in terms of ovarian cancer incidence relative to no or non-frequent use in women at all levels of risk, and the evidence also showed no evidence of an important difference in women with a family history of ovarian or breast cancer or in women with a family history of ovarian cancer only. This was also the case for different histological types of ovarian cancer in women with a family history of ovarian or breast cancer. This evidence was of low to moderate quality. Very low quality evidence showed no important difference in non-mucinous epithelial ovarian cancer incidence between frequent and infrequent/no aspirin use in women at all levels of risk.

The evidence also showed no evidence of important differences from frequent aspirin use on ovarian cancer risk relative to no or non-frequent use in women with a polygenic risk score for ovarian cancer at or above the median value, below the median value, or in any of the quintiles of polygenic risk score, with the exception of women with a polygenic risk score in the 60 – 80 percentile where an important benefit of frequent aspirin use was observed. However, this is likely to be a spurious finding since the interaction between polygenic score quintile and frequency of aspirin use was not statistically significant. There was also no evidence of important differences for the different histological types of ovarian cancer in women with a polygenic risk score for ovarian cancer at or above the median value. This evidence was of very low to low quality.

Oral contraceptive use versus no oral contraceptive use

When comparing oral contraceptive with no oral contraceptive use in women with *BRCA1* or *BRCA2* mutations there was an important benefit of oral contraceptive use in terms of reduced ovarian cancer incidence. This evidence was rated as moderate to high quality. However, there was some very low quality evidence that showed no evidence of important difference between oral contraceptive use and no use in terms of ovarian cancer incidence in women with *BRCA1* mutation only. However, in this study the population was mixed, that is women with ovarian cancer and a history of breast cancer.

Different duration of oral contraceptive use versus no oral contraceptive use

When comparing different durations (0 to 1 year, 1.1 to 3 years, 3.1 to 5 years and more than 5 years) of oral contraceptive with no oral contraceptive use in women with *BRCA1* or *BRCA2* mutations there was an important benefit of oral contraceptive use in terms of reduced ovarian cancer incidence. This evidence was rated as moderate to high quality. However, other very low to low quality evidence showed no evidence of important differences between short-term (3 to 11 months) or longer term (1 to 4 years, 5 to 9 years, more than 10 years) use and no oral contraceptive use in terms of ovarian cancer incidence in women with a family history of ovarian cancer.

No evidence was identified for health related quality of life, treatment related adverse effects or overall survival.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of included economic evidence

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Ovarian cancer incidence was prioritised as a critical outcome by the committee. This is because the aim of the question was to determine whether medicines could prevent ovarian cancer in women at increased risk. Additionally, health related quality of life was also chosen as a critical outcome to capture the impact of medicines on the day-to-day lives of these women, including psychological and emotional factors.

Treatment related adverse effects was selected as an important outcome because any benefits in terms of incidence of ovarian cancer must be balanced against side effects caused by the medicines themselves. Finally overall survival was an important outcome because both prevention of ovarian cancer and serious adverse effects of treatment could impact overall survival and the balance of these is an important consideration when making treatment decisions.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from very low to high quality. Evidence was downgraded mainly due to imprecision in the effect estimates, as well as risk of bias: in some studies aspirin use was determined retrospectively by asking women to recall their usage. The evidence was also downgraded for indirectness in some cases due to the inclusion of women at all risk levels or for unexplained heterogeneity or because of the indirect study population (women with ovarian and breast cancer). Moreover, in 1 case-control study cases and controls were not matched.

No evidence was identified for health-related quality of life, treatment related adverse effects or overall survival. Due to the lack of evidence on some outcomes the committee also relied on their experience when making recommendations.

Benefits and harms

Aspirin

The committee noted that there was some overlap in the study participants included in the studies comprising this evidence but also that the studies focused on and analysed different populations. They discussed the evidence that showed no important difference in terms of ovarian cancer incidence when comparing frequent aspirin use to no or non-frequent use in women at all levels of risk and the evidence that showed no evidence of an important

difference either in women with a family history of ovarian or breast cancer, in women with a family history of ovarian cancer only and in women with all levels of polygenic risk score values. They noted that this was also the case for different histological types of ovarian cancer. They therefore concluded that aspirin did not show a protective effect in terms of ovarian cancer and agreed that there was insufficient evidence to recommend the general use of aspirin for women with high risk of familial ovarian cancer. So, the committee did not recommend it for the sole purpose of reducing ovarian cancer risk. They discussed the quality of the evidence and noted that it was very low to moderate, despite the evidence not being of the highest quality rating it was consistent with their experience in expertise and so they did not recommend it for general protective use for ovarian cancer. The committee noted that there was existing NICE guidance on the use of aspirin to reduce the risk of colorectal cancer in people with Lynch syndrome. As people with Lynch syndrome were included in the scope of this guideline, the committee felt it was important to make cross reference to the NICE colorectal cancer guideline to ensure they were aware of this recommendation.

Combined oral contraceptives

The committee discussed the evidence for both comparisons (oral contraceptive use versus no use and different durations of use versus no use) that showed that there was an important benefit in reducing the risk of ovarian cancer associated with oral contraceptive. Whilst this was moderate to high quality evidence the committee drew on their knowledge that long-term use of oral contraceptives increased risk of breast cancer. They noted that this rather than the evidence quality was the important factor in clinical decision making and the strength of the recommendation that can be made because it is the balance between the protective benefit in relation to ovarian cancer and the risk of breast cancer that needs to be weight up. Although breast cancer was not an outcome in this evidence review, the committee agreed that this increased risk of breast cancer needs to be taken into account when thinking about oral contraceptives to prevent ovarian cancer. They agreed that the balance of risks and benefits will depend on the individual (for example how strong the family history is, which pathogenic variant the person may have and other potential risk factors). They therefore decided to only recommend oral contraceptives as a preventive medicine in particular circumstances: when the reduction in ovarian cancer risk (based on for example age, family history) may outweigh an increased breast cancer risk, and after taking into account whether the timing of risk-reducing surgery is appropriate or not (for example, it may not be appropriate because of age and planned pregnancy).

In the committee's experience people are not always fully informed about the potential risks (increased risk of developing breast cancer) and benefits (reduced risk of developing ovarian cancer) of combined oral contraceptives which is necessary for informed decision making.

Research recommendation

The committee noted a lack of relevant evidence on preventive medicines and its inconsistency in women at increased risk of ovarian cancer to support decision making. They thought that some women may not want to undergo risk-reducing surgery and preventative medicine would then be a good option. Therefore they agreed to make a research recommendation on the effectiveness on preventive medicines.

Cost effectiveness and resource use

No existing economic evidence was identified for this review. The recommendations in this area reinforce current practice and implementing them will not require additional resources. Furthermore, the recommendations regarding oral contraceptives to prevent ovarian cancer will only apply to a small number of people since risk-reducing surgery is the preferred first-line treatment option for the majority of people.

Recommendations supported by this evidence review

This evidence review supports one cross reference and recommendations 1.7.1 to 1.7.43 and research recommendation 6 (on primary preventive medicines) in the NICE guideline.

References – included studies

Effectiveness

Gross 1992

Gross, T P, Schlesselman, J J, Stadel, B V et al. The risk of epithelial ovarian cancer in short-term users of oral contraceptives. American journal of epidemiology 136(1): 46-53, 1992

Hurwitz 2021

Hurwitz, Lauren M; Michels, Kara A; Cook, Michael B et al. Associations between daily aspirin use and cancer risk across strata of major cancer risk factors in two large U.S. cohorts. Cancer causes & control: CCC; vol. 32 (no. 1); 57-65, 2021

Hurwitz 2022

Hurwitz, Lauren M, Townsend, Mary K, Jordan, Susan J et al. Modification of the Association Between Frequent Aspirin Use and Ovarian Cancer Risk: A Meta-Analysis Using Individual-Level Data From Two Ovarian Cancer Consortia. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40(36): 4207-4217, 2022

Hurwitz 2023

Hurwitz, Lauren M, Webb, Penelope M, Jordan, Susan J et al. Association of Frequent Aspirin Use With Ovarian Cancer Risk According to Genetic Susceptibility. JAMA network open 6(2): e230666, 2023

McLaughlin 2007

McLaughlin John R, Risch, Harwey A, Lubinski, Jan et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. The Lancet. Oncology; 2007; vol. 8 (no. 1); 26-34, 2007

Michels 2018

Michels, Kara A, Pfeiffer, Ruth M, Brinton, Louise A et al. Modification of the Associations Between Duration of Oral Contraceptive Use and Ovarian, Endometrial, Breast, and Colorectal Cancers. JAMA oncology 4(4): 516-521, 2018

Van Bommel 2023

van Bommel, Majke H D, IntHout, Joanna, Veldmate, Guus et al. Contraceptives and cancer risks in BRCA1/2 pathogenic variant carriers: a systematic review and meta-analysis. Human reproduction update 29(2): 197-217, 2023

Vicus 2009

Vicus D, Rosen B, Lubinski J, et al. Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers. Gynecol Oncol.115(1):135–137, 2009

Economic

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

Other

Burn 2020

Burn J, Sheth H, Elliott F et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet (London, England) 395(10240): 1855–1863, 2020

Appendices

Appendix A Review protocols

Review protocol for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022365400
1.	Review title	Effectiveness of preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer
2.	Review question	How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?
3.	Objective	To establish the effectiveness of preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language • Human Studies

ID	Field	Content
		The guideline committee will decide whether to re-run the searches 6 weeks before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: Women at increased risk of familial ovarian cancer Exclusion: none specified
7.	Intervention	Medicines: • oral contraceptives • NSAIDs
8.	Comparator	In comparison with: • each other • placebo
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews/meta-analyses of RCTs • In the absence of RCTs comparative non-randomised studies will be included
10.	Other exclusion criteria	Inclusion criteria: • Full text papers • Non-randomised studies should control for baseline differences in patient groups 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	Effectiveness of preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer in primary, secondary or tertiary care

ID	Field	Content
12.	Primary outcomes (critical outcomes)	• Ovarian cancer incidence • Health related quality of life (measured using a validated scale)
13.	Secondary outcomes (important outcomes)	• Treatment related adverse effects • Overall survival
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in

ID	Field	Content
		the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: 0.8 and 1.25 for all relative dichotomous outcomes, for continuous outcomes any published validated MIDs, if none are available then +/- 0.5x control group SD.
17.	Analysis of sub-groups	Evidence will be stratified by: • Type of medication 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 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

ID	Field	Content
		evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	2022
22.	Anticipated completion date	2023
23.	Stage of review at time of this submission	

ID	Field	Content		
		Review stage	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Institute for Health and Care Excellence (NICE)		

ID	Field	Content
		5b Named contact e-mail foc@nice.org.uk 5e Organisational affiliation of the review NICE
25.	Review team members	From the NGA • Senior systematic reviewer • Technical analyst
26.	Funding sources/sponsor	This systematic review is being completed by NICE
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: NICE guideline webpage.
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022365400

ID	Field	Content
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	Risk reducing medicines, familial ovarian cancer
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NSAIDs: non-steroidal anti-inflammatory drugs; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.

Appendix B Literature search strategies

Literature search strategies for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Database: Ovid MEDLINE ALL

Date of last search: 06/03/2023

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).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.
35	("breast cancer gene 1" or "breast cancer gene 2").ti,ab.
36	Rad51 Recombinase/

#	Searches
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	or/32-49
51	31 or 50
52	exp Contraceptives, Oral/
53	Contraceptive Agents/
54	((oral or combined or agent* or hormon* or pill* or use* or medic* or sequential) adj3 (contraceptive* or contraception)).tw,kf.
55	(COC or COCs or COCP or COCPs).tw,kf.
56	("ethinyl estradiol" or "ethynyl estradiol" or estinyl or ethinylestradiol or "ethinyl oestradiol" or lynoral or microfollin or "progynon c" or adepal or anteovin or pearl or eugynon or gravistat or leios or minisiston or nordette or ovidon or ovral or rigevidon or sequostat or stediril or trigynon or trinordiol or triphasil or triquilar or trisiston or trisistone or bimizza or gedarel or mercilon or cimizt or marvelon or ambelina or elevin or levest or maexeni or microgynon or ovranette or brevinor or norimin).tw,kf.
57	(algestone or alphasone or alfasone or dihydroxyprogesterone).tw,kf.
58	(chlormadinone or chlormadinon or "neo eunomin").tw,kf.
59	(desogestrel or cerazette or cerelle or desomono or desorex or feanolla or moonia or zelleta).tw,kf.
60	(ethynodiol or continuin or femulen).tw,kf.
61	dimethisterone.tw,kf.
62	(gestrinone or dimetriose or nemestran).tw,kf.
63	(levonorgestrel or norgeston or emerres or levonelle or melkine or upostelle or capronor or cerazet or "D norgestrel" or microlut or microval or norlevo or norgeston or norplant or "plan B" or vikela or duofem or "l norgestrel").tw,kf.
64	(lynestrenol or ethinylestrenol or exluton or linesterol or linestrenol or lynoestrenol).tw,kf.
65	(medroxyprogesterone or curretab or cycrin or provera or farlutal or gestapuran or perlutex or veramix or climanor).tw,kf.
66	(megestrol or megace).tw,kf.
67	mestranol.tw,kf.
68	(norethindrone or conceplan or ethinylnortestosterone or micronor or monogest or "nor qd" or norcolut or norcolute or norethisterone or norlutin or norpregneninolone or noriday or primolut or utovlan).tw,kf.
69	norethynodrel.tw,kf.
70	(norgestrel or neogest or ovrette or postinor).tw,kf.
71	(mifepristone or mifegyne or mifeprex).tw,kf.
72	norgestrienone.tw,kf.
73	exp Anti-Inflammatory Agents, Non-Steroidal/
74	(NSAID* or NSAIM* or NSAIA*).tw,kf.
75	((antiinflamm* or anti inflamm*) adj2 (non steroid* or nonsteroid*)).tw,kf.
76	((cyclo oxygenase* or cyclooxygenase* or cox*) adj2 inhibitor*).tw,kf.
77	Prostaglandin Antagonists/
78	(prostaglandin adj3 (inhibitor* or antagonist*)).tw,kf.
79	(aspirin or danamep or acetylsal* or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kf.

#	Searches
80	"bw 755c".tw,kf.
81	(adapalene or adaferin or differin*).tw,kf.
82	(ampyrone or aminophenazone or aminoantipyrine).tw,kf.
83	(antipyrine or anodynin or phenazone or pyramidone).tw,kf.
84	(apazone or azapropazone or prolixan or rheumox or tolyprin).tw,kf.
85	(bufexamac or allergipuran or bufal or bufederm or droxaryl or jomax or malipuran or paraderm or parfenac or windol or duradermal).tw,kf.
86	(celecoxib or celebrex).tw,kf.
87	clonixin.tw,kf.
88	(curcumin or diferuloylmethane or mervia or (turmeric adj yellow)).tw,kf.
89	(dichlofenal or diclofenac or diclonate or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or voltaren or voltarol).tw,kf.
90	(diflunisal or dolobid or dolobis or dolocid).tw,kf.
91	(dipyrone or algopyrin or analgin or biopyrin or dipyronium or metamizol or metamizole or methamizole or methampyrone or narone or noramidopyrine or normelubrine or novalgetol or novalgin or novamidazophen or novaminsulfone or optalgin or pyralgin or sulpyrin or sulpyrine).tw,kf.
92	(epirizole or mepirizole or methopyrimazole).tw,kf.
93	(etanercept or benepali or enbrel or erelzi or ((tnt or tntr or tnr or tnf or tnfr) adj5 fusion protein)).tw,kf.
94	(etodolac or etodolic or etolyn or etopan or lodine or ramodar or ultradol).tw,kf.
95	(etoricoxib or arcoxia).tw,kf.
96	(fenoprofen or nalfon or nalgesic).tw,kf.
97	(feprazone or brotazona or fenilprenazone or phenylprenazone or prenazone or zepelin).tw,kf.
98	(flurbiprofen or strefen or ocufen or ansaid or cebutid or dobrofen or flubiprofen or flugalin or fluriproben or froben or "neo artrol" or "novo flurprofen" or ocuflur).tw,kf.
99	(ibuprofen or feminax xxpress or nurofen or brufen or flarin or galprofen or calprofen or pedea or neoprofen or ibugel or ibuleve or phorpain or advil or benzeneacetic acid or ibumetin or motrin or nuprin or rufen or salprofen or "trauma dolgit gel").tw,kf.
100	(indometacin or indomethacin or amuno or indocid or indocin or indomet or metindol or osmosin).tw,kf.
101	(ketoprofen or oruvail or larafen or powergel or tiloket or alrheumat or alrheumum or benzoylhydratropic acid or orudis or profenid).tw,kf.
102	(ketorolac or toradol).tw,kf.
103	(meclofenamic or meclofenamate or meclomen).tw,kf.
104	(mefenamic or contraflam or coslan or dysman or mefac or mefic or mefacit or mefenaminic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstel or ponsyl or pontal).tw,kf.
105	(meloxicam or masflex or miloxicam or mobec or mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox).tw,kf.
106	(mesalamine or mesalazine or pentasa or mezavant or salofalk or octasa or zintasa or salcrozine or "5 aminosalicylate" or "5 aminosalicylic" or asacol or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesasal or rowasa or "novo 5 asa" or "m aminosalicylic" or "meta aminosalicylic").tw,kf.
107	(nabumetone or arthraxan or listran or mebutan or nabucox or nabumeton or relafen or relif or relifex).tw,kf.
108	(naproxen or naprosyn or stirlescent or nexocin or aleve or anaprox or methoxypropiocin or naprosin or proxen or naproxenate or synflex).tw,kf.
109	(niflumic or donalgin or flunir or niflactol or niflugel or nifluril).tw,kf.
110	(olopatadine or opatanol or patanol).tw,kf.
111	(oxaprozin or oxaprozinum or danoprox or daypro or dayrun).tw,kf.
112	(oxyphenbutazone or diflamil or hydroxyphenylbutazone or oxyphenylbutazone or tanderil or tandearil).tw,kf.
113	(phenylbutazone or butacote or butadion or butadione or butapirazol or butapyrazole or butazolidin or diphenylbutazone or fenilbutazon).tw,kf.
114	(piroxicam or feldene).tw,kf.
115	(salicylate* or salicylic or occlusal).tw,kf.
116	(sulfasalazine or sulfasalazin or salazopyrin or azulfidine or azulfadine or sulazine or sulphasalazine or asulfidine or "colo pleon" or pleon or pyralin or salazosulfapyridine or salicylazosulfapyridine or ucine or ulcol).tw,kf.
117	(sulindac or aclin or "apo sulin" or arthrobid or arthrocine or chibret or clinoril or copal or kenalin or klinoril or "novo sundac" or Sulindal).tw,kf.
118	suprofen.tw,kf.
119	(tolmetin or tolectin).tw,kf.
120	(indoprofen or dexindoprofen).tw,kf.
121	(masoprocol or actinex or dihydronorguaiaretic or nordihydroguaiaretic or NDGA).tw,kf.

#	Searches
122	or/52-121
123	51 and 122
124	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
125	randomized controlled trial/ or random*.ti,ab.
126	124 not 125
127	(animals/ not humans/) or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ or (rat or rats or rodent* or mouse or mice).ti.
128	126 or 127
129	123 not 128
130	limit 129 to English language
131	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
132	drug therapy.fs.
133	(groups or placebo or randomi#ed or randomly or trial).ab.
134	Clinical Trials as Topic/
135	trial.ti.
136	or/131-135
137	Meta-Analysis/
138	Meta-Analysis as Topic/
139	(meta analy* or metanaly* or metaanaly*).ti,ab.
140	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
141	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
142	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
143	(search* adj4 literature).ab.
144	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
145	cochrane.jw.
146	or/137-145
147	130 and (136 or 146)
148	Observational Studies as Topic/
149	Observational Study/
150	Epidemiologic Studies/
151	exp Case-Control Studies/
152	exp Cohort Studies/
153	Cross-Sectional Studies/
154	Controlled Before-After Studies/
155	Historically Controlled Study/
156	Interrupted Time Series Analysis/
157	Comparative Study.pt.
158	case control$.tw.
159	case series.tw.
160	(cohort adj (study or studies)).tw.
161	cohort analy$.tw.
162	(follow up adj (study or studies)).tw.
163	(observational adj (study or studies)).tw.
164	longitudinal.tw.
165	prospective.tw.
166	retrospective.tw.
167	cross sectional.tw.
168	or/148-167
169	130 and 168

Database: Ovid Embase

Date of last search: 06/03/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	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/

#	Searches
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	or/31-39,42-50
52	30 or 51
53	exp oral contraceptive agent/
54	contraceptive agent/
55	((oral or combined or agent* or hormon* or pill* or use* or medic* or sequential) adj3 (contraceptive* or contraception)).tw,kf.
56	(COC or COCs or COCP or COCPs).tw,kf.
57	("ethinyl estradiol" or "ethynyl estradiol" or estinyl or ethinylestradiol or "ethinyl oestradiol" or lynoral or microfollin or "progynon c" or adepal or anteovin or pearl or eugynon or gravistat or leios or minisiston or nordette or ovidon or ovral or rigevidon or sequostat or stediril or trigynon or trinordiol or triphasil or triquilar or trisiston or trisistone or bimizza or gedarel or mercilon or cimizt or marvelon or ambelina or elevin or levest or maexeni or microgynon or ovranette or brevinor or norimin).tw,kf.
58	(algestone or alphasone or alfasone or dihydroxyprogesterone).tw,kf.
59	(chlormadinone or chlormadinon or "neo eunomin").tw,kf.
60	(desogestrel or cerazette or cerelle or desomono or desorex or feanolla or moonia or zelleta).tw,kf.
61	(ethynodiol or continuin or femulen).tw,kf.
62	dimethisterone.tw,kf.
63	(gestrinone or dimetriose or nemestran).tw,kf.
64	(levonorgestrel or norgeston or emerres or levonelle or melkine or upostelle or capronor or cerazet or "D norgestrel" or microlut or microval or norlevo or norgeston or norplant or "plan B" or vikela or duofem or "l norgestrel").tw,kf.
65	(lynestrenol or ethinylestrenol or exluton or linesterol or linestrenol or lynoestrenol).tw,kf.
66	(medroxyprogesterone or curretab or cycrin or provera or farlutal or gestapuran or perlutex or veramix or climanor).tw,kf.
67	(megestrol or megace).tw,kf.
68	mestranol.tw,kf.
69	(norethindrone or conceplan or ethinylnortestosterone or micronor or monogest or "nor qd" or norcolut or norcolute or norethisterone or norlutin or norpregneninolone or noriday or primolut or utovlan).tw,kf.
70	norethynodrel.tw,kf.
71	(norgestrel or neogest or ovrette or postinor).tw,kf.
72	(mifepristone or mifegyne or mifeprex).tw,kf.
73	norgestrienone.tw,kf.
74	exp nonsteroid antiinflammatory agent/
75	(NSAID* or NSAIM* or NSAIA*).tw,kf.
76	((antiinflamm* or anti inflamm*) adj2 (non steroid* or nonsteroid*)).tw,kf.
77	((cyclo oxygenase* or cyclooxygenase* or cox*) adj2 inhibitor*).tw,kf.
78	prostaglandin inhibitor/
79	(prostaglandin adj3 (inhibitor* or antagonist*)).tw,kf.
80	(aspirin or danamep or acetylsal* or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kf.
81	"bw 755c".tw,kf.
82	(adapalene or adaferin or differin*).tw,kf.
83	(ampyrone or aminophenazone or aminoantipyrine).tw,kf.
84	(antipyrine or anodynin or phenazone or pyramidone).tw,kf.
85	(apazone or azapropazone or prolixan or rheumox or tolyprin).tw,kf.

#	Searches
86	(bufexamac or allergipuran or bufal or bufederm or droxaryl or jomax or malipuran or paraderm or parfenac or windol or duradermal).tw,kf.
87	(celecoxib or celebrex).tw,kf.
88	clonixin.tw,kf.
89	(curcumin or diferuloylmethane or mervia or (turmeric adj yellow)).tw,kf.
90	(dichlofenal or diclofenac or diclonate or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or voltaren or voltarol).tw,kf.
91	(diflunisal or dolobid or dolobis or dolocid).tw,kf.
92	(dipyrone or algopyrin or analgin or biopyrin or dipyronium or metamizol or metamizole or methamizole or methampyrone or narone or noramidopyrine or normelubrine or novalgetol or novalgin or novamidazophen or novaminsulfone or optalgin or pyralgin or sulpyrin or sulpyrine).tw,kf.
93	(epirizole or mepirizole or methopyrimazole).tw,kf.
94	(etanercept or benepali or enbrel or erelzi or ((tnt or tntr or tnr or tnf or tnfr) adj5 fusion protein)).tw,kf.
95	(etodolac or etodolic or etolyn or etopan or lodine or ramodar or ultradol).tw,kf.
96	(etoricoxib or arcoxia).tw,kf.
97	(fenoprofen or nalfon or nalgesic).tw,kf.
98	(feprazone or brotazona or fenilprenazone or phenylprenazone or prenazone or zepelin).tw,kf.
99	(flurbiprofen or strefen or ocufen or ansaid or cebutid or dobrofen or flubiprofen or flugalin or fluriproben or froben or "neo artrol" or "novo flurprofen" or ocuflur).tw,kf.
100	(ibuprofen or feminax xxpress or nurofen or brufen or flarin or galprofen or calprofen or pedea or neoprofen or ibugel or ibuleve or phorpain or advil or benzeneacetic acid or ibumetin or motrin or nuprin or rufen or salprofen or "trauma dolgit gel").tw,kf.
101	(indometacin or indomethacin or amuno or indocid or indocin or indomet or metindol or osmosin).tw,kf.
102	(ketoprofen or oruvail or larafen or powergel or tiloket or alrheumat or alrheumum or benzoylhydratropic acid or orudis or profenid).tw,kf.
103	(ketorolac or toradol).tw,kf.
104	(meclofenamic or meclofenamate or meclomen).tw,kf.
105	(mefenamic or contraflam or coslan or dysman or mefac or mefic or mefacit or mefenaminic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstel or ponsyl or pontal).tw,kf.
106	(meloxicam or masflex or miloxicam or mobec or mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox).tw,kf.
107	(mesalamine or mesalazine or pentasa or mezavant or salofalk or octasa or zintasa or salcrozine or "5 aminosalicylate" or "5 aminosalicylic" or asacol or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesasal or rowasa or "novo 5 asa" or "m aminosalicylic" or "meta aminosalicylic").tw,kf.
108	(nabumetone or arthraxan or listran or mebutan or nabucox or nabumeton or relafen or relif or relifex).tw,kf.
109	(naproxen or naprosyn or stirlescent or nexocin or aleve or anaprox or methoxypropiocin or naprosin or proxen or naproxenate or synflex).tw,kf.
110	(niflumic or donalgin or flunir or niflactol or niflugel or nifluril).tw,kf.
111	(olopatadine or opatanol or patanol).tw,kf.
112	(oxaprozin or oxaprozinum or danoprox or daypro or dayrun).tw,kf.
113	(oxyphenbutazone or diflamil or hydroxyphenylbutazone or oxyphenylbutazone or tanderil or tandearil).tw,kf.
114	(phenylbutazone or butacote or butadion or butadione or butapirazol or butapyrazole or butazolidin or diphenylbutazone or fenilbutazon).tw,kf.
115	(piroxicam or feldene).tw,kf.
116	(salicylate* or salicylic or occlusal).tw,kf.
117	(sulfasalazine or sulfasalazin or salazopyrin or azulfidine or azulfadine or sulazine or sulphasalazine or asulfidine or "colo pleon" or pleon or pyralin or salazosulfapyridine or salicylazosulfapyridine or ucine or ulcol).tw,kf.
118	(sulindac or aclin or "apo sulin" or arthrobid or arthrocine or chibret or clinoril or copal or kenalin or klinoril or "novo sundac" or Sulindal).tw,kf.
119	suprofen.tw,kf.
120	(tolmetin or tolectin).tw,kf.
121	(indoprofen or dexindoprofen).tw,kf.
122	(masoprocol or actinex or dihydronorguaiaretic or nordihydroguaiaretic or NDGA).tw,kf.
123	or/53-122
124	52 and 123
125	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.
126	randomized controlled trial/ or random*.ti,ab.
127	125 not 126

#	Searches
128	(animal/ not human/) or nonhuman/ or exp Animal Experiment/ or exp Experimental Animal/ or animal model/ or exp Rodent/ or (rat or rats or rodent* or mouse or mice).ti.
129	127 or 128
130	124 not 129
131	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
132	130 not 131
133	limit 132 to English language
134	random*.ti,ab.
135	factorial*.ti,ab.
136	(crossover* or cross over*).ti,ab.
137	((doubl* or singl*) adj blind*).ti,ab.
138	(assign* or allocat* or volunteer* or placebo*).ti,ab.
139	crossover procedure/
140	single blind procedure/
141	randomized controlled trial/
142	double blind procedure/
143	or/134-142
144	systematic review/
145	meta-analysis/
146	(meta analy* or metanaly* or metaanaly*).ti,ab.
147	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
148	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
149	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
150	(search* adj4 literature).ab.
151	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
152	((pool* or combined) adj2 (data or trials or studies or results)).ab.
153	cochrane.jw.
154	or/144-153
155	133 and (143 or 154)
156	Clinical study/
157	Case control study/
158	Family study/
159	Longitudinal study/
160	Retrospective study/
161	comparative study/
162	Prospective study/
163	Randomized controlled trials/
164	162 not 163
165	Cohort analysis/
166	cohort analy$.tw.
167	(Cohort adj (study or studies)).tw.
168	(Case control$ adj (study or studies)).tw.
169	(follow up adj (study or studies)).tw.
170	(observational adj (study or studies)).tw.
171	(epidemiologic$ adj (study or studies)).tw.
172	(cross sectional adj (study or studies)).tw.
173	case series.tw.
174	prospective.tw.
175	retrospective.tw.
176	or/156-161,164-175
177	133 and 176

Database: Cochrane Database of Systematic Reviews Issue 3 of 12, March 2023 and Cochrane Central Register of Controlled Trials, Issue 2 of 12, February 2023

Date of last search: 06/03/2023

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	{OR #9-#29}
#31	#8 AND #30
#32	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#33	(("Fanconi Anemia" or "fanconi anaemia") 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 NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#39	MeSH descriptor: [Checkpoint Kinase 2] this term only

#	Searches
#40	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#41	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#42	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#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"):ti,ab,kw
#44	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#45	(((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
#46	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#47	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#48	Epithelial cell adhesion NEXT molecule*:ti,ab,kw
#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 KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#50	{OR #32-#49}
#51	#31 OR #50
#52	MeSH descriptor: [Contraceptives, Oral] explode all trees
#53	MeSH descriptor: [Contraceptive Agents] this term only
#54	((oral or combined or agent* or hormon* or pill* or use* or medic* or sequential) NEAR/3 (contraceptive* or contraception)):ti,ab,kw
#55	(COC or COCs or COCP or COCPs):ti,ab,kw
#56	("ethinyl estradiol" or "ethynyl estradiol" or estinyl or ethinylestradiol or "ethinyl oestradiol" or lynoral or microfollin or "progynon c" or adepal or anteovin or pearl or eugynon or gravistat or leios or minisiston or nordette or ovidon or ovral or rigevidon or sequostat or stediril or trigynon or trinordiol or triphasil or triquilar or trisiston or trisistone or bimizza or gedarel or mercilon or cimizt or marvelon or ambelina or elevin or levest or maexeni or microgynon or ovranette or brevinor or norimin):ti,ab,kw
#57	(algestone or alphasone or alfasone or dihydroxyprogesterone):ti,ab,kw
#58	(chlormadinone or chlormadinon or "neo eunomin"):ti,ab,kw
#59	(desogestrel or cerazette or cerelle or desomono or desorex or feanolla or moonia or zelleta):ti,ab,kw
#60	(ethynodiol or continuin or femulen):ti,ab,kw
#61	dimethisterone:ti,ab,kw
#62	(gestrinone or dimetriose or nemestran):ti,ab,kw
#63	(levonorgestrel or norgeston or emerres or levonelle or melkine or upostelle or capronor or cerazet or "D norgestrel" or microlut or microval or norlevo or norgeston or norplant or "plan B" or vikela or duofem or "l norgestrel"):ti,ab,kw
#64	(lynestrenol or ethinylestrenol or exluton or linesterol or linestrenol or lynoestrenol):ti,ab,kw
#65	(medroxyprogesterone or curretab or cycrin or provera or farlutal or gestapuran or perlutex or veramix or climanor):ti,ab,kw
#66	(megestrol or megace):ti,ab,kw
#67	mestranol:ti,ab,kw
#68	(norethindrone or conceplan or ethinylnortestosterone or micronor or monogest or "nor qd" or norcolut or norcolute or norethisterone or norlutin or norpregneninolone or noriday or primolut or utovlan):ti,ab,kw
#69	norethynodrel:ti,ab,kw
#70	(norgestrel or neogest or ovrette or postinor):ti,ab,kw
#71	(mifepristone or mifegyne or mifeprex):ti,ab,kw
#72	norgestrienone:ti,ab,kw
#73	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#74	(NSAID* or NSAIM* or NSAIA*):ti,ab,kw
#75	((antiinflamm* or anti NEXT inflamm*) NEAR/2 (non NEXT steroid* or nonsteroid*)):ti,ab,kw
#76	((cyclo NEXT oxygenase* or cyclooxygenase* or cox*) NEAR/2 inhibitor*):ti,ab,kw
#77	MeSH descriptor: [Prostaglandin Antagonists] this term only
#78	(prostaglandin NEAR/3 (inhibitor* or antagonist*)):ti,ab,kw
#79	(aspirin or danamep or acetylsal* or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin):ti,ab,kw
#80	bw 755c:ti,ab,kw
#81	(adapalene or adaferin or differin*):ti,ab,kw
#82	(ampyrone or aminophenazone or aminoantipyrine):ti,ab,kw
#83	(antipyrine or anodynin or phenazone or pyramidone):ti,ab,kw

#	Searches
#84	(apazone or azapropazone or prolixan or rheumox or tolyprin):ti,ab,kw
#85	(bufexamac or allergipuran or bufal or bufederm or droxaryl or jomax or malipuran or paraderm or parfenac or windol or duradermal):ti,ab,kw
#86	(celecoxib or celebrex):ti,ab,kw
#87	clonixin:ti,ab,kw
#88	(curcumin or diferuloylmethane or mervia or (turmeric NEAR/1 yellow)):ti,ab,kw
#89	(dichlofenal or diclofenac or diclonate or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or voltaren or voltarol):ti,ab,kw
#90	(diflunisal or dolobid or dolobis or dolocid):ti,ab,kw
#91	(dipyrone or algopyrin or analgin or biopyrin or dipyronium or metamizol or metamizole or methamizole or methampyrone or narone or noramidopyrine or normelubrine or novalgetol or novalgin or novamidazophen or novaminsulfone or optalgin or pyralgin or sulpyrin or sulpyrine):ti,ab,kw
#92	(epirizole or mepirizole or methopyrimazole):ti,ab,kw
#93	(etanercept or benepali or enbrel or erelzi or ((tnt or tntr or tnr or tnf or tnfr) NEAR/5 fusion protein)):ti,ab,kw
#94	(etodolac or etodolic or etolyn or etopan or lodine or ramodar or ultradol):ti,ab,kw
#95	(etoricoxib or arcoxia):ti,ab,kw
#96	(fenoprofen or nalfon or nalgesic):ti,ab,kw
#97	(feprazone or brotazona or fenilprenazone or phenylprenazone or prenazone or zepelin):ti,ab,kw
#98	(flurbiprofen or strefen or ocufen or ansaid or cebutid or dobrofen or flubiprofen or flugalin or fluriproben or froben or "neo artrol" or "novo flurprofen" or ocuflur):ti,ab,kw
#99	(ibuprofen or "feminax xxpress" or nurofen or brufen or flarin or galprofen or calprofen or pedea or neoprofen or ibugel or ibuleve or phorpain or advil or "benzeneacetic acid" or ibumetin or motrin or nuprin or rufen or salprofen or "trauma dolgit gel"):ti,ab,kw
#100	(indometacin or indomethacin or amuno or indocid or indocin or indomet or metindol or osmosin):ti,ab,kw
#101	(ketoprofen or oruvail or larafen or powergel or tiloket or alrheumat or alrheumum or "benzoylhydratropic acid" or orudis or profenid):ti,ab,kw
#102	(ketorolac or toradol):ti,ab,kw
#103	(meclofenamic or meclofenamate or meclomen):ti,ab,kw
#104	(mefenamic or contraflam or coslan or dysman or mefac or mefic or mefacit or mefenaminic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstel or ponsyl or pontal):ti,ab,kw
#105	(meloxicam or masflex or miloxicam or mobec or mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox):ti,ab,kw
#106	(mesalamine or mesalazine or pentasa or mezavant or salofalk or octasa or zintasa or salcrozine or "5 aminosalicylate" or "5 aminosalicylic" or asacol or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesasal or rowasa or "novo 5 asa" or "m aminosalicylic" or "meta aminosalicylic"):ti,ab,kw
#107	(nabumetone or arthraxan or listran or mebutan or nabucox or nabumeton or relafen or relif or relifex):ti,ab,kw
#108	(naproxen or naprosyn or stirlescent or nexocin or aleve or anaprox or methoxypropiocin or naprosin or proxen or naproxenate or synflex):ti,ab,kw
#109	(niflumic or donalgin or flunir or niflactol or niflugel or nifluril):ti,ab,kw
#110	(olopatadine or opatanol or patanol):ti,ab,kw
#111	(oxaprozin or oxaprozinum or danoprox or daypro or dayrun):ti,ab,kw
#112	(oxyphenbutazone or diflamil or hydroxyphenylbutazone or oxyphenylbutazone or tanderil or tandearil):ti,ab,kw
#113	(phenylbutazone or butacote or butadion or butadione or butapirazol or butapyrazole or butazolidin or diphenylbutazone or fenilbutazon):ti,ab,kw
#114	(piroxicam or feldene):ti,ab,kw
#115	(salicylate* or salicylic or occlusal):ti,ab,kw
#116	(sulfasalazine or sulfasalazin or salazopyrin or azulfidine or azulfadine or sulazine or sulphasalazine or asulfidine or "colo pleon" or pleon or pyralin or salazosulfapyridine or salicylazosulfapyridine or ucine or ulcol):ti,ab,kw
#117	(sulindac or aclin or "apo sulin" or arthrobid or arthrocine or chibret or clinoril or copal or kenalin or klinoril or "novo sundac" or sulindal):ti,ab,kw
#118	suprofen:ti,ab,kw
#119	(tolmetin or tolectin):ti,ab,kw
#120	(indoprofen or dexindoprofen):ti,ab,kw
#121	(masoprocol or actinex or dihydronorguaiaretic or nordihydroguaiaretic or NDGA):ti,ab,kw
#122	{OR #52-#121}
#123	#51 AND #122
#124	conference:pt or (clinicaltrials or trialsearch):so
#125	#123 NOT #124

Database: Epistemonikos

Date of last search: 03/03/2023

#	Searches
1	(advanced_title_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR advanced_abstract_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer))
2	(advanced_title_en:((advanced_title_en:(((oral OR combined OR agent* OR hormon* OR pill* OR use* OR medic* OR sequential) AND (contraceptive* OR contraception))) OR advanced_abstract_en:(((oral OR combined OR agent* OR hormon* OR pill* OR use* OR medic* OR sequential) AND (contraceptive* OR contraception))))
3	(advanced_title_en:((COC OR COCs OR COCP OR COCPs)) OR advanced_abstract_en:((COC OR COCs OR COCP OR COCPs)))
4	(advanced_title_en:(((antiinflamm* OR anti inflamm*) AND (non steroid* OR nonsteroid*))) OR advanced_abstract_en:(((antiinflamm* OR anti inflamm*) AND (non steroid* OR nonsteroid*))))
5	(advanced_title_en:((NSAID* OR NSAIM* OR NSAIA*)) OR advanced_abstract_en:((NSAID* OR NSAIM* OR NSAIA*)))
6	(advanced_title_en:((cyclooxygenase* inhibitor*)) OR advanced_abstract_en:((cyclooxygenase* inhibitor*)))
7	(advanced_title_en:((prostaglandin AND (inhibitor* OR antagonist*))) OR advanced_abstract_en:((prostaglandin AND (inhibitor* OR antagonist*)))
8	2 OR 7
9	1 AND 8

Database: INAHTA International HTA Database

Date of last search: 03/03/2023

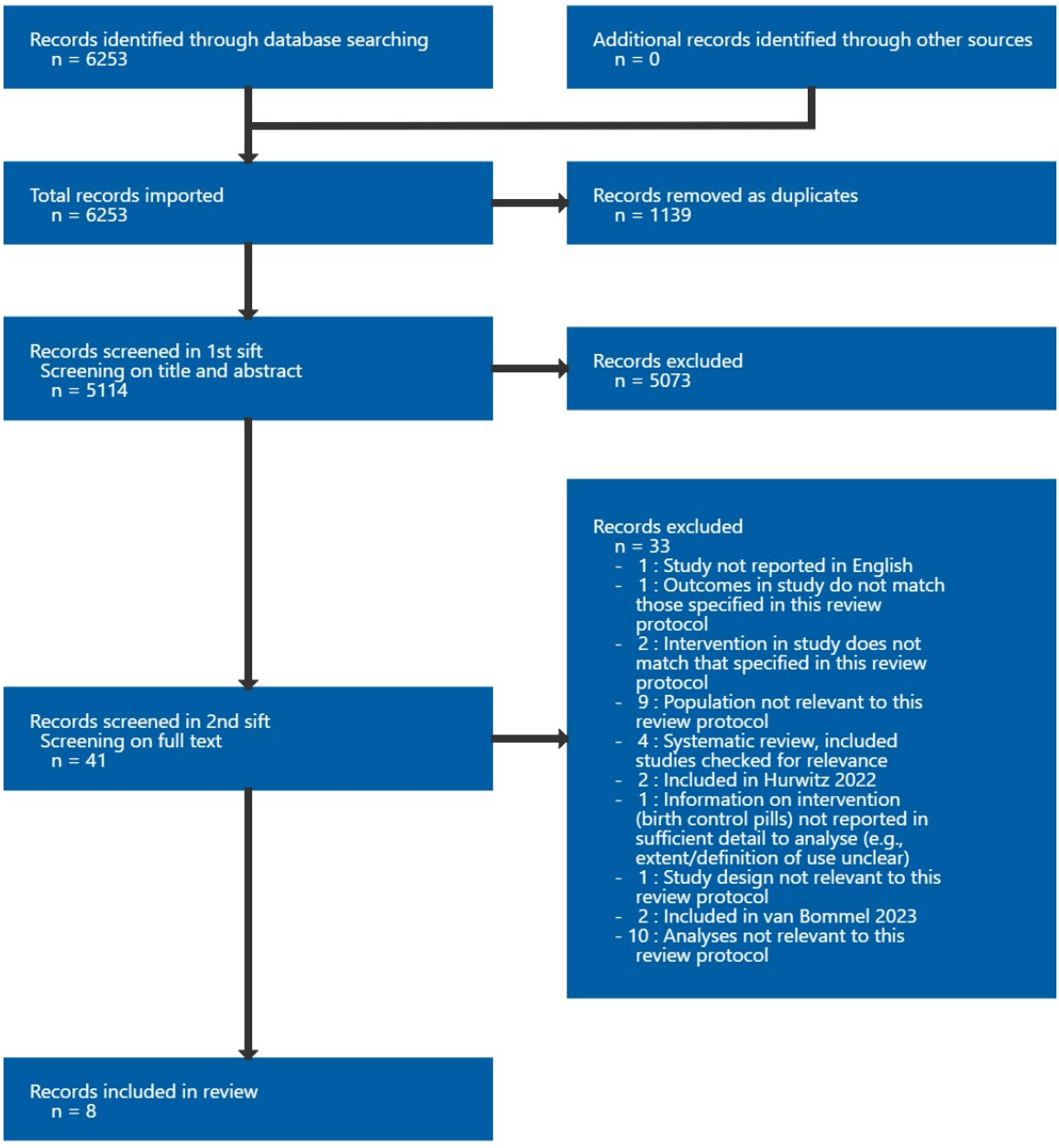
#	Searches
24	#23 AND #22
23	#13 AND #3
22	#21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14
21	((cyclooxygenase* AND inhibitor*))[Title] OR ((cyclooxygenase* AND inhibitor*))[abs]
20	((NSAID* OR NSAIM* OR NSAIA*))[Title] OR ((NSAID* OR NSAIM* OR NSAIA*))[abs]
19	(((antiinflamm* OR anti inflamm*) AND (non steroid* OR nonsteroid*)))[Title] OR (((antiinflamm* OR anti inflamm*) AND (non steroid* OR nonsteroid*)))[abs]
18	"Anti-Inflammatory Agents, Non-Steroidal"[mhe]
17	((COC OR COCs OR COCP OR COCPs))[Title] OR ((COC OR COCs OR COCP OR COCPs))[abs]
16	(((oral OR combined OR agent* OR hormon* OR pill* OR use* OR medic* OR sequential) AND (contraceptive* OR contraception)))[Title] OR (((oral OR combined OR agent* OR hormon* OR pill* OR use* OR medic* OR sequential) AND (contraceptive* OR contraception)))[abs]
15	"Contraceptive Agents"[mh]
14	"Contraceptives, Oral"[mhe]
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4
12	(((tumor* or tumour* or cancer* or metastasis or metastases or growth*) AND (suppress* AND (gene* or protein*)))[Title] OR (((tumor* or tumour* or cancer* or metastasis or metastases or growth*) AND (suppress* AND (gene* or protein*)))[abs]
11	(((carrier* or gene*) AND mutat*))[Title] OR (((carrier* or gene*) AND mutat*))[abs]
10	(((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[Title] OR (((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[abs]
9	(((famil* AND histor* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((famil* AND histor* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
8	(("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[Title] OR (("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[abs]
7	(((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
6	((MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((MUTYH or MYH or FAP or AFAP or APC))[abs]
5	((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[Title] OR ((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[abs]

#	Searches
4	(((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[Title] OR (((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[abs]
3	#2 OR #1
2	(((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
1	"Ovarian Neoplasms"[mhe]

Appendix C Effectiveness evidence study selection

Study selection for: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Gross, 1992

Bibliographic Reference	Gross, T P; Schlesselman, J J; Stadel, B V; Yu, W; Lee, N C; The risk of epithelial ovarian cancer in short-term users of oral contraceptives.; American journal of epidemiology; 1992; vol. 136 (no. 1); 46-53

Study details

Country/ies where study was carried out	USA
Study type	Case-control No details reported on matching case and controls for ovarian cancer
Study dates	December 1, 1990 to December 31, 1992
Inclusion criteria	US women aged 20-54 years old with one or more of the following three cancers (breast, ovary, and endometrium).
Exclusion criteria	Less than 3 months of oral contraceptive use
Patient characteristics	**Women with epithelial ovarian cancer (n=283)** Age at diagnosis or interview (years) Age mean (SD): not reported. Age by category (years) %: 20-29: 7

	30-39: 11 40-49: 40 50-54: 42 Age at first use of oral contraceptives (years) %: <20: 0 ≥20: 14 Never use: 86 Race or ethnic group %: White: 89 Black: 5 Hispanic: 3 Other: 3 n=16 used oral contraceptive and n=15 did not use it **Controls (n=1,929)** Age at diagnosis or interview (years) Age mean (SD): not reported. Age by category (years) %:

	20-29: 5 30-39: 12 40-49: 43 50-54: 40 Age at first use of oral contraceptives (years) %: <20: 2 ≥20: 19 Never use: 79 Race or ethnic group %: White: 81 Black: 11 Hispanic: 4 Other: 4 n=52 used oral contraceptive and n=47did not use it
Intervention(s)/control	Intervention: oral contractive use (variety of timeframes) Control: no oral contraceptive use
Duration of follow-up	Not reported
Sources of funding	National Cancer Centre

Sample size	**Whole population** Total N=2,212 Women with epithelial ovarian cancer n=283 Controls n=1,929 **Women with a family history of ovarian cancer n=130** Women with epithelial ovarian cancer n=31 Controls n=99 *Family history unknown for 184 cases and 1,500 controls.
Other information	Confidence intervals only available for short term use (3-11 months) of oral contractive relative risk, therefore the other timeframes for oral contraceptive use were not extracted.

Study arms

Ovarian cancer cases (N = 31)

Control (N = 99)

Outcomes

Association between short term oral contraceptive use 3-11 months and ovarian cancer incidence (*analyses adjusted for age and parity)

Outcome	Ovarian cancer cases vs Control, N2 = 31, N1 = 99
Association between short term oral contraceptive use 3-11 months and ovarian cancer incidence Adjusted* relative risk/95% CI	3.1 (0.7 to 14.1)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Can't tell *(Random telephone calling women aged 20-54 years who*

Section	Question	Answer
		lived in one of the eight study areas during the study interval, no details reported of matching controls to cases.)
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Potential for recall bias as data collected via a questionnaire)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age and parity
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	No association between short term (3-11 months) oral contraceptive use and ovarian cancer. No confidence intervals reported for longer time frames of oral contraceptive use, thus not included in review.
(B) What are the results?	8. How precise are the results?	Not very precise as 95% CI is 0.7 to 14.2, RR=3.1
(B) What are the results?	9. Do you believe the results?	No, finding is based on few exposed women, and represents the results of exploratory analyses.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Authors didn't focus on other available evidence in positive family history of ovarian cancer)*

Hurwitz, 2021

Bibliographic Reference	Hurwitz, Lauren M; Michels, Kara A; Cook, Michael B; Pfeiffer, Ruth M; Trabert, Britton; Associations between daily aspirin use and cancer risk across strata of major cancer risk factors in two large U.S. cohorts.; Cancer causes & control: CCC; 2021; vol. 32 (no. 1); 57-65

Study details

Country/ies where study was carried out	USA
Study type	IPD meta-analysis
Study dates	1993-2001
Inclusion criteria	NIH-AARP Diet and health study: Members aged 50-71 residing in one of six US states or 2 metropolitan areas. Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: Individuals aged 55-74 from ten US screening centres
Exclusion criteria	Individuals with a prevalent cancer at baseline (diagnosed with an in-situ, borderline, or non-epithelial malignancy of that site), cancer reported via death certificate only, or missing data on aspirin use or key effect modifiers. For analyses of ovarian cancer, women were excluded if: • bilateral oophorectomy or hysterectomy prior to baseline
Patient characteristics	Women with a family history of ovarian cancer only N=7074 For the whole cohort, information on family history of ovarian cancer was available for n=1446 daily aspirin and n=5628 not on daily aspirin of 151,371 women included in the ovarian cancer analyses (n=126,086 women had no family history of ovarian cancer). Data on family history of ovarian cancer was available for 88% of the ovarian cancer analyses (n=18,211 missing data on family history of ovarian cancer)

	Aspirin use for the whole cohort (no data for those with family history only) **Daily Aspirin use** Age in years (mean [SD]): 63.4 (5.3) Race: - White: 28,491 - Non-White: 2466 Family history of ovarian cancer: - No: 25,681 - Yes: 1446 - Missing: 3830 Duration of oral contraceptive in years: - None: 17211 - <5: 7110 - 6-9: 3268 - 10+: 3246 - Missing: 122 Number of live births:

	- 0: 3798 - 1: 2739 - 2: 7278 - 3+: 17045 - Missing: 97 **No daily Aspirin use** Age in years (mean [SD]): 62.21 (5.39) Race: - White: 108,508 - Non-White: 11,906 Family history of ovarian cancer: - No: 100,403 - Yes: 5628 - Missing: 14,381 Duration of oral contraceptive in years: - None: 63,906

	- <5: 28,689 - 6-9: 13,853 - 10+: 13,474 - Missing: 492 Number of live births: - 0: 15,782 - 1: 10,871 - 2: 30,469 - 3+: 63,039 - Missing: 253
Intervention(s)/control	Intervention: Daily Aspirin use Control: No daily Aspirin use
Duration of follow-up	Until diagnosis of the cancer of interest, loss-to-follow-up, death, or date of administrative censoring
Sources of funding	This work was supported by the Intramural Research Program of the National Cancer Institute at the National Institutes of Health (ZIA CP010128).
Sample size	N=7074 women with family history of ovarian cancer Daily aspirin use n=1446 No daily aspirin use n=5628 Ovarian cancer events

	Daily aspirin use n=17 No daily aspirin use n=51
Other information	Cancer cases were ascertained through linkage with state cancer registries and vital status was determined by linkage to the relevant registries. Aspirin use was ascertained through participants and they were asked to report whether they had taken any aspirin products (generic aspirin, Bayer, Bufferin, Anacin, Ecotrin, or Excedrin) in the past 12 months, and, if so, the frequency of use.

Study arms

Daily Aspirin use (N = 1446)

No daily aspirin use (N = 5628)

Outcomes

Association between daily aspirin use in the last 12 months and ovarian cancer incidence (*analyses adjusted for baseline age, race, study/arm, BMI, duration of oral contraceptive use, duration of hormonal therapy use, number of live births)

Outcome	**Daily aspirin use No daily aspirin use, N2 = 1446, N1 = 5628**
Association between daily aspirin use in the last 12 months and ovarian cancer incidence Adjusted* hazard ratio/95% CI	1.35 (0.77 to 2.35)

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(Only members of NIH-AARP Diet and health study, aged 50-71 residing in one of six US states or 2 metropolitan areas; and Prostate, Lunch, Colorectal and Ovarian (PLCO) cancer screening trial: aged 55-74 from ten US screening centres participated.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Low
Overall bias	Risk of bias variation across outcomes	None
Overall bias	Directness	Indirectly Applicable *(Whole population is 4 different cancers and sub-grouped as those with or without a*

Section	Question	Answer
		family history of that specific cancer. Nonetheless, there was a specific ovarian cancer population with a family history of ovarian cancer subgroup analysis)

Hurwitz, 2022

Bibliographic Reference	Hurwitz, Lauren M; Townsend, Mary K; Jordan, Susan J; Patel, Alpa V; Teras, Lauren R; Lacey, James V Jr; Doherty, Jennifer A; Harris, Holly R; Goodman, Marc T; Shvetsov, Yurii B; Modugno, Francesmary; Moysich, Kirsten B; Robien, Kim; Prizment, Anna; Schildkraut, Joellen M; Berchuck, Andrew; Fortner, Renee T; Chan, Andrew T; Wentzensen, Nicolas; Hartge, Patricia; Sandler, Dale P; O'Brien, Katie M; Anton-Culver, Hoda; Ziogas, Argyrios; Menon, Usha; Ramus, Susan J; Pearce, Celeste Leigh; Wu, Anna H; White, Emily; Peters, Ulrike; Webb, Penelope M; Tworoger, Shelley S; Trabert, Britton; Modification of the Association Between Frequent Aspirin Use and Ovarian Cancer Risk: A Meta-Analysis Using Individual-Level Data From Two Ovarian Cancer Consortia.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2022; vol. 40 (no. 36); 4207-4217

Study details

Country/ies where study was carried out	USA
Study type	IPD meta-analysis
Study dates	Not reported
Inclusion criteria	Studies were included if they collected information on frequency of aspirin use in women with at least one intact ovary, no history of cancer at baseline and non-missing age.
Exclusion criteria	Not reported
Patient characteristics	9 cohort studies: Mean age at baseline ranged from 46.0 to 68.2 years. Prevalence of frequent aspirin use ranged from 9.8% to 38% (self-reported).

	2600 out of 491,651 women were diagnosed with ovarian cancer. Types of ovarian cancer diagnosed: 56% high-grade serous, 2% low-grade serous, 9% endometrioid, 5% clear cell, 4% mucinous, and 23% other/unknown epithelial. 8 case-control studies: Median age of the cases ranged from 56.2 to 60.7 years. Not reported for controls. Prevalence of frequent aspirin use ranged from 5.6% to 29.8% (self-reported). 5,726 cases and 8,027 controls. Types of ovarian cancer diagnosed: 54% high-grade serous, 4% low-grade serous, 15% endometrioid, 9% clear cell, 5% mucinous, and 13% other/unknown epithelial.
Intervention(s)/control	Intervention: Frequent aspirin use (for ≥6 days/week or ≥28 days/month and for a duration of ≥6 months. Control: Non-frequent aspirin use (no or less frequent than intervention group use of aspirin).
Duration of follow-up	Mean follow-up ranged from 4.6 to 14.3 years for the cohort studies
Sources of funding	US Department of Defense Ovarian Cancer Research Program
Sample size	Cohort studies: 491,651 women at risk Case-control studies: 5726 cases and 8027 controls

Study arms

Case-control studies group: Ovarian cancer cases (N = 5726), controls (N = 8027)

Cohort studies group (N=491,651)

Associations between frequent aspirin use and ovarian cancer incidence (*Analyses adjusted for baseline age, number of full-term births, duration of oral contraception use. Duration of menopausal hormone therapy use, and body mass index)

Outcome	Adjusted* relative risk (95% CI)
Overall ovarian cancer (all 17 studies combined)	0.87 (0.8 to 0.94)
Ovarian cancer in women with a family history of breast or ovarian cancer (16 studies)	0.88 (0.72 to 1.06)
High-grade serous in women with a family history of breast or ovarian cancer (≤16 studies, not specified)	0.82 (0.66 to 1.01)
Endometrioid in women with a family history of breast or ovarian cancer (≤16 studies, not specified)	0.76 (0.52 to 1.12)
Clear cell in women with a family history of breast or ovarian cancer (≤16 studies, not specified)	1.12 (0.64 to 1.98)
Mucinous in women with a family history of breast or ovarian cancer (≤16 studies, not specified)	1.26 (0.36 to 4.41)
Other/unknown epithelial histotype in women with a family history of breast or ovarian cancer (≤16 studies, not specified)	1.01 (0.69 to 1.47)

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Low
Overall bias	Directness	Indirectly applicable *(Whole population is not high risk women. However, there are some relevant subgroup analyses)*

Hurwitz, 2023

Bibliographic Reference	Hurwitz, Lauren M; Webb, Penelope M; Jordan, Susan J; Doherty, Jennifer A; Harris, Holly R; Goodman, Marc T; Shvetsov, Yurii B; Modugno, Francesmary; Moysich, Kirsten B; Schildkraut, Joellen M; Berchuck, Andrew; Anton-Culver, Hoda; Ziogas, Argyrios; Menon, Usha; Ramus, Susan J; Wu, Anna H; Pearce, Celeste Leigh; Wentzensen, Nicolas; Tworoger, Shelley S; Pharoah, Paul D P; Trabert, Britton; Association of Frequent Aspirin Use With Ovarian Cancer Risk According to Genetic Susceptibility.; JAMA network open; 2023; vol. 6 (no. 2); e230666

Study details

Country/ies where study was carried out	USA
Study type	IPD meta-analysis
Study dates	November 1, 2021, to July 31, 2022
Inclusion criteria	Population-based case-control studies that collected data on self-reported frequency of aspirin use in women who also had genetic data available.
Exclusion criteria	Cases with mucinous ovarian cancer
Patient characteristics	Data from 8 case-control studies: **<u>Non-mucinous ovarian cancer patients</u>**

	Age Age mean (SD): not reported, but median (IQR): 58 (50-66) years Histotype, number High grade serous: 2584 (58%) Low grade serous: 140 (3%) Endometroid: 688 (15%) Clear cell: 375 (8%) Other: 680 (15%) Race and ethnicity, number Black: 122 (3%) White: 3995 (89%) Other: 348 (8%) Not reported: 11 (0%) Frequent aspirin use, number Yes: 575 (13%) No: 3901 (87%) Duration of oral contraceptive use in years, number

	Never: 1629 (36%) <5: 1524 (34%) 5-<10: 634 (14%) ≥10: 539 (12%) Not reported: 150 (3%) **Control patients** Age Age mean (SD): not reported, but median (IQR): 57 (49-65) years Race and ethnicity, number Black: 218 (3%) White: 5851 (88%) Other: 580 (9%) Not reported: 10 (0%) Frequent aspirin use, number Yes: 1030 (15%) No: 5629 (85%) Duration of oral contraceptive use in years, number

	Never: 1729 (26%) <5: 2315 (35%) 5-<10: 1224 (18%) ≥10: 1288(19%) Not reported: 103 (2%)
Intervention(s)/control	Intervention: Frequent aspirin use (daily or almost daily use of aspirin ≥6 months) Control: Non-frequent aspirin use (less frequent than the intervention group)
Duration of follow-up	Not reported
Sources of funding	Department of Defense Ovarian Cancer Research Program
Sample size	Total non-mucinous ovarian cancer patients N=4476 Total control patients N=6659

Study arms

Non-mucinous ovarian cancer patients (N = 4476)

Control patients (N = 6659)

Outcome	**Non-mucinous ovarian cancer patients, N = 4476**	**Control patients, N = 6659**
Polygenic score < Median No of events	n = 1755	n = 3330
Polygenic score ≥ Median No of events	n = 2721	n = 3329

Associations between frequent aspirin use and non-mucinous epithelial ovarian cancer risk overall and within strata of polygenic score (*Analyses adjusted for age, site, interaction between age and site, race and ethnicity, parity, duration of oral contraceptive use, menopausal status, and obesity)

Outcome	Adjusted* odds ratio (95% CI)
Overall non-mucinous epithelial ovarian cancer (8 studies)	0.87 (0.76 to 0.99)
Non-mucinous epithelial ovarian cancer in women with a polygenic score ≥ median	0.86 (0.74 to 1.01)
Non-mucinous epithelial ovarian cancer in women with a polygenic score < median	0.85 (0.7 to 1.02)
Non-mucinous epithelial ovarian cancer in women with a polygenic score quintile, percentile < 20	0.94 (0.69 to 1.26)
Non-mucinous epithelial ovarian cancer in women with a polygenic score quintile, percentile 20 to < 40	0.8 (0.59 to 1.09)
Non-mucinous epithelial ovarian cancer in women with a polygenic score quintile, percentile 40 to < 60	0.78 (0.59 to 1.03)
Non-mucinous epithelial ovarian cancer in women with a polygenic score quintile, percentile 60 to < 80	0.75 (0.58 to 0.96)
Non-mucinous epithelial ovarian cancer in women with a polygenic score quintile, percentile ≥ 80	1.02 (0.8 to 1.3)
High grade serous in women with a polygenic score ≥ median	0.84 (0.7 to 1.01)
Endometroid in women with a polygenic score ≥ median	0.76 (0.53 to 1.08)
Clear cell in women with a polygenic score ≥ median	1.22 (0.79 to 1.9)

Outcome	Adjusted* odds ratio (95% CI)
Other epithelial in women with a polygenic score ≥ median	0.97 (0.72 to 1.32)

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(Participants came from case-control studies – which asked about past aspirin use. Potential for recall bias.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Partially applicable

Section	Question	Answer
		(*High risk group defined using a polygenic risk score which aggregates the effect of many common variants rather than germline pathogenic variants.)*

McLaughlin, 2007

Bibliographic Reference	McLaughlin, John R; Risch, Harvey A; Lubinski, Jan; Moller, Pal; Ghadirian, Parviz; Lynch, Henry; Karlan, Beth; Fishman, David; Rosen, Barry; Neuhausen, Susan L; Offit, Kenneth; Kauff, Noah; Domchek, Susan; Tung, Nadine; Friedman, Eitan; Foulkes, William; Sun, Ping; Narod, Steven A; Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study.; The Lancet. Oncology; 2007; vol. 8 (no. 1); 26-34

Study details

Country/ies where study was carried out	Multinational, Canada
Study type	Case-control Controls were matched to cases on year of birth (within 3 years), mutation type (*BRCA1/2*), and country of residence. In Canada, cases were matched according to ethnic origin French-Canadian or other. Cases with ovarian cancer who had a history of breast cancer were matched to controls with breast cancer (with the age of diagnosis of breast cancer matched within 5 years)
Study dates	1994-2002
Inclusion criteria	Participants were identified through genetic counselling and risk-assessment programmes offered to women from families with high-risk of breast cancer, in the course of other research projects on families at high risk of breast cancer, and from a population-based study in Ontario. 90% of the women were identified through high-risk genetic oncology clinics.

	In 1995–2002, more mutation carriers were identified through a population-based study of women with invasive ovarian cancer who were residents of Ontario. These women were diagnosed with invasive ovarian cancer of any histological type, diagnosed at any age, and were not selected for family history. A woman was eligible for the current study if the molecular analysis established that she was a carrier of a deleterious mutation in the *BRCA1/2* gene. Diagnosis of ovarian cancers was restricted to invasive (not borderline) cancers in women with at least one intact ovary
Exclusion criteria	• women with other cancers other than breast or ovarian • those for whom data on key reproductive variables were missing • those with peritoneal or fallopian cancer diagnosed after oophorectomy
Patient characteristics	**Women with invasive ovarian cancer (cases) n=799** Age at diagnosis (median (range), years): 49 (24-75) Age at questionnaire (median (range), years): 53 (27-81) *BRCA1* mutation (%): 84 *BRCA2* mutation (%): 16 *BRCA1/2* mutations (n): 1 Breast cancer (%): 32 Ethnicity (%): French-Canadian 5, Jewish 25, Other White 66, Other 3 **Controls n=2424** Age at diagnosis (median (range), years): NA

	Age at questionnaire (median (range), years): 53 (33-82) *BRCA1* mutation (%): 84 *BRCA2* mutation (%): 16 *BRCA1/2* mutations (n): 1 Breast cancer (%): 42 Ethnicity (%): French-Canadian 5, Jewish 24, Other White 70, Other 1
Intervention(s)/control	Intervention: oral contractive use Control: no oral contraceptive use
Duration of follow-up	Median 3 years (range 0-38)
Sources of funding	Funded by the Canadian Breast Cancer Research Alliance, the National Cancer Institute Grants R01 CA 63682 (to HAR) and R01 CA 63678 (to SAN), and the Canadian Institutes for Health Research (salary award to JRM).
Sample size	Total N=3223 with *BRCA1/2* mutations Women with invasive ovarian cancer (cases) n=799 Women with no ovarian cancer (controls) n=2424 Oral contraceptive use n=1796 No oral contraceptive use n=1427 Ovarian cancer events Oral contraceptive use n=367

	No oral contraceptive use n=432 Oral contraceptive use 0 to 1 year n=476 No oral contraceptive use n=1427 Ovarian cancer events Oral contraceptive use 0 to 1 year n=118 No oral contraceptive use n=432 Oral contraceptive use 1.1 to 3 years n=364 No oral contraceptive use n=1427 Ovarian cancer events Oral contraceptive use 1.1 to 3 years n=86 No oral contraceptive use n=432 Oral contraceptive use 3.1 to 5 years n=279 No oral contraceptive use n=1427 Ovarian cancer events

	Oral contraceptive use 3.1 to 5 years n=48 No oral contraceptive use n=432 Oral contraceptive use >5 years n=654 No oral contraceptive use n=1427 Ovarian cancer events Oral contraceptive use >5 years n=113 No oral contraceptive use n=432
Other information	No use of oral contraceptive is a reference group

Study arms

No use of oral contraceptive

Ovarian cancer cases (N = 432)

Control patients (N = 995)

Ever use of oral contraceptive

Ovarian cancer cases (N = 367)

Control patients (N = 1429)

Oral contraceptive use 0 to 1 year

Ovarian cancer cases (N = 118)

Control patients (N = 358)

Oral contraceptive use 1.1 to 3 years

Ovarian cancer cases (N = 86)

Control patients (N = 278)

Oral contraceptive use 3.1 to 5 years

Ovarian cancer cases (N = 48)

Control patients (N = 231)

Oral contraceptive use >5 years

Ovarian cancer cases (N = 113)

Control patients (N = 541)

Outcomes

Association between ever use of oral contraceptive and ovarian cancer risk (*analyses adjusted for ethnic group, parity, breastfeeding, tubal ligation)

Outcome	Ovarian cancer cases vs Control patients, N2 = 367, N1 = 1429
Association between ever use of oral contraceptive and ovarian cancer incidence Adjusted* odds ratio/95% CI	0.53 (0.43 to 0.66)

Association between oral contraceptive use 0 to 1 year and ovarian cancer incidence (*analyses adjusted for ethnic group, parity, breastfeeding, tubal ligation)

Outcome	Ovarian cancer cases vs Control patients, N2 = 118, N1 = 358
Association between oral contraceptive use 0 to 1 year and ovarian cancer incidence Adjusted* odds ratio/95% CI	0.67 (0.5 to 0.89)

Association between oral contraceptive use 1.1 to 3 years and ovarian cancer incidence (*analyses adjusted for ethnic group, parity, breastfeeding, tubal ligation)

Outcome	Ovarian cancer cases vs Control patients, N2 = 86, N1 = 278
Association between oral contraceptive use 1.1 to 3 years and ovarian cancer incidence	0.63 (0.46 to 0.86)

Outcome	Ovarian cancer cases vs Control patients, N2 = 86, N1 = 278
Adjusted* odds ratio/95% CI	

Association between oral contraceptive use 3.1 to 5 years and ovarian cancer incidence (*analyses adjusted for ethnic group, parity, breastfeeding, tubal ligation)

Outcome	Ovarian cancer cases vs Control patients, N2 = 48, N1 = 231
Association between oral contraceptive use 3.1 to 5 years and ovarian cancer incidence Adjusted* odds ratio/95% CI	0.36 (0.25 to 0.53)

Association between oral contraceptive use >5 years and ovarian cancer incidence (*analyses adjusted for ethnic group, parity, breastfeeding, tubal ligation)

Outcome	Ovarian cancer cases vs Control patients, N2 = 113, N1 = 541
Association between oral contraceptive use >5 years and ovarian cancer incidence Adjusted* odds ratio/95% CI	0.47 (0.35 to 0.62)

Critical appraisal- CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell (Potential for recall bias as data collected via a questionnaire)
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Ethnic group, nulliparity, breastfeeding, tubal ligation. However, although most the centres used the same questionnaire, a modified version was used in some and not all centres requested information on breastfeeding
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	Reported that oral contraceptive use protects against ovarian cancer
(B) What are the results?	8. How precise are the results?	Relatively precise for ever use vs never use OR 0.53 (0.43 to 0.66), for 0 to 1 year use vs never use OR 0.67 (0.5 to 0.89), for 1.1 to 3 years use vs never use OR 0.63 (0.46 to 0.86), for 3.1 to 5 years use vs never use OR 0.36 (0.25 to 0.53), for >5 years use vs neve use OR 0.47 (0.35 to 0.62)

(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Michels, 2018

Bibliographic Reference Michels, Kara A; Pfeiffer, Ruth M; Brinton, Louise A; Trabert, Britton; Modification of the Associations Between Duration of Oral Contraceptive Use and Ovarian, Endometrial, Breast, and Colorectal Cancers.; JAMA oncology; 2018; vol. 4 (no. 4); 516-521

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	1995-1996
Inclusion criteria	AARP (American Association of Retired Persons) members who were aged 50 to 71 years and residing in California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Atlanta, Georgia or Detroit, Michigan
Exclusion criteria	• participants who completed questionnaires by proxy • men • had a history of cancer other than nonmelanoma skin cancer • were identified as having cancer through death reports only • showed disagreement with reported sex • indicated that their menses stopped due to chemotherapy or radiation • did not provide information on oral contraceptive use

	For analyses of ovarian cancer, women were excluded if: • they had a diagnosis of nonepithelial ovarian cancers • with unknown histological type • who had undergone a bilateral oophorectomy or were missing this information
Patient characteristics	Women with family history of ovarian cancer only N=5062 For the whole cohort, information on family history of ovarian cancer was available for n=624 cases and n=77254 non-cases (51%) of 150745 women included in the ovarian cancer analyses (n=76630 of non-cases included in the analyses) Ovarian cancer cases (total n=1241) included women with cancers of the ovary (n=1075), fallopian tube (n=48) or peritoneum (n=118) **Duration of oral contraceptive use for the whole cohort** (no data for those with family history only) **1 to 4 years (n=34866):** Age (median (IQR), years): 59 (55-64) Race (%): white 90.6, black 6, other 3.4 Menopausal status (%): pre-menopausal 6.5, post-menopausal 93.5 Has first degree relative with ovarian cancer (%): 6.3 Has first degree relative with breast cancer (%): 12.8 **5 to 9 years (n=24564):** Age (median (IQR), years): 59 (55-64)

	Race (%): white 91.2, black 5.9, other 2.8 Menopausal status (%): pre-menopausal 6.6, post-menopausal 93.4 Has first degree relative with ovarian cancer (%): 5.8 Has first degree relative with breast cancer (%): 12.9 **>=10 years (n=18962):** Age (median (IQR), years): 60 (56-64) Race (%): white 91.5, black 6, other 2.5 Menopausal status (%): pre-menopausal 6, post-menopausal 94 Has first degree relative with ovarian cancer (%): 6.7 Has first degree relative with breast cancer (%): 12.5 **No use or up to 1 year (n=118144)*:** Age (median (IQR), years): 64 (60-67) Race (%): white 90.4, black 5.7, other 3.9 Menopausal status (%): pre-menopausal 1.9, post-menopausal 98.1 Has first degree relative with ovarian cancer (%): 6.8 Has first degree relative with breast cancer (%): 13 *this is also a reference group

	Data on family history of ovarian cancer was available for 51% of the population; less than 5% data was missing for other variables
Intervention(s)/control	Intervention: oral contractive use Control: no or <1 year oral contraceptive use
Duration of follow-up	Participants were observed from enrolment until the first date of diagnosis for a given cancer of interest, the date of death, the end of study follow-up (December 31, 2011) or the date of loss to follow-up, whichever occurred first.
Sources of funding	Supported by the Intramural Research Program of the National Cancer Institute at the National Institutes of Health
Sample size	N=5062 women with a family history of ovarian cancer Women with ovarian cancer (cases) n=51 Women with no ovarian cancer (controls) n=5011 Oral contraceptive use 1 to 4 years n=34866 No oral contraceptive use n=118144 Ovarian cancer events Oral contraceptive use n=8 No oral contraceptive use n=38 Oral contraceptive use 5 to 9 years n=24564 No oral contraceptive use n=118144 Ovarian cancer events

	Oral contraceptive use n=2 No oral contraceptive use n=38 Oral contraceptive use >=10 years n=18962 No oral contraceptive use n=118144 Ovarian cancer events Oral contraceptive use n=3 No oral contraceptive use n=38
Other information	Cancer cases were ascertained through linkage with state cancer registries and vital status was determined by linkage to the relevant registries. No or <1 year oral contraceptive use is a reference group

Study arms

Oral contraceptive use 1 to 4 years

Ovarian cancer cases (N = 8)

Control patients (N = 877)

Oral contraceptive use 5 to 9 years

Ovarian cancer cases (N = 2)

Control patients (N = 591)

Oral contraceptive use 10+ years

Ovarian cancer cases (N = 3)

Control patients (N = 535)

Outcomes

Association between oral contraceptive use 1 to 4 years and ovarian cancer incidence (*analyses adjusted for age, race, BMI, age at menarche and the modifiers of interest)

Outcome	**Ovarian cancer cases vs Control patients, N2 = 8, N1 = 877**
Association between oral contraceptive use 1 to 4 years and ovarian cancer incidence Adjusted* hazard ratio/95% CI	0.6 (0.26 to 1.39)

Association between oral contraceptive use 5 to 9 years and ovarian cancer incidence (*analyses adjusted for age, race, BMI, age at menarche and the modifiers of interest)

Outcome	Ovarian cancer cases vs Control patients, N2 = 2, N1 = 591
Association between oral contraceptive use 5 to 9 years and ovarian cancer incidence Adjusted* hazard ratio/95% CI	0.27 (0.06 to 1.14)

Association between oral contraceptive use 10+ years and ovarian cancer incidence (*analyses adjusted for age, race, BMI, age at menarche and the modifiers of interest)

Outcome	Ovarian cancer cases vs Control patients, N2 = 3, N1 = 535
Association between oral contraceptive use 10+ years and ovarian cancer incidence Adjusted* hazard ratio/95% CI	0.43 (0.13 to 1.44)

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(Only members of the AARP (American Association of Retired Persons) who were aged 50 to 71 years and residing in particular states of the US were asked to participate)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Family history of ovarian cancer was available for 51% of the population only)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate *(Only members of the AARP (American Association of Retired Persons) who were aged 50 to 71 years and residing in particular states of the US were asked to participate; family history of ovarian cancer was available for 51% of the population only)*
Overall bias	Risk of bias variation across outcomes	None
Overall bias	Directness	Partially Applicable *(Only members of the AARP (American Association of Retired Persons) were asked to participate)*

van Bommel, 2023

Bibliographic Reference	van Bommel, Majke H D; IntHout, Joanna; Veldmate, Guus; Kets, C Marleen; de Hullu, Joanne A; van Altena, Anne M; Harmsen, Marline G; Contraceptives and cancer risks in BRCA1/2 pathogenic variant carriers: a systematic review and meta-analysis.; Human reproduction update; 2023; vol. 29 (no. 2); 197-217

Study details

Country/ies where study was carried out	Netherlands
Study type	Systematic review of case-control and cohort studies
Study dates	Studies published before 23 June 2021
Inclusion criteria	Studies that reported on contraception among *BRCA1/BRCA2* carriers and the association with risk of cancer
Exclusion criteria	Studies without *BRCA1/BRCA2* carrier populations, cancer risk outcomes, publication in English or Dutch, and original data.
Patient characteristics	Data from 10 studies **Age:** Mean (SD) not reported overall for the included studies, but of those reported, the means ranged from 40 to 57 years and the ranges ranged from 20 to 93 years **Ethnicity:** not reported
Intervention(s)/control	Intervention: Any use of oral contraceptive pills (formulation not specified) Control: No use of oral contraceptive pills
Duration of follow-up	The studies varied in follow-up period, but many followed up from birth to study entry or diagnosis of ovarian cancer, time of risk-reducing salpingo-oophorectomy or death
Sources of funding	None reported
Sample size	Total N=21,425 *BRCA1/2* carriers
Results	**Ovarian cancer risk and the oral contraceptive pill—hazard ratio** HR 0.62 (0.52-0.74) – evidence came from 2 cohort studies (N=10,981); not downgraded for risk of bias, inconsistency or indirectness. **Ovarian cancer risk and the oral contraceptive pill—odds ratio** OR 0.49 (0.38–0.63) – evidence came from 7 case-control and 1 cohort study (N=10,390); not downgraded for risk of bias or indirectness, but downgraded for serious heterogeneity.

	Ratio <1 favours oral contraceptive

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	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Directly applicable

Vicus, 2009

Bibliographic Reference	Vicus D; Rosen B; Lubinski J; Domchek S; Kauff ND; Lynch HT; Isaacs C; Tung N; Sun P; Narod SA; Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers.; Gynecologic oncology; 2009; vol. 115 (no. 1)

Study details

Country/ies where study was carried out	Multinational (Canada, France, Israel, Italy, Norway, Poland, UK and the USA)

Study type	Case-control Matched for year of birth, age at diagnosis of breast cancer and country of residence
Study dates	Not reported
Inclusion criteria	Women who carry a deleterious mutation in the *BRCA*1 gene identified at the clinical genetics centres
Exclusion criteria	• Women who had ovarian cancer diagnosed before breast cancer • for whom data was missing on one or more key variables (tamoxifen use, year of breast or ovarian cancer diagnosis, oophorectomy or year of oophorectomy) • with *BRCA2*
Patient characteristics	**Women with ovarian cancer and a previous history of breast cancer (cases) n=154** Date of birth (range, years): 1947.2 (1919-66) Age mean (SD): not reported Age at diagnosis of breast cancer (mean (range), years): 42.5 (27-66) Age at diagnosis of ovarian cancer (mean, years): 51.4 (35-75) Tamoxifen treatment (%): 20.1 Oral contraceptive use (%): 53.2 Hormone replacement therapy (%): 4.6 Race or ethnic group: not reported **Women with a history of breast cancer (controls) (n=560)**

	Date of birth (range, years): 1946.7 (1916-68) Age mean (SD): not reported Age at diagnosis of breast cancer (mean (range), years): 43 (26-68) Age at diagnosis of ovarian cancer (mean, years): NA Tamoxifen treatment (%): 20.7 Oral contraceptive use (%): 55.5 Hormone replacement therapy (%): 6.5 Race or ethnic group: not reported Cases and controls were matched for year of birth, age at diagnosis of breast cancer and country of residence
Intervention(s)/control	Intervention: oral contractive use Control: no oral contraceptive use
Duration of follow-up	Not reported
Sources of funding	Supported by a grant from the Canadian Breast Cancer Research Alliance, the Department of Defence Breast Cancer Research Program (DAMD17–03-1-0375 to N.D.K.), Project Hope for Ovarian Cancer Research and Education and The American Physicians Fellowship for Medicine in Israel.
Sample size	Total N=714 with *BRCA1* mutation **Women with ovarian cancer and a previous history of breast cancer** (cases) n=154 Women with a previous history of breast cancer (controls) n=560

	Oral contraceptive use n=393 No oral contraceptive use n=321 Ovarian cancer events Oral contraceptive use n=not reported No oral contraceptive use n=not reported

Study arms

Women with ovarian cancer and a previous history of breast cancer (N = 154)

Control patients (N = 560)

Outcomes

Association between oral contraceptive use and ovarian cancer risk (*analyses adjusted for hormone replacement treatment (yes/no), parity (trend), year of birth (trend), age at diagnosis of breast cancer (trend), radiotherapy (yes/no), chemotherapy (yes/no) and type of breast cancer surgery (mastectomy vs. lumpectomy))

Outcome	**Patients with ovarian cancer and a previous history of breast cancer vs Control patients, N2 = 154, N1 = 560**
Ovarian cancer incidence Adjusted odds ratio/95% CI	0.84 (0.49 to 1.44)

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Cannot tell *(Potential for recall bias as data collected via a questionnaire)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Hormone replacement treatment (yes/no), parity (trend), year of birth (trend), age at diagnosis of breast cancer (trend), radiotherapy (yes/no), chemotherapy (yes/no) and type of breast cancer surgery (mastectomy vs. lumpectomy)
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	No association between oral contraceptive use and ovarian cancer
(B) What are the results?	8. How precise are the results?	Not very precise as 95%CI is 0.49 to 1.44, OR=0.84
(B) What are the results?	9. Do you believe the results?	Yes

Section	Question	Answer
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Cannot tell *(Mixed population: women with ovarian cancer and a history of breast cancer)*

Appendix E Forest plots

Forest plots for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

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

Appendix F GRADE tables

GRADE tables for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Table 4: Evidence profile for comparison between frequent aspirin use and infrequent/no aspirin use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frequent aspirin use	Infrequent/ no aspirin use	Relative (95% CI)	Absolute		
Ovarian cancer incidence in women at all levels of risk. Mean follow-up in studies 4.6 to 14.3 years												
17 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	serious indirectness[1]	serious[2]	none	NR	NR	RR 0.87 (0.8 to 0.94)[3]	Not calculable	LOW	CRITICAL
Ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	NR	NR	RR 0.88 (0.72 to 1.06)[3]	Not calculable	MODERATE	CRITICAL
High-grade serous ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
≤ 16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	NR	NR	RR 0.82 (0.66 to 1.01)[3]	Not calculable	MODERATE	CRITICAL
Endometrioid ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
≤ 16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	NR	NR	RR 0.76 (0.52 to 1.12)[3]	Not calculable	MODERATE	CRITICAL
Clear cell ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
≤ 16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR	NR	RR 1.12 (0.64 to 1.96)[3]	Not calculable	LOW	CRITICAL
Mucinous ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
≤ 16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR	NR	RR 1.26 (0.36 to 4.41)[3]	Not calculable	LOW	CRITICAL
Other/unknown epithelial histotype ovarian cancer incidence in women with a family history of breast or ovarian cancer. Mean follow-up in studies 4.6 to 14.3 years												
≤ 16 (in IPD by Hurwitz 2022)	case-control and cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	NR	NR	RR 1.01 (0.69 to 1.47)[3]	Not calculable	LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women at all levels of risk. Follow-up not reported												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frequent aspirin use	Infrequent/ no aspirin use	Relative (95% CI)	Absolute		
8 (in IPD by Hurwitz 2023)	case-control studies	serious[5]	no serious inconsistency	serious[1]	serious[2]	none	cases 4476, controls 6659		OR 0.87 (0.76 to 0.99)[6]	Not calculable[6]	VERY LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score ≥ median. Follow-up not reported												
8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	cases 2721, controls 3329		OR 0.86 (0.74 to 1.01)[6]	Not calculable[6]	LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score < median. Follow-up not reported												
8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	serious[7]	serious[2]	none	cases 1755, controls 3330		OR 0.85 (0.7 to 1.02)[6]	Not calculable[6]	VERY LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score < 20 percentile. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	serious[7]	very serious[4]	none	cases 613, controls 1332		OR 0.94 (0.69 to 1.26)[6]	Not calculable[6]	VERY LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score 20 < 40 percentile. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	serious[7]	serious[2]	none	cases 695, controls 1332		OR 0.8 (0.59 to 1.09)[6]	Not calculable[6]	VERY LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score 40 < 60 percentile. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	serious[7]	serious[2]	none	cases 922, controls 1332		OR 0.78 (0.59 to 1.03)[6]	Not calculable[6]	VERY LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score 60 < 80 percentile. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	cases 969, controls 1332		OR 0.75 (0.58 to 0.96)[6,8]	Not calculable[6]	LOW	CRITICAL
Overall non-mucinous epithelial ovarian cancer incidence in women with polygenic risk score ≥ 80 percentile. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	cases 1277, controls 1331		OR 1.02 (0.8 to 1.3)[6]	Not calculable[6]	VERY LOW	CRITICAL
High grade serous ovarian cancer incidence in women with polygenic risk score ≥ median. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	cases 1661, controls 3329		OR 0.84 (0.7 to 1.01)[6]	Not calculable[6]	LOW	CRITICAL
Endometroid ovarian cancer incidence in women with polygenic risk score ≥ median. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	cases 383, controls 3329		OR 0.76 (0.53 to 1.08)[6]	Not calculable[6]	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frequent aspirin use	Infrequent/ no aspirin use	Relative (95% CI)	Absolute		
Clear cell ovarian cancer incidence in women with polygenic risk score ≥ median. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	cases 185, controls 3329		OR 1.22 (0.79 to 1.9)[6]	Not calculable[6]	VERY LOW	CRITICAL
Other epithelial ovarian cancer incidence in women with polygenic risk score ≥ median. Follow-up not reported												
≤ 8 (in IPD by Hurwitz 2023)	case-control studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	cases 410, controls 3329		OR 0.97 (0.72 to 1.32)[6]	Not calculable[6]	VERY LOW	CRITICAL

CI: confidence interval; IPD: individual patient data; NR: not reported; OR: odds ratio; RR: relative risk
1 Studies conducted in women at all levels of ovarian cancer risk
2 95% CI crosses 1 MID
3 Relative risks adjusted for baseline age, number of full-term births, duration of oral contraception use. Duration of menopausal hormone therapy use, and body mass index
4 95% CI crosses 2 MIDs
5 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
6 Odds ratios adjusted for age, site, interaction between age and site, race and ethnicity, parity, duration of oral contraceptive use, menopausal status, and obesity
7 Studies conducted in women at low level of non-mucinous epithelial ovarian cancer risk
8 This is likely to be a spurious finding since the interaction between polygenic score quintile and frequency of aspirin use was not statistically significant (p = 0.43)

Table 5: Evidence profile for comparison between daily aspirin use and no daily no aspirin use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily use	No daily use	Relative (95% CI)	Absolute		
Ovarian cancer incidence in women with family history of ovarian cancer. Follow-up until diagnosis of the cancer of interest, loss-to-follow-up, death, or date of administrative censoring												
1 (Hurwitz 2021)	IPD	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17/1446 (1.2%)	51/5628 (0.9%)	HR 1.35 (0.77 to 2.35)[2]	3 more per 1000 (from 2 fewer to 12 more)	LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; IPD: individual patient data
1 95% CI crosses 2 MIDs
2 Adjusted for baseline age, race, study/arm, BMI, duration of oral contraceptive use, duration of hormonal therapy use, number of live births

Table 6: Evidence profile for comparison between oral contraceptive and no oral contraceptive use in women with *BRCA1/2* pathogenic variant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral contraceptive use	No oral contraceptive use	Relative (95% CI)	Absolute		
Ovarian cancer incidence (in studies reporting hazard ratios)												
2 (in SR by Van Bommel 2023)	cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported; total number across both groups = 10,981		HR 0.62 (0.52 to 0.74)	Not calculable	HIGH	CRITICAL
Ovarian cancer incidence (in studies reporting odds ratios)												
8 (in SR Van Bommel 2023)	case-control and cohort studies	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	Not reported; total number across both groups = 10,390		OR 0.49 (0.38 to 0.63)	Not calculable	MODERATE	CRITICAL
Ovarian cancer incidence												
1 (McLaughlin 2007)	case-control	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	367/1796 (20.4%)	432/1427 (30.3%)	OR 0.53 (0.43 to 0.66)[2]	116 fewer per 1000 (from 80 fewer to 142 fewer)	HIGH	CRITICAL
Ovarian cancer incidence (in women with a BRCA1 mutation)												
1 (Vicus 2009)	case-control	no serious risk of bias	no serious inconsistency	serious indirectness[3]	very serious imprecision[4]	none	Number of ovarian cancer cases per group not reported		OR 0.84 (0.49 to 1.44)[5]	Not calculable	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; OR: odds ratio; SR: Systematic review
1 Serious heterogeneity unexplained by subgroup analysis
2 Adjusted for ethnic group, parity, breastfeeding, tubal ligation
3 Mixed population: women with ovarian cancer and a history of breast cancer
4 95% CI crosses 2 MIDs
5 Adjusted for hormone replacement treatment, parity, year of birth, age at diagnosis of breast cancer, radiotherapy, chemotherapy and type of breast cancer surgery

Table 7: Evidence profile for comparison between different durations of oral contraceptive and no oral contraceptive use in women with *BRCA1/2* pathogenic variant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral contraceptive use	No oral contraceptive use	Relative (95% CI)	Absolute		
Ovarian cancer incidence: oral contraceptive use 0 to 1 year												
1 (McLaughlin 2007)	case-control	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	118/476 (24.8%)	432/1427 (30.3%)	OR 0.67 (0.5 to 0.89)[2]	77 fewer per 1000 (from 24 fewer to 124 fewer)	MODERATE	CRITICAL
Ovarian cancer incidence: oral contraceptive use 1.1 to 3 years												

1 (McLaughlin 2007)	case-control	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	86/364 (23.6%)	432/1427 (30.3%)	OR 0.63 (0.46 to 0.86)[2]	88 fewer per 1000 (from 31 fewer to 136 fewer)	MODERATE	CRITICAL
Ovarian cancer incidence: oral contraceptive use 3.1 to 5 years												
1 (McLaughlin 2007)	case-control	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/279 (17.2%)	432/1427 (30.3%)	OR 0.36 (0.25 to 0.53)[2]	168 fewer per 1000 (from 116 fewer to 205 fewer)	HIGH	CRITICAL
Ovarian cancer incidence: oral contraceptive use >5 years												
1 (McLaughlin 2007)	case-control	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious	none	113/654 (17.3%)	432/1427 (30.3%)	OR 0.47 (0.35 to 0.62)[2]	133 fewer per 1000 (from 91 fewer to 171 fewer)	HIGH	CRITICAL

CI: confidence interval; OR: odds ratio
1 95% CI crosses 1 MID
2 Adjusted for ethnic group, parity, breastfeeding, tubal ligation

Table 8: Evidence profile for comparison between different durations of oral contraceptive and no oral contraceptive use in women with a family history of ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral contraceptive use**	**No oral contraceptive use**	**Relative (95% CI)**	**Absolute**		
Ovarian cancer incidence: oral contraceptive use 3 to 11 months												
1 (Gross 1992)	case-control	serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	No data according to family history		RR 3.1 (0.7 to 14.1)[3]	Not calculable	VERY LOW	CRITICAL
Ovarian cancer incidence: oral contraceptive use 1 to 4 years												
1 (Michels 2018)	cohort study	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	8/34866 (0.02%)	38/118144 (0.03%)	HR 0.6 (0.26 to 1.39)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
Ovarian cancer incidence: oral contraceptive use 5 to 9 years												
1 (Michels 2018)	cohort study	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious imprecision[6]	none	2/24564 (0.01%)	38/118144 (0.03%)	HR 0.27 (0.06 to 1.14)	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
Ovarian cancer incidence: oral contraceptive use >=10 years												
1 (Michels 2018)	cohort study	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	3/18962 (0.02%)	38/118144 (0.03%)	HR 0.43 (0.13 to 1.44)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; RR: relative risk
1 Finding is based on few exposed women and represents the results of exploratory analyses
2 95% CI crosses 2 MIDs
3 Adjusted for age and parity

4 Only members of the AARP (American Association of Retired Persons) who were aged 50 to 71 years and residing in particular states of the US were asked to participate; family history of ovarian cancer was available for 51% of the population only
5 Adjusted for age, race, BMI, age at menarche and the modifiers of interest
6 95% CI crosse 1 MID

Appendix G Economic evidence study selection

Study selection for: How effective are preventive medicines for reducing the incidence of ovarian cancer 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: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

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

Appendix I Economic model

Economic model for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Baandrup, Louise, Faber, Mette T, Christensen, Jane et al. (2013) Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. Acta obstetricia et gynecologica Scandinavica 92(3): 245-55	- Population not relevant to this review protocol
Beral, Valerie, Bull, Diana, Green, Jane et al. (2007) Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet (London, England) 369(9574): 1703-10	- Intervention in study does not match that specified in this review protocol
Burn J, Gerdes AM, Macrae F et al. (2011) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet (London, England) 378(9809): 2081-2087	- Population not relevant to this review protocol *Results not reported separately for women (% of women not reported)*
Burn J, Sheth H, Elliott F et al. (2020) Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet (London, England) 395(10240): 1855-1863	- Population not relevant to this review protocol *Results not reported separately for women (55.3% women)*
Cook, Nancy R, Lee, I-Min, Gaziano, J Michael et al. (2005) Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 294(1): 47-55	- Population not relevant to this review protocol
D'Alessandro, G., Frigerio, M., Barra, F. et al. (2021) Systematic review and meta-analysis on the impact of the levonorgestrel-releasing intrauterine system in reducing risk of ovarian cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics	- Intervention in study does not match that specified in this review protocol
Dixon, Suzanne C, Nagle, Christina M, Wentzensen, Nicolas et al. (2017) Use of common analgesic medications and ovarian cancer survival: results from a pooled analysis in the Ovarian Cancer Association Consortium. British journal of cancer 116(9): 1223-1228	- Population not relevant to this review protocol
Dorjgochoo, Tsogzolmaa, Shu, Xiao-Ou, Li, Hong-Lan et al. (2009) Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006. International journal of cancer 124(10): 2442-9	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Fairfield, Kathleen M, Hunter, David J, Fuchs, Charles S et al. (2002) Aspirin, other NSAIDs, and ovarian cancer risk (United States). Cancer causes & control : CCC 13(6): 535-42	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Ferris, J.S., Daly, M.B., Buys, S.S. et al. (2014) Oral contraceptive and reproductive risk factors for ovarian cancer within sisters in the breast cancer family registry. British Journal of Cancer 110(4): 1074-1080	- Included in van Bommel 2023
Friebel, Tara M; Domchek, Susan M; Rebbeck, Timothy R (2014) Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers:	- Systematic review, included studies checked for relevance

Study	Code [Reason]
systematic review and meta-analysis. Journal of the National Cancer Institute 106(6): dju091	
Gross, T P and Schlesselman, J J (1994) The estimated effect of oral contraceptive use on the cumulative risk of epithelial ovarian cancer. Obstetrics and gynecology 83(3): 419-24	- Analyses not relevant to this review protocol *All estimates appear to be unadjusted*
Huang, Wen-Yi, Daugherty, Sarah E, Shiels, Meredith S et al. (2018) Aspirin Use and Mortality in Two Contemporary US Cohorts. Epidemiology (Cambridge, Mass.) 29(1): 126-133	- Analyses not relevant to this review protocol *No ovarian cancer-specific analyses in high-risk women*
Huang, Zhezhou, Gao, Yutang, Wen, Wanqing et al. (2015) Contraceptive methods and ovarian cancer risk among Chinese women: A report from the Shanghai Women's Health Study. International journal of cancer 137(3): 607-14	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Huber, D, Seitz, S, Kast, K et al. (2020) Use of oral contraceptives in BRCA mutation carriers and risk for ovarian and breast cancer: a systematic review. Archives of gynecology and obstetrics 301(4): 875-884	- Systematic review, included studies checked for relevance
Iodice, S, Barile, M, Rotmensz, N et al. (2010) Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. European journal of cancer (Oxford, England : 1990) 46(12): 2275-84	- Systematic review, included studies checked for relevance
Iversen, Lisa, Sivasubramaniam, Selvaraj, Lee, Amanda J et al. (2017) Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. American journal of obstetrics and gynecology 216(6): 580e1-580e9	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Moorman, Patricia G, Havrilesky, Laura J, Gierisch, Jennifer M et al. (2013) Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31(33): 4188-98	- Systematic review, included studies checked for relevance
Movahedi, Mohammad, Bishop, D Timothy, Macrae, Finlay et al. (2015) Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(31): 3591-7	- Outcomes in study do not match those specified in this review protocol
Murphy, Megan A, Trabert, Britton, Yang, Hannah P et al. (2012) Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP Diet and Health Study and systematic review. Cancer causes & control : CCC 23(11): 1839-52	- Population not relevant to this review protocol
Ness, Roberta B, Dodge, Rhiannon C, Edwards, Robert P et al. (2011) Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer. Annals of epidemiology 21(3): 188-96	- Included in Hurwitz 2022
Park, Boyoung, Park, Sohee, Shin, Hai-Rim et al. (2016) Population attributable risks of modifiable reproductive factors for breast and ovarian cancers in Korea. BMC cancer 16: 5	- Analyses not relevant to this review protocol *No analyses of in high-risk women, instead family history was one of the factors adjusted for in the analyses, but with no results reported for that*
Pinheiro, Simone P, Tworoger, Shelley S, Cramer, Daniel W et al. (2009) Use of nonsteroidal antiinflammatory agents and incidence	- Included in Hurwitz 2022

Study	Code [Reason]
of ovarian cancer in 2 large prospective cohorts. American journal of epidemiology 169(11): 1378-87	
Piver, M S, Baker, T R, Jishi, M F et al. (1993) Familial ovarian cancer. A report of 658 families from the Gilda Radner Familial Ovarian Cancer Registry 1981-1991. Cancer 71(2suppl): 582-8	- Information on intervention (birth control pills) not reported in sufficient detail to analyse (e.g., extent/definition of use unclear)
Pragout, D., Laurence, V., Baffet, H. et al. (2018) Contraception and cancer: CNGOF Contraception Guidelines. Gynecologie Obstetrique Fertilite et Senologie 46(12): 834-844	- Study not reported in English
Santucci, C., Gallus, S., Martinetti, M. et al. (2021) Aspirin and the risk of nondigestive tract cancers: An updated meta-analysis to 2019. International Journal of Cancer 148(6): 1372-1382	- Population not relevant to this review protocol
Schlesselman, J J (1995) Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstetrics and gynecology 85(5pt1): 793-801	- Population not relevant to this review protocol
Schuler, Susanne, Ponnath, Marvin, Engel, Jorg et al. (2013) Ovarian epithelial tumors and reproductive factors: a systematic review. Archives of gynecology and obstetrics 287(6): 1187-204	- Study design not relevant to this review protocol *Even though the study calls itself a systematic review, it is not reported accordingly, e.g., no inclusion/exclusion criteria reported, no analysis method reported*
Soegaard, Marie, Jensen, Allan, Hogdall, Estrid et al. (2007) Different risk factor profiles for mucinous and nonmucinous ovarian cancer: results from the Danish MALOVA study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 16(6): 1160-6	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Sorensen, H T, Friis, S, Norgard, B et al. (2003) Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. British journal of cancer 88(11): 1687-92	- Analyses not relevant to this review protocol *No ovarian cancer-specific analyses in high-risk women*
Tworoger, Shelley S, Fairfield, Kathleen M, Colditz, Graham A et al. (2007) Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. American journal of epidemiology 166(8): 894-901	- Analyses not relevant to this review protocol *No analyses in high-risk women*
Whelan, Eilbhe, Kalliala, Ilkka, Semertzidou, Anysia et al. (2022) Risk Factors for Ovarian Cancer: An Umbrella Review of the Literature. Cancers 14(11)	- Population not relevant to this review protocol
Whittemore, A S, Balise, R R, Pharoah, P D P et al. (2004) Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. British journal of cancer 91(11): 1911-5	- Included in van Bommel 2023

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: How effective are preventive medicines for reducing the incidence of ovarian cancer for women at increased risk of familial ovarian cancer?

K.1.1. Research recommendation

What is the effectiveness of primary preventive medicines for reducing the incidence of ovarian cancer in women at increased risk of familial ovarian cancer?

Why this is important

Women at increased risk of familial ovarian cancer can take steps to reduce their risk of developing ovarian cancer, for example, by undergoing risk-reducing surgery. However, not all women at risk of familial ovarian cancer wish to have surgery. Data from the evidence review suggests that oral contraceptives reduce the risk of ovarian cancer and the committee knew of other data that possibly suggests anti-inflammatory medications may also reduce this risk but this evidence did not meet inclusion criteria and more research is needed. However, oral contraceptive use may increase breast cancer risk in women who are at increased risk of ovarian cancer. The potential role of novel therapeutic drugs in medical prevention (if any) is also not yet established.

Rationale for research recommendation

Table 10: Research recommendation rationale

Research question	
Why is this needed	
Importance to 'patients' or the population	This research question is important to women who are at increased risk of ovarian cancer and may not want to undergo risk-reducing surgery. This would enable these women to make an informed decision on taking alternative medicines to potentially reduce their risk of ovarian cancer.
Relevance to NICE guidance	The lack of evidence regarding the effectiveness of preventive medicines currently restricts NICE guidance. The committee did not make strong recommendations as the evidence was insufficient to recommend the general use of preventive medicines for women with high risk of familial ovarian cancer.
Relevance to the NHS	Potential to help women to make an informed decision about taking preventive medicines if risk-reducing surgery is not a preferred option. This aligns with the NHS Long Term Plan as one of the roles of the NHS is preventing deterioration of health to improve quality of life.
National priorities	Cancer prevention and survival are the key priorities for patients and the government, as stated in the NHS long term plan for cancer.
Current evidence base	Current evidence regarding effectiveness of preventive medicines in women at increased risk of ovarian cancer is limited.
Equality	Access to information on preventive medicines may be different in women from different ethnic and socio-economic backgrounds. Research to explore this question could increase inclusivity and reduce disparity in health outcomes.

Research question	
Feasibility	Randomised study or window of opportunity study of preventive medicines vs each other or placebo or no medication may be possible. Long-term cohort studies may also be feasible.
Other comments	None

Modified PICO table

Table 11: Research recommendation modified PICO table

Criterion	Explanation
Population	Women at increased risk of familial ovarian cancer. The committee agreed that research would be particularly welcome in groups of people with characteristics under the Equality 2010 Act (for example trans-men and non-binary people register female at birth or people from different ethnic backgrounds).
Intervention	Medicines: • oral contraceptives • non-steroidal anti-inflammatory drugs (NSAIDs) • novel therapeutics
Comparator	In comparison with: • each other • placebo • no medication
Outcomes	• ovarian cancer incidence • health-related quality of life • treatment related adverse effects • overall survival
Study design	• randomised controlled trials (RCTs) • cohort studies
Timeframe	Up to 10-15 years follow-up
Additional information	None