National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[P] Hormone replacement therapy after risk-reducing surgery

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.10.1 to 1.10.4 and research recommendation 5 in the NICE guideline

September 2023

Draft for consultation

These evidence reviews were developed by NICE

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Hormone replacement therapy after risk-reducing surgery

Review question

What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Introduction

Women with a familial ovarian cancer risk may be offered risk reducing surgery before the age of their menopause. This surgery often involves removal of their ovaries in their entirety to mitigate their ovarian cancer risk. If removed before the menopause this surgery will lead to an immediate surgical menopause. It has been shown that an early menopause has negative implications for a woman's long-term health including increased risk of cardiovascular disease and decreased bone strength. Therefore, if women are put into a surgical menopause, they are often offered hormone replacement therapy to reduce the health impact of their menopause and improve the symptoms they experience.

Women with a familial ovarian cancer risk are a unique group as they are at an increased lifetime risk of cancer. Therefore, we do not want to offer them interventions that may further increase their risk of developing cancers associated with their pathogenic variant. For example, progesterone (a hormone often given in hormone replacement therapy) is thought to increase the risk of breast cancer which, could be pertinent in a woman with a pathogenic variant in the BRCA genes which are associated with breast cancer. Therefore, if and what hormone replacement therapy we should offer women with a familial ovarian cancer risk is nuanced. This review will investigate the benefits and risks of hormone replacement therapy after risk reducing surgery in women 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 with or without breast cancer after risk-reducing surgery

Intervention	Hormone replacement therapy (HRT):
	• Systemic HRT (oral or transdermal):
	  ○ oestrogen only
	  ○ combined oestrogen + progestogen:
	  – continuous combined
	  – sequential combined
	• Vaginal/vulval oestrogen
	• Tibolone
	• Ospemifene
	• Testosterone

Comparator	• No HRT (including non-hormonal treatments) • Against another HRT
Outcomes	**Critical**

	• Cancer incidence:
	  ○ breast
	  ○ ovarian
	  ○ endometrial
	  ○ primary peritoneal
	Important
	• Health related quality of life
	• Life expectancy
	• All-cause mortality
	• Cardiac events
	• Bone health and fracture
	• Mood changes associated with menopause
	• Vasomotor symptoms
	• Neurocognitive outcomes
	• Genitourinary outcomes
	• Sexual function

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

Overall, 18 studies were in included in this review. These were 17 observational studies (Challberg 2011, Do Valle 2021, Do Valle 2022, Eisen 2008, Gaba 2021, Hall 2019, Hickey 2021, Jiang 2021, Johansen 2016, Kotsopoulos 2018, Kotsopoulos 2019, Madalinska 2006, Michaelson-Cohen 2021, Terra 2022, Terra 2023, Tucker 2016, Vermeulen 2017) and 1 non-randomised controlled trial (Steenbeek 2021). Most of the evidence identified relates to salpingo-oophorectomy and compares women who used hormone replacement therapy (HRT) after risk-reducing surgery with those who did not use HRT. There was also some evidence on vaginal oestrogen as well as on different routes of HRT administration.

The included studies are summarised in Table 2.

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

Excluded studies

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

1 Summary of included studies

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

3 **Table 2: Summary of included studies**

Study	Population	Intervention	Comparison	Outcomes
Challberg 2011 Observational study UK	N=212 women with *BRCA1/2* or at increased risk of ovarian cancer who had undergone bilateral risk-reducing salpingo-oophorectomy Age at surgery (mean (range), years): 41.2 (24-48)	HRT user (79% used oestrogen-only preparations, 7% used combination oestrogen and progesterone therapies, 14% used other preparations, such as tibolone and raloxifene)	HRT non-user	• Bone health and fracture • Mood changes associated with menopause • Vasomotor symptoms • Sexual function
Do Valle 2021 Observational study Canada	N=360 women with *BRCA1/2* mutations after risk reducing bilateral salpingo-oophorectomy prior to age 50 Age at surgery (mean (SD), years): HRT 40.7 (4.76), no HRT 44 (4.43)	HRT user (54% used oral formulations, 21% used transdermal oestrogen, 26% used both HRT formulations)	HRT non-user	• Cardiac events
Do Valle 2022 Observational study Canada	N=329 women with *BRCA1/2* mutations after risk reducing bilateral salpingo-oophorectomy prior to age 50 Age at surgery (mean (SD), years): 42.4 (4.8)	HRT user (any use of HRT was defined as the dispensation of at least 30 days of systemic oestrogen or oestrogen plus progestogen preparations)	HRT non-user	• Bone health and fracture
Eisen 2008 Observational study International	N=62 pairs (cases: women with *BRCA1* mutation and surgical menopause and breast cancer; controls: women with *BRCA1* mutation and surgical menopause and no breast cancer) Age at surgery (mean (range), years): 58.2 (32-85)	HRT user (HRT preparations contained oestrogen only or oestrogen and progesterone)	HRT non-user	• Breast cancer incidence
Gaba 2021 Observational study	N=88 women with *BRCA1/2* mutations or increased ovarian/breast cancer risk after	HRT user (no details on HRT given)	HRT non-user	• Bone health and fracture

Study	Population	Intervention	Comparison	Outcomes
UK	premenopausal risk reducing bilateral salpingo-oophorectomy Current age (mean (SD), years): 51.53 (9.56)			• Mood changes associated with menopause • Neurocognitive symptoms • Genitourinary symptoms • Sexual function
Hall 2019 Observational study Canada	N=93 women with *BRCA1/2* and at increased risk of ovarian cancer who had undergone bilateral salpingo-oophorectomy Age at surgery (mean (range), years): 43.8 (35-53)	HRT user (89% used oestrogen-alone HRT, others [11%] used a combination therapy [oestrogen plus testosterone or oestrogen plus progesterone])	HRT non-user	• Health related quality of life • Vasomotor symptoms • Sexual function
Hickey 2021 Observational study International	N=95 women at high risk of ovarian cancer after risk reducing salpingo-oophorectomy Age at surgery (mean (SD), years): 42.1 (4.2)	HRT user (40% used oral oestrogen formulations, 54% used transdermal oestrogen formulations and 5%) used tibolone)	HRT non-user	• Vasomotor symptoms
Jiang 2021 Observational study Australia	N=30 premenopausal women at high inherited risk of ovarian cancer due to mutations in the *BRCA1/2* gene or family history Age (mean (SD), years): HRT group 42.1 (2.9), no HRT group 42.8 (4.5)	HRT user (59% used oestrogen-only HRT, 49% used combined HRT)	HRT non-user	• Bone health and fracture
Johansen 2016 Observational study Norway	N=168 women with increased risk of breast/ovarian cancer after risk reducing salpingo-oophorectomy Age at surgery (mean (range), years): 48 (31-76)	Systemic HRT user Different systemic HRT preparations (66 used systemic preparations exclusively, 11 used local applications only. Among the 66 users of systemic HRT, 25 used oestrogen preparations, 20 used combination [oestrogen and	HRT non-user	• Sexual function

Study	Population	Intervention	Comparison	Outcomes
		progestin] preparations, and 21 used tibolone)		
Kotsopoulos 2018 Observational study International	N=872 women with *BRCA1* mutation and who had a preventive bilateral oophorectomy in the follow-up period Age at surgery (mean (range), years): HRT group: <=44 =63.9%, 45-49=23.6%, >=50=12.5%, no HRT group: <=44=34.3%, 45-49=22.6%, >=50=43%	HRT user (69% used oestrogen alone, 18% used oestrogen plus progesterone, 11% used progesterone alone, and 21% used another formulation)	HRT non-user	• Breast cancer incidence
Kotsopoulos 2019 Observational study Canada	N=50 women with *BRCA1/2* mutations who elected to undergo prophylactic bilateral salpingo-oophorectomy Age at surgery (mean (SD), years): 44 (4.2)	HRT user (no details on HRT given)	HRT non-user	• Bone health and fracture
Madalinska 2006 Observational study The Netherlands	N=164 women with an increased risk of breast/ovarian cancer after prophylactic bilateral salpingo-oophorectomy Current age (mean (SD), years): HRT 45 (5), no HRT 47 (7)	HRT user (70% used oestrogen/ progesterone, 30% used tibolone)	HRT non-user	• Mood changes associated with menopause • Vasomotor symptoms • Genitourinary symptoms • Sexual function
Michaelson-Cohen 2021 Observational study Israel	N=306 women with *BRCA1/2* mutations after risk-reducing salpingo-oophorectomy Age at surgery (median (range), years): HRT 41 (32-67), no HRT 48 (35-75)	HRT user (most used combined oestrogen and progesterone)	HRT non-user	• Breast cancer incidence
Steenbeek 2021	N=577 women with *BRCA1/2* after risk reducing surgery	HRT user (54%-60% used tibolone, 22%-28% used	HRT non-user	• Health related quality of life • Vasomotor/sexual function

Study	Population	Intervention	Comparison	Outcomes
Non-randomized controlled trial The Netherlands	(n=413 chose RRS with delayed RRO n=164 chose RRSO) Age at surgery (mean (SD), years): RRS without HRT 36.8 (3.5), RRSO without HRT 39 (3), RRS total 36.8 (3.5), RRSO with HRT 38.8 (2.9)	oestradiol/ dydrogesterone, 6%-89% used transdermal oestradiol)		
Terra 2022 Observational study The Netherlands	N=499 women with a high familial risk of breast/ovarian cancer having undergone risk-reducing salpingo-oophorectomy Age at surgery (mean (SD), years): 41.7 (2.8)	HRT user (29.1% used tibolone, 23.6% used oestradiol or progesterone, 8.7% used oestradiol only, 1.6% used vaginal oestrogen, 37% unknown)	HRT non-user	• Sexual function
Terra 2023 Observational study The Netherlands	N=406 women with a high familial risk of breast/ovarian cancer having undergone risk-reducing salpingo-oophorectomy Age at surgery (mean (SD), years): 41.8 (2.7)	HRT user (23.1% used tibolone, 17.6% used oestradiol or progestogen, 5.6% used oestradiol only, 54% unknown)	HRT non-user	• Neurocognitive function
Tucker 2016 Observational study Australia	N=119 women who had undergone risk-reducing salpingo-oophorectomy Age at surgery (mean (SD), years): 50 (8)	HRT user Current topical vaginal oestrogen user (20% used systemic HRT, 8% used vaginal topical oestrogen)	HRT non-user	• Health related quality of life • Vasomotor symptoms • Sexual function
Vermeulen 2017 Observational study The Netherlands	N=57 women at high risk of familiar breast/ovarian cancer after risk-reducing salpingo-oophorectomy Age (mean (SD), years): HRT 39.2 (3.9), no HRT 43.8 (4.7)	HRT user (a standard dosage of hormones (tibolone or oestrogen and progestin) administered either orally, transdermally or topically)	HRT non-user	• Mood changes associated with menopause • Vasomotor symptoms • Genitourinary symptoms • Sexual function

HRT: hormone replacement therapy; RRS: risk-reducing salpingectomy; RRSO: risk-reducing salpingo-oophorectomy; SD: standard deviation

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

Summary of the evidence

Breast cancer incidence

Two out of 3 low quality evidence outcomes related to breast cancer incidence showed no important difference (at 6 and 10 year follow-up) between women who had any HRT after oophorectomy or salpingo-oophorectomy compared to those who did not and one very low outcome showed a reduction in breast cancer incidence up to a mean age of 58 years. There was also no evidence of an important difference in terms of breast cancer incidence between women who had any HRT, combined (oestrogen plus progesterone) HRT, or oestrogen alone HRT (very low to low quality evidence) as compared to those who did not.

Health related quality of life

In terms of health-related quality of life (overall and change from baseline), very low to moderate quality evidence showed no important difference between those who received HRT after salpingo-oophorectomy or salpingectomy and those who did not.

Cardiac events

Low quality evidence showed no important difference in terms of cardiac events measured as a composite outcome of incident myocardial infarction, heart failure, and/or cerebrovascular disease (consisting of ischemic or haemorrhagic stroke, unspecified cerebrovascular disease, and occlusion of cerebral or precerebral arteries) between those who received HRT after salpingo-oophorectomy and those who did not.

Bone health and fracture

Very low to low quality evidence showed no important difference in terms of bone fractures, change in bone mineral density T score and change in the areal bone mineral density at the lumbar spine, femoral neck or total hip between women who received HRT after salpingo-oophorectomy and those who did not. However, one study reported a benefit of HRT for mean annual change (%) in bone mineral density at the lumbar spine and total hip in those who received HRT after surgery as compared to those who did not. However, the same study also reported no difference in terms of change at the femoral neck.

In terms of osteoporosis, moderate quality evidence showed an important benefit in women who had DEXA scan as women who received HRT were less likely to have osteoporosis. However, there was also no evidence of an important difference for the same outcome from another study (very low quality).

There was no evidence of an important difference between the different lengths of oestrogen deprivation (such as 0, 1-23 months and >=24 months) and osteopenia or osteoporosis (very low quality evidence) between women who received HRT after salpingo-oophorectomy and those who did not. Very low quality evidence also showed no important difference between 1-23 months of oestrogen deprivation as compared to 24 or more months for osteopenia.

Mood changes associated with menopause and vasomotor symptoms

Very low quality evidence showed no important difference in terms of mood changes associated with menopause between women who received HRT after surgery as compared to those who did not. There was also no evidence of an important difference in relation to vasomotor symptoms such as hot flushes or night sweats (very low quality evidence) and no

important difference in terms of change in vasomotor symptoms from baseline to 3.5 years follow-up (low quality evidence) between those who received HRT after surgery and those who did not. However, very low to moderate quality evidence showed an important benefit of HRT after surgery for overall vasomotor symptoms and for change in these symptoms from baseline to 1 year follow-up as women who received HRT after surgery reported fewer symptoms than those did not receive HRT.

Neurocognitive outcomes

In terms of neurocognitive outcomes such as memory loss, reasoning, forgetfulness, attention, concentration, multitasking and slow thinking, very low to low quality evidence showed no important difference between women who received HRT after salpingo-oophorectomy as compared to those who did not.

Genitourinary outcomes

Very low quality evidence showed an important benefit of HRT after salpingo-oophorectomy for some genitourinary outcomes such as vaginal dryness as women who received HRT after surgery reported less symptoms as compared to those who did not receive HRT. However, there was no evidence of an important difference in terms of urinary incontinence between the 2 groups.

Sexual function

Most of the very low to high quality evidence showed no important difference in terms of sexual symptoms or sexual function (overall and change from baseline) between women who received HRT after surgery and those who did not. However, there was some very low to low quality evidence which showed an important benefit of HRT in terms of overall sexual function (when measured with the FSFI scale (Female Sexual Functioning Index)) and sexual discomfort as women who received HRT after salpingo-oophorectomy had better overall sexual function and less sexual discomfort as compared to women who did not use HRT. There was no evidence of an important difference in terms of change in sexual symptoms from baseline to 1 year follow-up between those who received HRT and those who did not.

Very low or low quality evidence regarding composite outcomes such as Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) scale which evaluates commonly reported menopausal symptoms such as vasomotor symptoms, vaginal symptoms and sexual dysfunction, and Greene Climacteric Scale (GCS) scale which evaluates 4 domains: depression/anxiety, somatic, vasomotor, and sexual problems, showed less symptoms in women who had HRT after salpingo-oophorectomy or salpingectomy as compared to those who had not.

Moderate quality evidence showed an important benefit of oestrogen systemic HRT, combined (oestrogen and progestin) HRT and tibolone after salpingo-oophorectomy for sexual discomfort but not for sexual pleasure as compared to no HRT.

Vaginal oestrogen

Very low quality evidence showed an important benefit of HRT for sexual function when measured with the FSFI scale (Female Sexual Functioning Index) between women after salpingo-oophorectomy who used topical vaginal oestrogen as compared to women who used no topical vaginal oestrogen. However, very low quality evidence also showed no important difference in terms of overall health-related quality of life and sexual symptoms between the two groups. In terms vasomotor symptoms, there was no evidence of an important difference between the two groups (very low quality evidence).

Similarly, moderate quality evidence showed no important difference in terms of sexual pleasure or sexual discomfort between women after salpingo-oophorectomy who had local HRT or local oestrogen only HRT as compared to those who had no HRT.

Route of administration

Very low quality evidence showed no important difference in terms of overall health-related quality of life, vasomotor or sexual symptoms/function between women who received systemic HRT after surgery as compared to those who received topical vaginal oestrogen.

Moderate quality evidence showed no important difference in terms of sexual pleasure or sexual discomfort between women who received systemic HRT as compared to women who received local oestrogen HRT.

In terms of different HRT preparations, moderate to high quality evidence showed no important difference for sexual function nor discomfort between women who received systemic HRT as compared to those who had oestrogen systemic HRT, combined (oestrogen plus progestin) HRT or tibolone.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of included economic evidence

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

Economic model

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

Evidence statements

Economic

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Incidence of breast, ovarian, endometrial and primary peritoneal cancers was prioritised as a critical outcome by the committee because it indicates whether receiving HRT after risk-

reducing surgery may be associated with an increased risk of developing these hormone-sensitive cancers.

Health related quality of life was chosen as an important outcome because it may help to determine whether receiving HRT after risk-reducing surgery is associated with an overall impairment of quality of life or whether it has overall benefits.

Life expectancy and all-cause mortality were chosen as important outcomes because they may provide an indication for the potential overall impact of HRT use after risk-reducing surgery. The surgical menopause caused by risk reducing surgery could be linked to increased risk of cardiovascular mortality, HRT may counteract this but could increase mortality risks from other causes – for example due to stroke or breast cancer.

Women undergoing risk-reducing surgery before the age of their menopause will experience an early menopause, therefore symptoms, usually associated with the menopause, such as impaired bone health, mood changes, vasomotor symptoms, neurocognitive and genitourinary outcomes as well as sexual function were chosen as important outcomes because they can help to identify whether the use or HRT after risk-reducing surgery helps to relieve the symptoms.

The quality of the evidence

The quality of the evidence from the included studies was assessed with GRADE and was very low to high, with most of the evidence being of very low or low quality. This was predominately due to serious risk of bias for a couple of outcomes and serious or very serious imprecision around the effect estimates.

The committee discussed methodological issues related to the studies. They mentioned that most of the studies were not statistically powered enough to detect a difference and that most of them had a short follow-up which is especially important for long-term outcomes such as cardiovascular events and fractures. The population of interest are young women therefore these events are rare, therefore any HRT effect would take many years to affect event rates for the above outcomes.

There was no evidence identified for the following outcomes: ovarian, endometrial and primary peritoneal cancer incidence, life expectancy and all-cause mortality.

Benefits and harms

The committee noted that most studies were small and with short follow-up times, and for some outcomes, for example bone health and sexual function, different outcome measures were used which makes it somewhat difficult to compare and generalise the results. They discussed that, for example, whilst very low quality evidence from one study showed no important difference of HRT after risk-reducing surgery on sexual dysfunction, low quality evidence from two studies (a meta-analysis) showed an important benefit of HRT for the same outcome. Despite that, the committee agreed that there was sufficient evidence showing an important benefit of HRT after risk-reducing surgery on some bone health, genitourinary, sexual and vasomotor symptoms outcomes and no evidence of an important harm. This was in line with the general literature on menopause and consistent with the committee's experience, therefore they agreed to recommend offering HRT after bilateral salpingo-oophorectomy for women without a personal history of breast cancer.

The committee recommended that for those who undergo salpingo-oophorectomy and have a history of breast cancer, HRT should be offered after discussion with their breast cancer treatment team. The committee wanted to ensure that prescribing HRT after risk-reducing surgery in such cases would not increase the risk of breast cancer reoccurrence as these people often have other potential risks factors for breast cancer such as strong family history.

Based on some of the evidence which showed an important benefit of topical vaginal oestrogen on sexual function and in line with the committee's experience as well as with the guidance on genitourinary symptoms in the NICE guidance on menopause, the committee agreed to offer vaginal oestrogen to women who experience these symptoms. They noted that some healthcare professionals were reluctant to prescribe vaginal oestrogen to people with a pathogenic variant and wanted to stress that it was safe (because there is little absorption), therefore healthcare professionals, especially GPs, should feel comfortable prescribing it. This is particularly relevant to women who do not want to take systemic HRT.

The committee agreed to make a research recommendation for this question because they felt that available evidence is based on rather small studies with a short follow-up. They agreed that this was particularly relevant for some outcomes such as bone, cardiovascular and neurocognitive health where larger study samples with much longer follow-up times are required.

Cost effectiveness and resource use

No existing economic evidence was identified for this review. The committee explained that the recommendations on HRT reinforce current practice and are in line with other NICE guidance, such as menopause, and will not require additional resources to implement.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.1 to 1.10.4 and research recommendation 5 on the long-term benefits and risks of hormone replacement therapy after risk-reducing surgery in the NICE guideline.

References – included studies

Effectiveness

Challberg 2011

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Kotsopoulos 2018

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Steenbeek 2021

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Life in BRCA1/2 Pathogenic Variant Carriers: A Nonrandomized Controlled Trial. JAMA oncology 7(8): 1203-1212, 2021

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Terra 2023

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Vermeulen 2017

Vermeulen, Ravi F M, Beurden, Marc van, Kieffer, Jacobien M et al. Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: A prospective study. European journal of cancer (Oxford, England: 1990) 84: 159-167, 2017

Appendices

Appendix A Review protocol

Review protocol for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022371251
1.	Review title	Benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer
2.	Review question	What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?
3.	Objective	To establish the benefits and risks of hormone replacement therapy after risk-reducing surgery 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, MEDLINE in Process & MEDLINE Epub Ahead of Print • Epistemonikos • International Health Technology Assessment (INAHTA) database

ID	Field	Content
		Searches will be restricted by: • English language studies • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: Women at increased risk of familial ovarian cancer with or without breast cancer after risk-reducing surgery Exclusion: none

7.	Intervention	Hormone replacement therapy (HRT):
		• Systemic HRT (oral or transdermal)
		  ○ oestrogen only
		  ○ combined oestrogen + progestogen
		  ▪ continuous combined
		  ▪ sequential combined
		• Vaginal/vulval oestrogen
		• Tibolone
		• Ospemifene
		• Testosterone

8.	Comparator	• No hormone replacement therapy (including non-hormonal treatments) • Against another HRT
9.	Types of study to be included	• RCTs and systematic reviews of RCTs • Non randomised studies and systematic reviews of non randomised studies

ID	Field	Content
10.	Other exclusion criteria	**Inclusion criteria**: • Full text papers • Observational 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	Overlap with other NICE guidelines:
		
		Women at increased risk of familial ovarian cancer who **have not** had risk reducing surgery
		• Effectiveness of HRT for menopausal symptoms:
		  ○ not covered in NG23 (due to exclusion of familial breast cancer which would also have excluded *BRCA1/2* mutation carriers),
		  ○ partially covered in Familial breast cancer guideline CG14 (due to overlap with *BRCA1/2* population for familial breast/ovarian cancer risk)
		• Risk of developing ovarian cancer with HRT:
		  ○ covered in Menopause guideline update (as a subgroup analysis)
		
		Women at increased risk of familial ovarian cancer (with or without breast cancer) after risk-reducing surgery
		• Effectiveness of HRT for menopausal symptoms:
		  ○ covered in this review
		  ○ partially covered in Familial breast cancer guideline CG14 (due to overlap with *BRCA1/2* population for breast/ovarian cancer risk)
		• Risk of breast, ovarian, endometrial, primary peritoneal cancer with HRT:
		  ○ covered in this review
		  ○ partially covered in Familial breast cancer guideline CG14 (due to overlap with *BRCA1/2* population for breast/ovarian cancer risk)

ID	Field	Content

12.	Primary outcomes (critical outcomes)	• Cancer incidence:
		  ○ breast
		  ○ ovarian
		  ○ endometrial
		  ○ primary peritoneal

13.	Secondary outcomes (important outcomes)	• Health related quality of life • Life expectancy • All-cause mortality • Cardiac events • Bone health and fracture • Mood changes associated with menopause • Vasomotor symptoms • Neurocognitive outcomes • Genitourinary outcomes • Sexual function Where possible, reports outcomes measured using validated scales/questionnaires
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.

ID	Field	Content
		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 • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the 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/

ID	Field	Content
		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 surgery (extent) • Type of HRT • Hormone receptor negative breast cancer patients • People who have an increased risk of breast cancer and those that do not, for example those that have had bilateral mastectomy Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Type of genetic mutation (including unknown mutation) 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)

ID	Field	Content
		• 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 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	March 2023

ID	Field	Content		
22.	Anticipated completion date	13 March 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐

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

ID	Field	Content
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=371251
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	Hormone replacement therapy, risk-reducing surgery, familiar 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

ID	Field	Content
36.	Details of final publication	www.nice.org.uk

HRT: hormone replacement therapy; MID: minimum important difference; NICE: National Institute for Health and Care Excellence; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Database: Ovid MEDLINE ALL

Date of last search: 13/02/2023

#	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 Salpingectomy/
53	exp Ovariectomy/
54	(oophorectom* or salping* or ovar??ctom* or ovar??tom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO).tw,kf.
55	(((fallopian* or ovar* or tubal) adj4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*).tw,kf.
56	Hysterectomy, Vaginal/ or Hysterectomy/
57	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*).tw,kf.
58	((supervaginal or supravaginal or uterus* or uteri*) adj3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)).tw,kf.
59	(gyn?ecolog* adj2 surg*).tw,kf.
60	exp Prophylactic Surgical Procedures/
61	(((risk adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
62	risk reduction behavior/
63	(risk adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
64	or/52-63
65	51 and 64
66	exp Hormone Replacement Therapy/
67	((hormon* or menopaus*) adj2 (replac* or therap* or substitut* or treatment*)).tw,kf.
68	(HRT or HT or MHT or ERT or EPRT or SEPRT).tw,kf.
69	exp Estrogens/
70	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol* or ethinylestradiol* or diethylstilbestrol* or prasterone*).tw,kf.
71	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel* or pregnenedione)).tw,kf.
72	((("body identical*" or bio-identical* or bioidentical*) adj2 hormon*) or BHRT).tw,kf.
73	(tibolone or Livial).tw,kf.
74	(Ospemifene or senshio or osphena).tw,kf.
75	Testosterone/
76	testosterone.tw,kf.
77	or/66-76
78	65 and 77
79	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
80	randomized controlled trial/ or random*.ti,ab.
81	79 not 80
82	(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.

#	Searches
83	81 or 82
84	78 not 83
85	limit 84 to English language

1 Database: Ovid Embase

2 Date of last search: 13/02/2023

#	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.

#	Searches
38	checkpoint kinase 2/
39	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
40	small cell carcinoma/
41	genetics/
42	40 and 41
43	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
44	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
45	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
46	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
47	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
48	epithelial cell adhesion molecule/
49	Epithelial cell adhesion molecule*.tw,kf.
50	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
51	or/31-39,42-50
52	30 or 51
53	salpingectomy/
54	exp ovariectomy/
55	(oophorectom* or salping* or ovar??ctom* or ovar??tom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO).tw,kf.
56	(((fallopian* or ovar* or tubal) adj4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*).tw,kf.
57	exp hysterectomy/
58	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*).tw,kf.
59	((supervaginal or supravaginal or uterus* or uteri*) adj3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)).tw,kf.
60	(gyn?ecolog* adj2 surg*).tw,kf.
61	prophylactic surgical procedure/
62	(((risk* adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
63	risk reduction/
64	(risk* adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
65	or/53-64
66	52 and 65
67	exp hormone substitution/
68	((hormon* or menopaus*) adj2 (replac* or therap* or substitut* or treatment*)).tw,kf.
69	(HRT or HT or MHT or ERT or EPRT or SEPRT).tw,kf.
70	exp estrogen/
71	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol* or ethinylestradiol* or diethylstilbestrol* or prasterone*).tw,kf.
72	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel* or pregnenedione)).tw,kf.
73	((("body identical*" or bio-identical* or bioidentical*) adj2 hormon*) or BHRT).tw,kf.
74	(tibolone or Livial).tw,kf.
75	(Ospemifene or senshio or osphena).tw,kf.
76	testosterone/
77	testosterone.tw,kf.
78	or/67-77
79	66 and 78
80	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.
81	randomized controlled trial/ or random*.ti,ab.
82	80 not 81
83	(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.
84	82 or 83
85	79 not 84

#	Searches
86	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
87	85 not 86
88	limit 87 to English language

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

Date of last search: 13/02/2023

#	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

#	Searches
#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
#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: [Salpingectomy] explode all trees
#53	MeSH descriptor: [Ovariectomy] explode all trees
#54	(oophorectom* or salping* or ovariectom* or ovarectom* or ovariotom* or ovarotom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO):ti,ab,kw
#55	(((fallopian* or ovar* or tubal) NEAR/4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*):ti,ab,kw
#56	MeSH descriptor: [Hysterectomy, Vaginal] this term only
#57	MeSH descriptor: [Hysterectomy] this term only
#58	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*):ti,ab,kw
#59	((supervaginal or supravaginal or uterus* or uteri*) NEAR/3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)):ti,ab,kw
#60	((gynecolog* or gynaecolog*) NEAR/2 surg*):ti,ab,kw
#61	MeSH descriptor: [Prophylactic Surgical Procedures] explode all trees
#62	(((risk* NEAR/2 reduc*) or prevent* or prophyla*) NEAR/2 surg*):ti,ab,kw
#63	MeSH descriptor: [Risk Reduction Behavior] this term only
#64	(risk* NEAR/2 reduc* NEAR/2 (behavior* or behaviour* or choice* or strateg* or decision*)):ti,ab,kw
#65	{OR #52-#64}
#66	#51 AND #65
#67	MeSH descriptor: [Hormone Replacement Therapy] explode all trees
#68	((hormon* or menopaus*) NEAR/2 (replac* or therap* or substitut* or treatment*)):ti,ab,kw
#69	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab,kw
#70	MeSH descriptor: [Estrogens] explode all trees
#71	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol* or ethinylestradiol* or diethylstilbestrol* or prasterone*):ti,ab,kw
#72	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel* or pregnenedione)):ti,ab,kw
#73	(((body NEXT identical* or bio-identical* or bioidentical*) NEAR/2 hormon*) or BHRT):ti,ab,kw
#74	(tibolone or Livial):ti,ab,kw
#75	(Ospemifene or senshio or osphena):ti,ab,kw
#76	MeSH descriptor: [Testosterone] this term only
#77	testosterone:ti,ab,kw
#78	{OR #67-#77}
#79	#66 AND #78
#80	conference:pt or (clinicaltrials or trialsearch):so
#81	#79 NOT #80

1 **Database: Epistemonikos**

2 **Date of last search: 13/02/2023**

#	Searches
1	((ovarian OR breast) AND (familial OR hered*) AND cancer)
2	(oophorectom* OR salping* OR ovariectom* OR ovariotom* OR BSO OR RRSO* OR RRBSO OR RRSDO OR RRESDO OR colpohysterectom* OR panhysterectom* OR hysterocolpectom* OR hysterectom*)
3	(((hormone OR menopaus*) AND (replac* OR therap* OR substitut*)) OR (HRT OR HT OR MHT OR ERT OR EPRT OR SEPRT OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR ethinylestradiol* OR diethylstilbestrol* OR prasterone* OR BHRT OR tibolone OR Livial OR Ospemifene OR senshio OR osphena OR testosterone*) OR ((combin* OR sequen* OR continu* OR plus) AND (progest* OR gestagen* OR gestogen* OR medroxyprogesterone* OR norgestrel* OR drospirenone* OR norethisterone* OR dydrogesterone* OR levonorgestrel* OR pregnenedione)) OR (("body identical*" OR bio-identical* OR bioidentical*) AND hormon*))
4	1 AND 2 AND 3

3 **Database: INAHTA International HTA Database**

4 **Date of last search: 13/02/2023**

#	Searches
37	#36 AND #34
36	#35 AND #26
35	#31 OR #30 OR #29 OR #28 OR #27
34	#33 OR #32
33	((HRT or HT or MHT or ERT or EPRT or SEPRT))[Title] OR ((HRT or HT or MHT or ERT or EPRT or SEPRT))[abs]
32	(((hormon* or menopaus*) AND (replac* or therap* or substitut* or treatment*)))[Title] OR (((hormon* or menopaus*) AND (replac* or therap* or substitut* or treatment*)))[abs]
31	((oophorectom* or salping* or ovariectom* or ovarectom* ovariotom* or ovarotom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO))[Title] OR ((oophorectom* or salping* or ovariectom* or ovarectom* ovariotom* or ovarotom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO))[abs]
30	(((gynecolog* or gynaecolog*) AND surg*))[Title] OR (((gynecolog* or gynaecolog*) AND surg*))[abs]
29	(((supervaginal or supravaginal or uterus* or uteri*) AND (amputat* or resect* or excis* or surg* or remov* or extirpat*)))[Title] OR (((supervaginal or supravaginal or uterus* or uteri*) AND (amputat* or resect* or excis* or surg* or remov* or extirpat*)))[abs]
28	((colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*))[Title] OR ((colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*))[abs]
27	(((fallopian* or ovar* or tubal) AND (amputat* or resect* or excis* or surg* or remov* or extirpat*)))[Title] OR (((fallopian* or ovar* or tubal) AND (amputat* or resect* or excis* or surg* or remov* or extirpat*)))[abs]
26	#25 OR #19
25	#24 OR #23 OR #22 OR #21 OR #20
24	((EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[Title] OR ((EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[abs]
23	(("small cell"AND (cancer* or carcinoma*) AND gene*))[Title] OR (("small cell"AND (cancer* or carcinoma*) AND gene*))[abs]
22	(((checkpoint or "check point" or "serine threonine") AND (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2))[Title] OR (((checkpoint or "check point" or "serine threonine") AND (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2))[abs]
21	((("Ataxia telangiectasia" AND mutated AND (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1))[Title] OR ((("Ataxia telangiectasia" AND mutated AND (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1))[abs]
20	((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))[Title] OR ((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2))[abs]
19	#18 AND #8
18	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
17	(((tumo?r* or cancer* or metastas?s or growth*) AND (suppress* AND (gene* or protein*)))[Title] OR (((tumo?r* or cancer* or metastas?s or growth*) AND (suppress* AND (gene* or protein*)))[abs]
16	(((carrier* or gene*) AND mutat*))[Title] OR (((carrier* or gene*) AND mutat*))[abs]

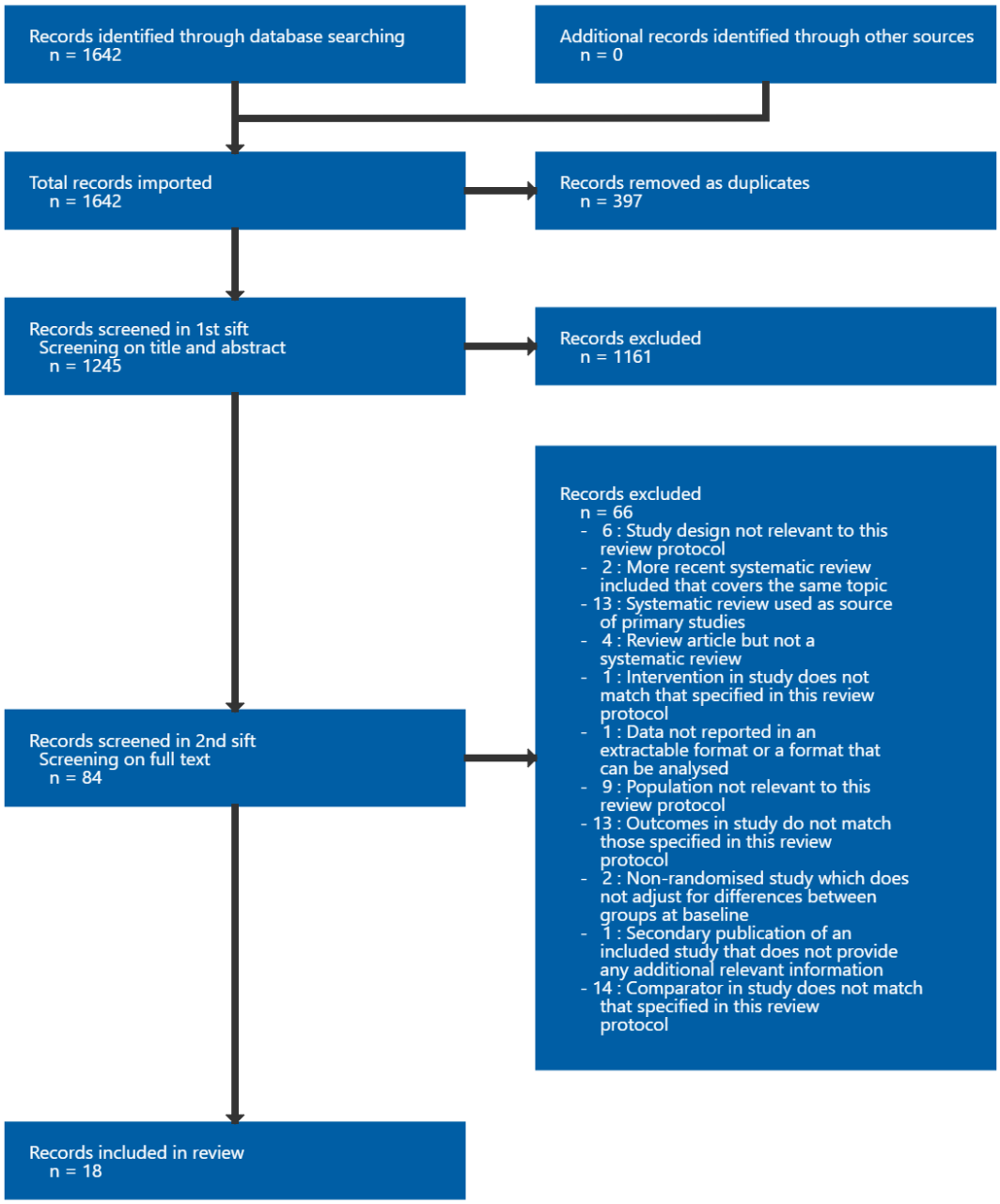
#	Searches
15	(((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[Title] OR (((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[abs]
14	((famil* AND histor* AND (cancer* or 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]
13	(("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]
12	(((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]
11	((MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((MUTYH or MYH or FAP or AFAP or APC))[abs]
10	((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]
9	(((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]
8	#7 OR #3
7	#6 OR #5 OR #4
6	(((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[Title] OR (((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[abs]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]
4	"Breast Neoplasms"[mhe]
3	#2 OR #1
2	((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
1	"Ovarian Neoplasms"[mhe]

1
2

Appendix C Effectiveness evidence study selection

Study selection for: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Figure 1: Study selection flow chart



1

Appendix D Evidence tables

Evidence tables for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Challberg, 2011

Bibliographic Reference	Challberg, J; Ashcroft, L; Lalloo, F; Eckersley, B; Clayton, R; Hopwood, P; Selby, P; Howell, A; Evans, D G; Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT.; British journal of cancer; 2011; vol. 105 (no. 1); 22-7

Study details

Country/ies where study was carried out	UK
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	• women *BRAC1/2* mutation carriers or • other women with at least a 10% lifetime risk of ovarian cancer due to family history of ovarian ± breast cancer or Lynch syndrome and • who had undergone bilateral risk-reducing salpingo-oophorectomy (BRRSPO)
Exclusion criteria	• women with BRRSPO >48 years
Patient characteristics	N=212 women with *BRCA1/2* or at increased risk of ovarian cancer who had undergone bilateral risk-reducing salpingo-oophorectomy **Age (mean (range), years) at surgery:** 41.2 (24-48) **Gender (n):** women 100%

	Ethnicity (n): not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **From *BRCA1/2* family:** 58%
Intervention(s)/control	• HRT user (HRT taken at some point 134/212 (63%)) • HRT non-user (never users of HRT 78/212 (37%)) The majority used oestrogen-only preparations (79%). Only 7% used combination oestrogen and progesterone therapies, and 14% used other preparations, such as tibolone (n=12) and raloxifene (n=2)
Duration of follow-up	The mean time of HRT use was 3.4 years (0.1 –19 years). The mean period of non-HRT use among 139 women who were without oestrogen protection at some stage before age 50 was 5.2 years (range 1 –19 years; median 5 years). The questionnaire was completed at different times after oophorectomy ranging from months to 36 years.
Sample size	N=212
Sources of funding	Not reported

1

Study arms

Length of oestrogen deprivation: 0 (N = 31)

Length of oestrogen deprivation: 1-23 months (N = 10)

Length of oestrogen deprivation: >=24 months (N = 78)

HRT user (N = 65)

HRT non-user (N = 76)

Outcomes

Bone health and fracture

Outcome	Length of oestrogen deprivation: 0, N = 31	Length of oestrogen deprivation: 1-23 months, N = 10	Length of oestrogen deprivation: >=24 months, N = 78	HRT user, N = NR	HRT non-user, N = NR
Osteopenia (defined as DXA T score -1.0 to -2.4) No of events	n = 4; % = 13	n = 3; % = 30	n = 26; % = 33	n = NR	n = NR
Osteoporosis (defined as DXA T score <-2.4) No of events	n = 1; % = 3	n = 1; % = 10	n = 10; % = 13	n = NR	n = NR

DXA: was performed on a Hologic Discovery A DXA scanner with Apex System Software Version 2.3.2 software. NR: not relevant

Mood changes associated with menopause, vasomotor symptoms, urogenital outcomes and sexual function

Outcome	Length of oestrogen deprivation: 0, N = NR	Length of oestrogen deprivation: 1-23 months, N = NR	Length of oestrogen deprivation: >=24 months, N = NR	HRT user, N = 65	HRT non-user, N = 76
FACT-ES score Mean (SD)	NR (*empty data*)	NR (*empty data*)	NR (*empty data*)	58.7 (11)	55.6 (10.8)

FACT-ES score - Polarity - Higher values are better

FACT-ES: the 18-item Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) assesses menopausal symptoms (includes hot flushes, cold/night sweats, vaginal discharge/itching/irritation/bleeding/dryness, pain/discomfort with intercourse, lost interest in sex, gained weight, lightheaded/dizzy, vomited, diarrhoea, headaches, feel bloated, breast sensitivity/tenderness, mood swings, irritable, a total score ranges from 0 to 72). NR: not relevant. SD: standard deviation

Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies

1

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Unclear *(not reported if the analysis was adjusted for any confounders)*
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear *(not reported if the analysis was adjusted for any confounders)*
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes *(However, not reported if the analysis was adjusted for any confounders)*
Overall bias and directness	Risk of bias judgment	Some concerns *(Not reported if there were any significant differences between*

Section	Question	Answer
		the 2 groups; not reported if the analysis was adjusted for any confounders. 73% response rate, some differences between respondents and non-respondents)
Overall bias and directness	Directness	Directly applicable

do Valle, 2021

Bibliographic Reference	do Valle, H.A.; Kaur, P.; Kwon, J.S.; Cheifetz, R.; Dawson, L.; Hanley, G.E.; Risk of cardiovascular disease among women carrying BRCA mutations after risk-reducing bilateral salpingo-oophorectomy: A population-based study; Gynecologic Oncology; 2021; vol. 162 (no. 3); 707-714

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study
Study dates	Between 1996 and 2017
Inclusion criteria	• women with documented deleterious *BRCA* mutations who underwent risk-reducing bilateral salpingo-oophorectomy (RRBSO) prior to age 50
Exclusion criteria	• women with a diagnosis of gynaecologic cancer (ovarian, fallopian tube, peritoneal, cervical, endometrial, uterine, vaginal or vulvar cancers) but those with other cancers, including breast cancer, were not excluded

	• exclusion criteria also included a diagnosis of relevant cardiovascular outcomes in the two years before the start of the follow-up, and women who were not registered in the universal provincial insurance program in the year of the index surgery
Patient characteristics	N=360 women with *BRCA1/2* mutations after risk reducing bilateral salpingo-oophorectomy prior to age 50 n=161 HRT n=199 no HRT **Age (mean (SD), years) at surgery:** HRT 40.7 (4.76), no HRT 44 (4.43) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** Income quintile 1=12.5%, 2=18.3%, 3=18.6%, 4=24.2%, 5=24.2% **Disabilities:** not reported **People with communication needs:** not reported **Duration HRT (mean (SD), years):** 3.36 (2.53) **Breast cancer before surgery:** HRT 23%, no HRT74.9%
Intervention(s)/control	• HRT user • HRT non-user Any use of HRT was defined as the dispensation of at least 30 days of systemic oestrogen or oestrogen plus progestogen preparations. 54% used oral formulations, 21% used transdermal oestrogen, 26% used both HRT formulations
Duration of follow-up	Mean follow-up 7.3 (4.40) years
Sample size	N=360

Sources of funding	This study was supported by the Canadian Institutes of Health Research, as well as by donor funds from the Vancouver General Hospital and University of British Columbia Hospital Foundation. GEH is supported as a Canadian Institutes of Health Research New Investigator and a Michael Smith Foundation for Health Research Scholar. GEH is also a Janet D. Cottrelle Foundation scholar.

1

2 **Study arms**

3 **HRT user (N = 161)**

4 **HRT non-user (N = 199)**

5

6 **Outcomes**

7 **Cardiac events in premenopausal women**

Outcome	**HRT user vs HRT non-user, N2 = 199, N1 = 161**
Cardiovascular disease (a composite of incident myocardial infarction, heart failure, and/or cerebrovascular disease (consisting of ischemic or haemorrhagic stroke, unspecified cerebrovascular disease, and occlusion of cerebral or precerebral arteries) Mean follow-up 7.34 (SD 4.40) years. Hazard ratio adjusted for age Hazard ratio/95% CI	1.24 (0.54 to 2.88)

8

9 **Critical appraisal – NGA Critical appraisal - ROBINS I**

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Low

Section	Question	Answer
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
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	Directly applicable

Do Valle, 2022

Bibliographic Reference	Do Valle, H.A.; Kaur, P.; Kwon, J.S.; Cheifetz, R.; Dawson, L.; Hanley, G.E.; Bone health after RRBSO among BRCA1/2 mutation carriers: a population-based study; Journal of Gynecologic Oncology; 2022; vol. 33 (no. 4); e51

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study
Study dates	Between 1996 to 2017

Inclusion criteria	Women with *BRCA1/2* mutations who underwent risk-reducing bilateral salpingo-oophorectomy (RRBSO) prior to age 50 and who: • did not have a diagnosis of ovarian, fallopian tube, or peritoneal cancers, and • did not have gynaecologic cancer listed as an indication for the index surgery • had at least 1 year of follow-up • were registered in the universal provincial insurance program in the year of their surgery. Women with a history of breast cancer were included.
Exclusion criteria	Women who: • had a DEXA-scan in the two years before the start of the follow-up • with a diagnosis of osteoporosis, or hip or vertebral fractures (prototypical osteoporotic fractures) in the 2 years preceding the study entry
Patient characteristics	N=329 women with *BRCA1/2* mutations after risk reducing bilateral salpingo-oophorectomy prior to age 50 n=153 HRT [of whom 82 (53.6%) received oral formulations, 32 (20.9%) received transdermal oestrogen, and 39 (25.5%) received both HRT formulations)] n=176 no HRT **Age (mean (SD), years) at surgery:** 42.4 (4.8) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** Income quintile 1=12.8%, 2=18.5%, 3=17.6%, 4=24.6%, 5=24.3% **Disabilities:** not reported **People with communication needs:** not reported

	Duration HRT (mean (SD), years): 3.5 (2.5) **Breast cancer before surgery:** 48.9%
Intervention(s)/control	• HRT user • HRT non-user Any use of HRT was defined as the dispensation of at least 30 days of systemic oestrogen or oestrogen plus progesterone preparations.
Duration of follow-up	The median follow-up time for women with *BRCA1/2* mutations was 6.9 years (range, 1.1–19.9)
Sample size	N=329
Sources of funding	This study was supported by the Canadian Institutes of Health Research, as well as by donor funds from the Vancouver General Hospital and University of British Columbia Hospital Foundation. Gillian E. Hanley is supported as a CIHR New Investigator and a Michael Smith Foundation for Health Research Scholar. Dr. Hanley is also a Janet D. Cottrelle foundation scholar. The funding sources played no role in study design, collection of data, interpretation of data, writing of the report or decision to submit the article for publication.

Study arms

HRT user (N = 153)

HRT non-user (N = 176)

Outcomes

Bone health and fracture

Outcome	HRT user vs HRT non-user, N2 = 176, N1 = 153
Bone fractures Median follow-up 6.9 years. Hazard ratio adjusted for age and breast cancer Hazard ratio/95% CI	0.88 (0.43 to 1.81)
Osteoporosis in women who had DEXA scan Median follow-up 6.9 years. Hazard ratio not adjusted due to low number of events Hazard ratio/95% CI	0.35 (0.13 to 0.95)

Critical appraisal – NGA Critical appraisal - ROBINS I

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
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Low
Overall bias	Directness	Directly applicable

1

2 **Eisen, 2008**

Bibliographic Reference	Eisen, Andrea; Lubinski, Jan; Gronwald, Jacek; Moller, Pal; Lynch, Henry T; Klijn, Jan; Kim-Sing, Charmaine; Neuhausen, Susan L; Gilbert, Lucy; Ghadirian, Parviz; Manoukian, Siranoush; Rennert, Gad; Friedman, Eitan; Isaacs, Claudine; Rosen, Eliot; Rosen, Barry; Daly, Mary; Sun, Ping; Narod, Steven A; Hereditary Breast Cancer Clinical Study, Group; Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers.; Journal of the National Cancer Institute; 2008; vol. 100 (no. 19); 1361-7

3

4 **Study details**

Country/ies where study was carried out	International
Study type	Matched case-control Breast cancer case patients and control subjects were matched with respect to age, age at menopause, and type of menopause (surgical or natural)
Study dates	Not reported
Inclusion criteria	• women when molecular analysis established that she was a carrier of a deleterious mutation in *BRCA1/2* but participants for the current study were drawn from the 6062 women within the cohort with a *BRCA1* mutation
Exclusion criteria	• women who had been diagnosed with ovarian, fallopian, peritoneal, or omental cancer • were diagnosed with another form of cancer • who underwent bilateral preventive mastectomy

	• who took tamoxifen for prophylaxis
Patient characteristics	N=62 pairs (cases: women with *BRCA1* mutation and surgical menopause and breast cancer; controls: women with *BRCA1* mutation and surgical menopause and no breast cancer) Surgical oophorectomy n=57 HRT (cases 34, controls 23) n=67 no HRT (cases 28, controls 39) **Age (mean (range), years) at surgery:** 58.2 (32-85) **Gender (n):** women 100% **Ethnicity (n):** Other White: controls 82%, cases 78%, Jewish: controls 14%, cases 17%, French Canadian: controls 3%, controls 4% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Mean HRT use in users:** controls 3.7 years, cases 4 years
Intervention(s)/control	• HRT user • HRT non-user HRT preparations contained oestrogen only or oestrogen and progesterone
Duration of follow-up	Not reported
Sample size	N=62 pairs
Sources of funding	Funded by Canadian Breast Cancer Research Alliance (15340) to S.A.N.; National Institutes of Health (CA 74415) to S.L.N.

Study arms

HRT user (N = 57)

HRT non-user (N = 67)

Outcomes

Breast cancer incidence

Outcome	HRT user vs HRT non-user, N2 = 67, N1 = 57
Risk of breast cancer Odds ratio/95% CI	0.48 (0.19 to 1.21)

Analyses adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence

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

Section	Question	Answer
(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?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Analyses adjusted for parity (0, 1, 2, or ≥3), oral contraceptive use (never vs ever), and country of residence
(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 difference in risk of breast cancer in women who had never used HRT as compared to women who had used HRT
(B) What are the results?	8. How precise are the results?	Not very precise: OR 0.48 (0.19 to 1.21)
(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

Gaba, 2021

Bibliographic Reference	Gaba, F; Blyuss, O; Chandrasekaran, D; Osman, M; Goyal, S; Gan, C; Izatt, L; Tripathi, V; Esteban, I; McNicol, L; Ragupathy, K; Crawford, R; Evans, D G; Legood, R; Menon, U; Manchanda, R; Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study.; BJOG : an international journal of obstetrics and gynaecology; 2021; vol. 128 (no. 4); 714-726

1 Study details

Country/ies where study was carried out	UK
Study type	Cross-sectional
Study dates	Between October 2017 and June 2019
Inclusion criteria	• UK women aged ≥18 years, at increased ovarian cancer (OC) risk either due to pathogenic variants in an OC gene (*BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1*) or • strong family history (FH) of OC or breast cancer (BC) + OC. A strong FH was defined as ≥2 first-degree relatives with OC in *BRCA1/BRCA2*-negative or untested women. Exclusion criteria were: non-UK residents or women with a personal history of OC
Exclusion criteria	• non-UK residents or women with a personal history of OC
Patient characteristics	N=88 women with *BRCA1/2* mutations or increased ovarian/breast cancer risk after premenopausal risk reducing bilateral salpingo-oophorectomy n=? HRT (not reported) n=? no HRT (not reported) **Age (mean (SD), years):** 51.53 (9.56) **Gender (n):** women 100% **Ethnicity:** Caucasian 88%, non-Caucasian 12% **Socioeconomic and geographical factors: Education:** PhD, Masters, Bachelor's degree 42% **Disabilities:** not reported **People with communication needs:** not reported

	Previous breast cancer: 46.2%
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	None reported
Sample size	N=88
Sources of funding	The study is supported by researchers at the Barts Cancer Research UK Centre for Excellence, Queen Mary University of London (C16420/A18066). We are particularly grateful to the women who participated in the study. We are grateful to the entire medical, nursing and administrative staff who work on the RRESDO Survey Study. We are grateful to *BRCA* Umbrella for increasing awareness of our study. We are grateful to Barts Health NHS Trust, University College London Hospitals NHS Foundation Trust, Guy's and St Thomas' NHS Foundation Trust, Manchester University NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust and NHS Tayside for their support of the study. We are grateful to Nicola Flaum and Robert D. Morgan for their support. DGRE is supported by the Manchester National Institute for Health Research Biomedical Research Centre (IS-BRC-1215- 20007)

Study arms

HRT user (N = NR)

HRT non-user (N = NR)

NR: not reported

Outcomes

Bone health and fracture in premenopausal women

Outcome	**HRT user vs HRT non-user, N2 = NR, N1 = NR**
Osteoporosis	0.72 (0.31 to 1.67)

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Odds ratio/95% CI	

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

Mood changes associated with menopause in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Mood alterations Odds ratio/95% CI	1.05 (0.49 to 2.23)

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

Vasomotor symptoms in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Hot flushes Odds ratio/95% CI	0.45 (0.19 to 1.02)
Night sweats Odds ratio/95% CI	0.78 (0.36 to 1.69)

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

Neurocognitive symptoms in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Memory loss	1.14 (0.55 to 2.37)

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Odds ratio/95% CI	

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

Genitourinary outcomes in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Vaginal dryness Odds ratio/95% CI	0.4 (0.17 to 0.88)
Urinary incontinence Odds ratio/95% CI	1.37 (0.58 to 3.29)

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

Sexual function in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = NR, N1 = NR
Sexual dysfunction Odds ratio/95% CI	0.9 (0.41 to 1.94)

NR: not reported. The total N=88. Odds ratio adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer. Analysis excludes women with a previous history of breast cancer who were ineligible for HRT

1 **Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies**

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	No
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Low
Overall bias and directness	Directness	Directly applicable

2

3 **Hall, 2019**

Bibliographic Reference	Hall, Elizabeth; Finch, Amy; Jacobson, Michelle; Rosen, Barry; Metcalfe, Kelly; Sun, Ping; Narod, Steven A; Kotsopoulos, Joanne; Effects of bilateral salpingo-oophorectomy on menopausal symptoms and sexual functioning among women with a BRCA1 or BRCA2 mutation.; Gynecologic oncology; 2019; vol. 152 (no. 1); 145-150

4

1 Study details

Country/ies where study was carried out	Canada
Study type	Prospective cohort study
Study dates	Between Jan 2000 and May 2013
Inclusion criteria	• women between the ages of 30 and 70 years who elected to undergo prophylactic salpingo-oophorectomy to reduce their risk of ovarian, fallopian tube or primary peritoneal cancer • if they had: 1) a documented *BRCA1*/2 mutation 2) at least one ovary intact, and 3) no personal history of any cancer other than breast cancer
Exclusion criteria	Not reported
Patient characteristics	N=93 women with *BRCA1/2* and at increased risk of ovarian cancer who had undergone bilateral salpingo-oophorectomy n=37 and n=34 HRT for QOL/vasomotor and sexual function outcome, respectively n=50 and n=39 no HRT for QOL/vasomotor and sexual function outcome, respectively **Age (mean (range), years) at surgery:** 43.8 (35-53) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* status:** *BRAC1* 52.7%, *BRCA2* 46.2%, both mutations 1.1%

	HRT use at the end of follow-up: no 57.5%, yes 42.5% (Most women used oestrogen-alone HRT (89%) and some used a combination therapy (that is, oestrogen plus testosterone or oestrogen plus progesterone (11%))
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Mean follow-up of 3.5 years (range 2.9-6.4)
Sample size	N=93
Sources of funding	JK and SAN are recipients of a Canada Research Chair. This study was partially funded by the Canadian Institutes of Health Research

Study arms

HRT user (QOL and vasomotor outcome) (N = 37)

HRT non-user (QOL and vasomotor outcome) (N = 50)
QOL: quality of life

HRT user (sexual function outcome) (N = 34)

HRT non-user (sexual function outcome) (N = 39)

Outcomes

Health related quality of life in premenopausal women

Outcome	HRT user (QOL and vasomotor outcome), N = 37	HRT non-user (QOL and vasomotor outcome), N = 50	HRT user (sexual function outcome), N = NR	HRT non-user (sexual function outcome), N = NR
Change in quality of life from baseline Mean follow-up 3.5 years (reported p=0.39 for change between the 2 groups) Mean (95% CI)	-0.02 (-3 to 2) SD 7.5*	-0.23 (-5 to 2) SD 12.3*	NR	NR

Change in quality of life from baseline - Polarity - Higher values are better
Measured with 1 question: 'How do you rate your overall quality of life?' and based on a scale of 0 (poor) to 6 (excellent). NR: not relevant. CI: confidence interval. Analyses adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire. Reported that no significant difference in change from baseline between the 2 groups
*calculated by the NGA Technical Team

Vasomotor and sexual symptoms in premenopausal women

Outcome	HRT user (QOL and vasomotor outcome), N = 37	HRT non-user (QOL and vasomotor outcome), N = 50	HRT user (sexual function outcome), N = 34	HRT non-user (sexual function outcome), N = 39
Change in vasomotor symptoms from baseline (measured with MENQOL scale)[#] Mean follow-up 3.5 years Mean (95% CI)	1.27 (-2 to 5) SD 10.5*	1.41 (-3 to 7) SD 17.6* Baseline SD 8.8*	NR	NR

Outcome	HRT user (QOL and vasomotor outcome), N = 37	HRT non-user (QOL and vasomotor outcome), N = 50	HRT user (sexual function outcome), N = 34	HRT non-user (sexual function outcome), N = 39
Change in sexual symptoms from baseline (measured with MENQOL scale)[##] Mean follow-up 3.5 years Mean (95% CI)	NR	NR	1.19 (-5 to 6) SD 15.8*	1.72 (-4 to 7) SD 17* Baseline SD 12.3*

1 Change in vasomotor/sexual symptoms from baseline - Polarity - Lower values are better
2 Measured with The MENQOL-Intervention questionnaire. NR: not relevant. CI: confidence interval.
3 [#]Analyses adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up, baseline score and time between
4 surgery and follow-up questionnaire
5 [##]Analyses adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-
6 up questionnaire
7 Reported that no significant difference in change from baseline between the 2 groups
8 *calculated by the NGA Technical Team

9 **Sexual function in premenopausal women**

Outcome	HRT user (QOL and vasomotor outcome), N = NR	HRT non-user (QOL and vasomotor outcome), N = NR	HRT user (sexual function outcome), N = 34	HRT non-user (sexual function outcome), N = 39
Change in sexual function - pleasure - from baseline[#] (SAQ) Mean follow-up 3.5 years Mean (95% CI)	NR	NR	-2.38 (-15 to 8) SD 33*	-1.68 (-15 to 6) SD 32.4* Baseline SD 27.8*
Change in sexual function - discomfort - from	NR	NR	-1.76 (-5 to 1) SD 8.6*	-1.71 (-5 to 4)

Outcome	HRT user (QOL and vasomotor outcome), N = NR	HRT non-user (QOL and vasomotor outcome), N = NR	HRT user (sexual function outcome), N = 34	HRT non-user (sexual function outcome), N = 39
baseline[##](SAQ) Mean follow-up 3.5 years Mean (95% CI)				SD 13.9* Baseline SD 9.3*
Change in sexual function - habit - from baseline[##] (SAQ) Mean follow-up 3.5 years Mean (95% CI)	NR	NR	-0.12 (-2 to 3) SD 7.2*	-0.06 (-1 to 3) SD 6.2* Baseline SD 3.1*

Change in sexual function - pleasure - from baseline - Polarity - Higher values are better
Change in sexual function - discomfort - from baseline - Polarity - Lower values are better
Change in sexual function - habit - from baseline - Polarity - Higher values are better
Measured with the Sexual Activity Questionnaire (SAQ). NR: not relevant. CI: confidence interval.
[#]Analyses adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire.
[##]Analyses adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up, baseline score and time between surgery and follow-up questionnaire
Reported that no significant difference in change from baseline between the 2 groups

Critical appraisal – NGA Critical appraisal - ROBINS I

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

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	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	Directness	Directly applicable

Hickey, 2021

Bibliographic Reference	Hickey, Martha; Moss, Katrina M; Krejany, Efrosinia O; Wrede, C David; Brand, Alison; Kirk, Judy; Symecko, Heather L; Domchek, Susan M; Tejada-Berges, Trevor; Trainer, Alison; Mishra, Gita D; What happens after menopause? (WHAM): A prospective controlled study of vasomotor symptoms and menopause-related quality of life 12months after premenopausal risk-reducing salpingo-oophorectomy.; Gynecologic oncology; 2021; vol. 163 (no. 1); 148-154

Study details

Country/ies where study was carried out	International
Study type	Prospective cohort study
Study dates	Between 2013 and 2019
Inclusion criteria	• premenopausal women at high risk of ovarian cancer planning RRSO, identified by treating clinicians in gynaecology-oncology and familial cancer centres

Exclusion criteria	• pregnancy or lactation in the past 3 months • unscheduled vaginal bleeding or • use of anti-oestrogens
Patient characteristics	N=95 women at high risk of ovarian cancer after risk reducing salpingo-oophorectomy n=57 initiated HRT after surgery, n=10 delayed initiation beyond 3 months after surgery n=28 no HRT **Age (mean (SD), years) at surgery:** 42.1 (4.2) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* status:** *BRCA1* 37.9%, *BRCA2* 33.7%, both mutations 4.2% **HRT use:** 57 out of 95 initiated HRT after surgery mostly within 3 months (of the 57 HRT users, 23 (40.4%) used oral oestrogen formulations, 31 (54.4%) used transdermal oestrogen formulations and 3 (5.2%) used tibolone. Of those taking oestrogen containing HRT, most (45/57, 78.9%) took doses equivalent to 50 µg/day or greater of transdermal oestradiol or 1 mg/day or greater of oral oestradiol. 3 participants (5.3%) took <50 µg/d. 4 participants used vaginal oestrogen after RRSO - 2 in addition to systemic HRT and two used vaginal oestrogen alone). **Previous breast cancer at baseline:** 11.6%
Intervention(s)/control	• HRT user • HRT non-user

Duration of follow-up	12 months
Sample size	N=95
Sources of funding	This study was supported by Register4 through its members' participation in research and/or provision of samples and information (register4.org.au). In Australia this study was supported by public funding provided by the National Health and Medical Research Council of Australia (NHMRC; Grant # APP1048023), and by philanthropic funding provided by The Royal Women's Hospital (Melbourne, Australia), The Women's Foundation (Melbourne, Australia), Australia New Zealand Gynaecological Oncology Group (ANZGOG, Sydney, Australia) and the Westmead Hospital Familial Cancer Service (Sydney, Australia). In the USA this study was supported by philanthropic funding provided by the Basser Centre for *BRCA* and the Susan G. Komen organization (Grant # SAC150003)

Study arms

HRT user (N = 55)

HRT non-user (N = 34)

Outcomes

Vasomotor symptoms and sexual function in premenopausal women

Outcome	HRT user, N = 55	HRT non-user, N = 34
MENQOL-I - Vasomotor symptoms at baseline Mean (95% CI)	1.54 (1.27 to 1.8) SD 0.9*	1.5 (1.24 to 1.76) SD 0.7*
MENQOL-I - Vasomotor symptoms at 12 months Mean (95% CI)	2.04 (1.66 to 2.42) SD 1.4; change from baseline 0.5 (SD 0.6)*	3.12 (2.51 to 3.72) SD 1.7; change from baseline 1.6 (SD 0.5)*
MENQOL-I - Sexual symptoms at baseline	1.81 (1.41 to 2.22)	1.45 (1.18 to 1.72)

Outcome	HRT user, N = 55	HRT non-user, N = 34
Mean (95% CI)	SD 1.5*	SD 0.8*
MENQOL-I - Sexual symptoms at 12 months Mean (95% CI)	2.37 (1.91 to 2.83) SD 1.7; change from baseline 0.6 (SD 10.6)*	2.62 (2.02 to 3.21) SD 1.7; change from baseline 1.2 (SD 0.6)*

MENQOL-I overall at baseline - Polarity - Lower values are better
MENQOL-I overall at 12 months - Polarity - Lower values are better
MENQOL-I - Vasomotor symptoms at baseline - Polarity - Lower values are better
MENQOL-I - Vasomotor symptoms at 12 months - Polarity - Lower values are better
MENQOL-I - Sexual symptoms at 12 months - Polarity - Lower values are better
MENQOL-I: Menopause-Specific Quality of Life Intervention Version (MENQOL-I); N values for HRT users and non-users are based on 12-month follow up reported in Table S3 in the paper.
*calculated by the NGA Technical Team

Critical appraisal – NGA Critical appraisal - ROBINS I

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
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Low
Overall bias	Directness	Directly applicable

Jiang 2021

Bibliographic Reference	Jiang H; Robinson DL; Lee PVS; Krejany EO; Yates CJ; Hickey M; Wark JD; Loss of bone density and bone strength following premenopausal risk-reducing bilateral salpingo-oophorectomy: a prospective controlled study (WHAM Study).; Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2021; vol. 32 (no. 1)

Study details

Country/ies where study was carried out	Australia
Study type	Matched case-control
Study dates	Not reported
Inclusion criteria	Inclusion criteria for risk-reducing bilateral salpingo-oophorectomy (RRBSO) group: • Age 18–50 years inclusive • Regular menstrual cycles (if uterus intact) • No vasomotor symptoms (hot flushes or night sweats) • Early follicular phase serum FSH ≤ 15 IU/L (if not taking hormonal contraception) • Early follicular phase serum oestradiol > 100 pmol/L (if not taking hormonal contraception) • Confirmed elevated risk of developing breast/ovarian cancer (i.e., either confirmed carrier of BRCA1/2, BRIP1, RAD51C, or Lynch syndrome gene mutation, or based on family history) • Planning to undergo RRBSO within the recruitment period

Exclusion criteria	Exclusion criteria for RRBSO group: • Previous bilateral salpingo-oophorectomy • Taking antioestrogen endocrine therapy in the previous 3 months • Pregnant, lactating or within 3 months of pregnancy • Undiagnosed abnormal vaginal bleeding • Non-English speakers or unable to provide informed consent
Patient characteristics	N=72 (but n=30 in the RRBSO group) premenopausal women at high inherited risk of ovarian cancer due to mutations in the BRCA1/2 gene or family history, planning RRBSO n=17 (57%) 57 women took systemic HRT at any time during the 2-year follow-up n=13 (43%) did not take HRT at any time point **Age (mean (SD), years):** HRT group 42.1 (2.9), no HRT group 42.8 (4.5) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **BRCA1/2 status:** not reported **HRT use:** In HT users, the average dosage of oestradiol was 50 mcg/day. Ten (58.8%) participants took oestrogen-only HRT (following hysterectomy), and 7 (41.2%) took combined HRT (oestrogen and progestin) and 14 (82.4%) used HRT for more than 75% of the follow-up period.
Intervention(s)/control	• HRT user

	• HRT non-user
Duration of follow-up	24 months
Sample size	N=30
Sources of funding	MH is funded by an Australian Government National Health and Medical Research Council (NHMRC) Practitioner Fellowship (reference: APP1058935). The study was funded by NHMRC Project Grant to MH and JDW (reference: APP1048023). HJ was funded by a joint PhD scholarship by China Scholarship Council (reference: CSC201608240003) and the University of Melbourne).

Study arms

HRT user (N = 17)

HRT non-user (N = 13)

Outcomes

Bone health and fracture

Outcome	**HRT user, N = 17**	**HRT non-user, N = 13**
Mean change in areal BMD (g/cm2) in the lumbar spine from baseline to 24 months follow-up Mean (SD)	-0.03 (0.12)*	-0.09 (0.07)*
Mean change in areal BMD (g/cm2) in the femoral neck from baseline to 24 months follow-up Mean (SD)	0 (0.096)*	-0.05 (0.07)*
Mean change in areal BMD (g/cm2) in the total hip from baseline to 24 months follow-up Mean (SD)	0 (0.096)*	-0.05 (0.07)*

BMD: bone mineral density

Polarity - Lower values are better
Analyses adjusted for age, height, and weight
*calculated by the NGA Technical Team

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?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	age, height, and weight
(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?	More reduction in bone mineral density in those who did not use any HRT after risk-reducing surgery as compared to those who did use HRT.
(B) What are the results?	8. How precise are the results?	Difficult to say as no confidence intervals reported. The sample is very small (n=30), so it is likely that the result is not very precise.

Section	Question	Answer
(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

Johansen, 2016

Bibliographic Reference	Johansen, Nora; Liavaag, Astrid H; Tanbo, Tom G; Dahl, Alv A; Pripp, Are H; Michelsen, Trond M; Sexual activity and functioning after risk-reducing salpingo-oophorectomy: Impact of hormone replacement therapy.; Gynecologic oncology; 2016; vol. 140 (no. 1); 101-6

Study details

Country/ies where study was carried out	Norway
Study type	Retrospective cohort study
Study dates	Between 1978 and 2005
Inclusion criteria	• women who had undergone RRSO because of an increased risk of breast and ovarian cancer
Exclusion criteria	Not reported
Patient characteristics	N=168 women with increased risk of breast/ovarian cancer after risk reducing salpingo-oophorectomy, included in the analyses sexually active women only (46% current users of HRT: the majority used systemic preparations exclusively (66 women), and 11 women reported the use of local applications only. Among the 66 users of systemic HRT, 25 women used oestrogen preparations, 20 women used combination (oestrogen and progestin) preparations, and 21 women used tibolone)

	n=77 HRT n=91 no HRT **Age (median (range), years):** 54 (33-83) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors: Education:** high (>12 years) 42%, low (<-12 years) 58% **Disabilities:** not reported **People with communication needs:** not reported **Age at RRSO:** 48 years (range 31-76) **Current use of HRT:** 119 (44%)
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Not reported
Sample size	N=168
Sources of funding	NJ received a part-time grant from Sørlandet Hospital HF and is now the recipient of a Ph.D. grant funded by The Norwegian Women's Public Health Association (grant number H1/2014). The funding organization had no role in the study design, data collection, and analysis, or in the preparation of the manuscript.

Study arms

Systemic HRT user (N = 66)

HRT non-user (N = 91)

Different systemic preparations:

Oestrogen systemic HRT user (N = 25)

Combination (oestrogen and progestin) HRT user (N = 20)

Tibolone user (N = 21)

Local oestrogen user (N = 11)

Outcomes

Sexual function

Outcome	Systemic HRT user, N = 66	HRT non-user, N = 91	Oestrogen syst. HRT user, N = 25	Combined HRT user, N = 20	Tibolone user, N = 21	Local oestrogen user, N = 11
SAQ-Pleasure (Mean score) Custom value	11.2 (SD 4.2)	10.3 (SD 4.5)	11.1 (SD 4.1)	10.8 (SD 4.5)	11.8 (SD 4.0)	8.8 (SD 5.8)
SAQ-Discomfort (Mean score) Custom value	1.2 (SD 1.4)	2.4 (SD 2.1)	1.3 (SD 1.4)	1.2 (SD 1.3)	1.0 (SD 1.5)	1.7 (SD 2.0)

Sexual function: pleasure - Polarity - Higher values are better
Sexual function: discomfort - Polarity - Lower values are better
Measured with the Sexual activity questionnaire (SAQ-F) questionnaire. SD: standard deviation. Adjusted for age and history of cancer

Critical appraisal – NGA Critical appraisal - ROBINS I

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
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	Directly applicable

Kotsopoulos, 2018

Bibliographic Reference	Kotsopoulos, Joanne; Gronwald, Jacek; Karlan, Beth Y; Huzarski, Tomasz; Tung, Nadine; Moller, Pal; Armel, Susan; Lynch, Henry T; Senter, Leigha; Eisen, Andrea; Singer, Christian F; Foulkes, William D; Jacobson, Michelle R; Sun, Ping; Lubinski, Jan; Narod, Steven A; Hereditary Breast Cancer Clinical Study, Group; Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers.; JAMA oncology; 2018; vol. 4 (no. 8); 1059-1065

1

2 **Study details**

Country/ies where study was carried out	International
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	• women with a *BRCA1* mutation and who considered HRT use following oophorectomy
Exclusion criteria	Women if they had: • a previous diagnosis of any cancer, • did not have an oophorectomy during the follow-up period, • did not complete at least 1 follow-up questionnaire, • had an oophorectomy prior to completion of the baseline questionnaire, • were missing information on prophylactic mastectomy, • or had a bilateral mastectomy at baseline or prior to an oophorectomy
Patient characteristics	N=872 women with *BRCA1* mutation and who had a preventive bilateral oophorectomy in the follow-up period n=377 HRT [(among the HRT users, 259 (69%) used oestrogen alone, 66 (18%) used oestrogen plus progesterone, 40 (11%) used progesterone alone, and 80 (21%) used another formulation)] n=495 no HRT **Age (mean (range), years):** HRT: 40.3 (21-67), no HRT: 45.8 (21-74) **Gender (n):** women 100% **Ethnicity (n):** not reported

	Socioeconomic and geographical factors: not reported **Disabilities:** not reported **People with communication needs:** not reported **Age at bilateral oophorectomy:** HRT group: <=44 =63.9%, 45-49=23.6%, >=50=12.5%, no HRT group: <=44=34.3%, 45-49=22.6%, >=50=43%
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Mean follow-up: HRT group 7.9 (0.4-22.1) years, no HRT group 7.4 (0.8-20.9) years
Sample size	N=872
Sources of funding	Dr Kotsopoulos is the recipient of a Cancer Care Ontario Research Chair in Population Studies and a Canadian Cancer Society Career Development Award in Prevention. Dr Narod is the recipient of a Tier I Canada Research Chair. This study was supported by a Canadian Cancer Society Research Institute grant (703058). This work was supported by revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Funding was also received from the Liz's Legacy fund through Kicks for a Cure. Dr Lynch's work is partially funded through the Charles F. and Mary C. Heider Chair in Cancer Research, which he holds at Creighton University.

Study arms

HRT user (N = 377)

HRT non-user (N = 495)

Oestrogen alone user (N = 259)

Oestrogen plus progesterone user (N = 66)

Outcomes

Breast cancer incidence HRT vs no HRT

Outcome	HRT user vs HRT non-user, N2 = 496, N1 = 377
Risk of breast cancer Mean follow-up 7.9 and 7.4 years, respectively Hazard ratio/95% CI	0.97 (0.62 to 1.52)

Analyses adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline

Breast cancer incidence oestrogen alone vs no HRT

Outcome	Oestrogen alone vs HRT non-user, N2 = 495, N1 = 259
Risk of breast cancer Mean follow-up 7.9 years Hazard ratio/95% CI	0.73 (0.41 to 1.32)

Analyses adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline

Breast cancer incidence oestrogen plus progesterone vs no HRT

Outcome	Oestrogen plus progesterone vs HRT non-user, N2 = 495, N1 = 66
Breast cancer risk Mean follow-up 7.9 years Hazard ratio/95% CI	1.31 (0.66 to 2.57)

Analyses adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline

Critical appraisal – NGA Critical appraisal - ROBINS I

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
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	Directly applicable

Kotsopoulos, 2019

Bibliographic Reference	Kotsopoulos, Joanne; Hall, Elizabeth; Finch, Amy; Hu, Hanxian; Murphy, Joan; Rosen, Barry; Narod, Steven A; Cheung, Angela M; Changes in Bone Mineral Density After Prophylactic Bilateral Salpingo-Oophorectomy in Carriers of a BRCA Mutation.; JAMA network open; 2019; vol. 2 (no. 8); e198420

1 Study details

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study
Study dates	From January 2000 to May 2013
Inclusion criteria	• having a documented BRCA mutation, • being aged 30 to 75 years, • having at least 1 intact ovary prior to surgery, • having no history of cancer other than breast cancer
Exclusion criteria	Not reported
Patient characteristics	N=50 women with *BRCA1/2* mutations who elected to undergo prophylactic bilateral salpingo-oophorectomy For the current analysis, only women who had a baseline and at least 1 follow-up DXA scan conducted at the same centre, on the same machine, and using the same measurement procedure were eligible for inclusion. **Age (mean (SD), years) at surgery:** 44 (4.2) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* status:** *BRAC1* 60%, *BRCA2* 40% **Type of surgery:** bilateral salpingo oophorectomy 10%, oophorectomy with hysterectomy 90%

	Previous breast cancer: 28%
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Mean follow-up 22 (SD 12.7) months
Sample size	N=95
Sources of funding	Dr Kotsopoulos is supported by a Canada Research Chair (Tier II). Drs Narod and Cheung are supported by Canada Research Chairs (Tier I). This study was partially funded by grant 123324 from the Canadian Institutes of Health Research.

Study arms

HRT user (for lumbar spine outcome) (N = 23)

HRT non-user (for lumbar spine outcome) (N = 27)

HRT user (for femoral neck outcome) (N = 21)

HRT non-user (for femoral neck outcome) (N = 24)

HRT user (for total hip outcome) (N = 23)

HRT non-user (for total hip outcome) (N = 19)

Outcomes

Bone health and fracture in premenopausal women

Outcome	HRT user (for lumbar spine outcome), N = 23	HRT non-user (for lumbar spine outcome), N = 27	HRT user (for femoral neck outcome), N = 21	HRT non-user (for femoral neck outcome), N = 24	HRT user (for total hip outcome), N = 23	HRT non-user (for total hip outcome), N = 19
BMD score in the lumbar spine at baseline (BMD T score with 95% CI) Custom value	-0.4 (-0.9 to 0.1) SD 1.2*	0.1 (-0.4 to 0.5) SD 1.1*	NR	NR	NR	NR
BMD score in the lumbar spine at follow-up (22 months) (BMD T score with 95% CI) Custom value	-0.6 (-1.2 to 0) Change from baseline -0.2 (0.8)]*	-0.7 (-1.2 to -0.3) Change from baseline -0.8 (0.8)]*	NR	NR	NR	NR
BMD score in the femoral neck at baseline (BMD T score with 95% CI) Custom value	NR	NR	-0.3 (-0.8 to 0.2) SD 1.1*	-0.5 (-0.9 to -0.1) SD 0.9*	NR	NR
BMD score in the femoral neck at follow-up (22 months) (BMD T score with 95% CI) Custom value	NR	NR	-0.5 (-1.0 to 0) Change from baseline -0.2 (0.8)]*	-0.9 (-1.2 to -0.5) Change from baseline -0.4 0.6)]*	NR	NR

Outcome	HRT user (for lumbar spine outcome), N = 23	HRT non-user (for lumbar spine outcome), N = 27	HRT user (for femoral neck outcome), N = 21	HRT non-user (for femoral neck outcome), N = 24	HRT user (for total hip outcome), N = 23	HRT non-user (for total hip outcome), N = 19
BMD score in the total hip at baseline (BMD T score with 95% CI) Custom value	NR	NR	NR	NR	-0.1 (-0.6 to 0.3) SD 1*	0.2 (-0.2 to 0.5) SD 0.7*
BMD score in the total hip at follow-up (22 months) (BMD T score with 95% CI) Custom value	NR	NR	NR	NR	-0.3 (-0.7 to 0.2) Change from baseline -0.2 (0.7)]*	-0.3 (-0.6 to 0.1) Change from baseline -0.5 (0.5)]*

BMD: bone mineral density measured with DXA (dual-energy x-ray absorptiometry) scan. The standard BMD measurement is by T-score is a standard BMD measurement, which is a comparison between the person's BMD and the mean BMD of a healthy young person. CI: confidence interval. NR: not relevant. HRT defined as a use of HRT in the months from surgery to follow-up

Bone health and fracture: lumbar spine in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = 27, N1 = 23
Mean annual change in BMD in the lumbar spine from baseline to follow-up (22 months) between women who used HRT and those who did not The annual change in BMD expressed as the percentage change in BMD (100 × [follow-up BMD − baseline BMD] / baseline BMD) divided by the time between the baseline and follow-up BMD measurements in years Custom value	Reported -2% vs -4.69% (p=0.02)

BMD: bone mineral density measured with DXA (dual-energy x-ray absorptiometry) scan. HRT use defined as a use of HRT in the months from surgery to follow-up

Bone health and fracture: femoral neck in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = 24, N1 = 21
Mean annual change in BMD in the femoral neck from baseline to follow-up (22 months) between women who used HRT and those who did not The annual change in BMD expressed as the percentage change in BMD (100 × [follow-up BMD − baseline BMD] / baseline BMD) divided by the time between the baseline and follow-up BMD measurements in years Custom value	Reported -2.32% vs -3.32% (p=0.31)

BMD: bone mineral density measured with DXA (dual-energy x-ray absorptiometry) scan. HRT use defined as a use of HRT in the months from surgery to follow-up
*Calculated by the NGA Technical Team

Bone health and fracture: total hip in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = 19, N1 = 23
Mean annual change in BMD in the total hip from baseline to follow-up (22 months) between women who used HRT and those who did not The annual change in BMD expressed as the percentage change in BMD (100 × [follow-up BMD − baseline BMD] / baseline BMD) divided by the time between the baseline and follow-up BMD measurements in years Custom value	Reported -1.38% vs -3.21% (p=0.04)

BMD: bone mineral density measured with DXA (dual-energy x-ray absorptiometry) scan. HRT use defined as a use of HRT in the months from surgery to follow-up

1 **Critical appraisal – NGA Critical appraisal - ROBINS I**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(not reported if analysis was adjusted for potential confounders)*
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
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
Overall bias	Directness	Directly applicable

2

3 **Madalinska, 2006**

Bibliographic Reference	Madalinska, Joanna B; van Beurden, Marc; Bleiker, Eveline M A; Valdimarsdottir, Heiddis B; Hollenstein, Judith; Massuger, Leon F; Gaarenstroom, Katja N; Mourits, Marian J E; Verheijen, Rene H M; van Dorst, Eleonora B L; van der Putten, Hans; van der Velden, Ko; Boonstra, Henk; Aaronson, Neil K; The impact of hormone replacement therapy on menopausal

symptoms in younger high-risk women after prophylactic salpingo-oophorectomy.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2006; vol. 24 (no. 22); 3576-82

1

2 **Study details**

Country/ies where study was carried out	The Netherlands
Study type	Cross-sectional
Study dates	Between 1996 and 2001
Inclusion criteria	• women between 30 and 75 years of age, • if they came from a hereditary breast/ovarian cancer family, and • had sought gynaecologic advice on preventive measures at one of the clinics The current analysis was restricted to data of women who were premenopausal at the time of prophylactic bilateral salpingo-oophorectomy (PBSO) or were currently premenopausal (periodic gynaecologic screening) group
Exclusion criteria	• women who had undergone oophorectomy as treatment for a medical condition, or had metastatic cancer or any other severe comorbidity
Patient characteristics	N=164 women with an increased risk of breast/ovarian cancer after prophylactic bilateral salpingo-oophorectomy n=77 HRT (oestrogen/progesterone 70%, tibolone 30%) n=87 no HRT **Age (mean (SD), years):** HRT 45 (5), no HRT 47 (7) **Gender (n):** women 100% **Ethnicity (n):** not reported

	Socioeconomic and geographical factors: Education level: HRT primary school/lower level high school=13%, middle level high school=53%, advanced vocational/university=34%; no HRT primary school/lower level high school=22%, middle level high school=51%, advanced vocational/university=27%; **Disabilities:** not reported **People with communication needs:** not reported ***BRCA* status:** *BRCA1/2* carrier in HRT=79%, in no HRT=77% **Mean HRT use in users:** 3 (SD 2.3) years
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Not applicable
Sample size	N=164
Sources of funding	None reported

Study arms

HRT user (N = 77)

HRT non-user (N = 87)

Outcomes

Mood changes associated with menopause, vasomotor, urogenital outcomes and sexual function in premenopausal women

Outcome	HRT user, N = 77	HRT non-user, N = 87
FACT-ES score Mean (SD)	58 (10.9)	54.6 (9.7)

FACT-ES score - Polarity - Higher values are better
FACT-ES: the 18-item Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) assesses menopausal symptoms (includes hot flushes, cold/night sweats, vaginal discharge/itching/irritation/bleeding/dryness, pain/discomfort with intercourse, lost interest in sex, gained weight, lightheaded/dizzy, vomited, diarrhoea, headaches, feel bloated, breast sensitivity/tenderness, mood swings, irritable). Reported % are nod adjusted. SD: standard deviation

Sexual function in premenopausal women

Outcome	HRT user, N = 64	HRT non-user, N = 67
SAQ-Pleasure Mean (SD)	10.2 (3.2)	9.8 (3.6)
SAQ-Discomfort (SAQ) Mean (SD)	4.8 (1.5)	4.4 (1.7)
SAQ-Habit (SAQ) Mean (SD)	1 (0.5)	0.9 (0.6)

SAQ scale - pleasure - Polarity - Higher values are better
SAQ scale - discomfort - Polarity - Lower values are better
SAQ scale - habit - Polarity - Higher values are better
SAQ: the Sexual Activity Questionnaire. Analysis adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy

1 **Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies**

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes *(but not for all outcomes)*
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns *(Not all analyses were adjusted for potential confounders)*
Overall bias and directness	Directness	Directly applicable

2

3 **Michaelson-Cohen, 2021**

Bibliographic Reference	Michaelson-Cohen, Rachel; Gabizon-Peretz, Shira; Armon, Shunit; Srebnik-Moshe, Naama; Mor, Pnina; Tomer, Ariela; Levy-Lahad, Ephrat; Paluch-Shimon, Shani; Breast cancer risk and hormone replacement therapy among BRCA carriers after risk-reducing salpingo-oophorectomy.; European journal of cancer (Oxford, England : 1990); 2021; vol. 148; 95-102

1 Study details

Country/ies where study was carried out	Israel
Study type	Retrospective cohort study
Study dates	Between July 2012 and June 2019
Inclusion criteria	• *BRCA1/2* carrier who attended and were followed up at the high-risk, multidisciplinary clinic for unaffected *BRCA1/2* mutation carriers
Exclusion criteria	• women with intact ovaries, bilateral risk-reducing mastectomy or past breast cancer diagnosis before risk-reducing salpingo-oophorectomy (RRSO), • previous diagnosis of ovarian cancer or missing information regarding the use of HRT
Patient characteristics	N=306 women with *BRCA1/2* mutations after risk-reducing salpingo-oophorectomy but analysed n=303 as 3 women were excluded due to missing dates of RRSO n=150 HRT n=156 no HRT **Age (median (range), years) at surgery:** HRT=41 (32-67), no HRT=48 (35-75) **Gender (n):** women 100% **Ethnicity (%):** HRT: Ashkenazi Jewish=70, partly Ashkenazi Jewish=16.7, Non-Ashkenazi Jewish=4, no HRT: Ashkenazi Jewish=76.9, partly Ashkenazi Jewish=8.3, Non-Ashkenazi Jewish=3.8 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported
Intervention(s)/control	• HRT user

	• HRT non-user Most used combined oestrogen and progesterone)
Duration of follow-up	Median follow-up in those who used HRT 4.7 years, in those who did not use HRT 7.5 years
Sample size	N=306
Sources of funding	This study was supported by a grant from the BCRF, NY, (to E.L.-L.) and by the Israeli Cancer Association Hereditary Breast Cancer Consortium (to S.G.-P.).

Study arms

HRT user (N = 148)

HRT non-user (N = 155)

Outcomes

Breast cancer incidence in premenopausal women

Outcome	**HRT user vs HRT non-user, N2 = 155, N1 = 148**
Breast cancer incidence Odds ratio/95% CI	1.4 (0.7 to 2.7)

Analysis adjusted for age at surgery, ethnicity and gene mutated

Critical appraisal – NGA Critical appraisal - ROBINS I

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
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	Directly applicable

Steenbeek, 2021

Bibliographic Reference	Steenbeek, Miranda P; Harmsen, Marline G; Hoogerbrugge, Nicoline; de Jong, Marieke Arts; Maas, Angela H E M; Prins, Judith B; Bulten, Johan; Teerenstra, Steven; van Bommel, Majke H D; van Doorn, Helena C; Mourits, Marian J E; van Beurden, Marc; Zweemer, Ronald P; Gaarenstroom, Katja N; Slangen, Brigitte F M; Brood-van Zanten, Monique M A; Vos, M Caroline; Piek, Jurgen M J; van Lonkhuijzen, Luc R C W; Apperloo, Mirjam J A; Coppus, Sjors F P J; Massuger, Leon F A G; IntHout, Joanna; Hermens, Rosella P M G; de Hullu, Joanne A; Association of Salpingectomy With Delayed Oophorectomy Versus Salpingo-oophorectomy With Quality of Life in BRCA1/2 Pathogenic Variant Carriers: A Nonrandomized Controlled Trial.; JAMA oncology; 2021; vol. 7 (no. 8); 1203-1212

1 Study details

Country/ies where study was carried out	The Netherlands
Study type	Non-randomised controlled trial A nationwide prospective, multicentre, nonrandomized controlled preference trial comparing women choosing RRS with delayed RRO vs RRSO was initiated in 13 Dutch hospitals
Study dates	Between January 16, 2015, and November 7, 2019
Inclusion criteria	• women with a documented *BRCA1/2* • they had to be aged 25 to 40 years (*BRCA1*) or 25 to 45 years (*BRCA2*), premenopausal, and capable of reading and speaking Dutch, and to have completed childbearing
Exclusion criteria	• women who had, in advance, anticipated an oophorectomy within 2 years after RRS; • were legally incapable of providing informed consent; • had prior bilateral salpingectomy or ovarian, fallopian tube, or peritoneal cancer; or had a malignant disease at enrolment
Patient characteristics	Women could choose between the standard and novel strategies. The standard strategy consisted of reducing salpingo-oophorectomy (RRSO) within the current guideline age range with postoperative HRT recommended if not contraindicated. The novel strategy consisted of risk-reducing salpingectomy (RRS) after the completion of childbearing and delayed oophorectomy (RRO) at the age of 40 to 45 years (*BRCA1*) or 45 to 50 years (*BRCA2*) N=577 women with *BRCA1/2* after risk reducing surgery n=413 chose RRS with delayed RRO n=164 chose RRSO At 1-year follow-up analysed: • n=302 with RRS +delayed RRO including n=296 without HRT

	• n=119 with RRSO including n=40 without HRT **Age (mean (SD), years) at first surgery:** RRS without HRT 36.8 (3.5), RRS total 36.8 (3.5), RRSO without HRT 39 (3), RRSO with HRT 38.8 (2.9) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors: Educational level:** low: RRS without HRT 10.9%, RRS total 10.7%, RRSO without HRT 14.3%, RRSO with HRT 10.3%; medium: RRS without HRT 35.6%, RRS total 35.5%, RRSO without HRT 47.6%, RRSO with HRT 34%; high: RRS without HRT 53%, RRS total 53.5%, RRSO without HRT 38.1%, RRSO with HRT 55.7% **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* status:** RRS without HRT *BRCA1* 48.1%, *BRCA2* 51.9%, RRS total *BRCA1* 48%, *BRCA2* 52%, RRSO without HRT *BRCA1* 50%, *BRCA2* 50%, RRSO with HRT *BRCA1* 63.9%, *BRCA2* 36.1% **Previous breast cancer:** RRS without HRT 15.2%, RRS total 14.9%, RRSO without HRT 40.5%, RRSO with HRT 2.1% **HRT use at 3-month and 12-month follow-up, respectively:** tibolon (2.5mg/day): 60% and 54%; oestradiol/dydrogesterone 22% and 28%; transdermal oestradiol 6% and 89%
Intervention(s)/control	• HRT user • HRT non-user Women who underwent RRS used oestrogen-based HRT for menstrual cycle regulation after surgery
Duration of follow-up	Follow-up at 3 and 12 months after surgery
Sample size	N=577 but at 1-year follow-up analysed n=421
Sources of funding	Funded by Dutch Cancer Society grant KUN 2014-7187

1

Study arms

HRT user after RRSO (N = 79)
RRSO: risk-reducing salpingo-oophorectomy

HRT non-user after RRSO (N = 40)
RRSO: risk-reducing salpingo-oophorectomy

HRT user after RRS (N = 302)
RRS: risk-reducing salpingectomy

HRT non-user after RRS (N = 296)
RRS: risk-reducing salpingectomy

Outcomes

Health related quality of life in premenopausal women

Outcome	HRT user after RRSO, N = 79	HRT non-user after RRSO, N = 40	HRT user after RRS, N = 302	HRT non-user after RRS, N = 296
Mean change in SF-36 - Physical component summary score from baseline to 12-month follow-up Mean (SD)	-1.1 (7.1)	0.8 (12.3)	0.7 (7.4)	0.1 (7.5)
Mean change in SF-36 - Mental component summary score from baseline to 12-month follow-up Mean (SD)	-8 (12.7)	-1.4 (13.5)	-5 (12.6)	-5 (12.6)

Mean change in SF-36 - Physical component summary score from baseline to 12-month follow-up - Polarity - Higher values are better
Mean change in SF-36 - Mental component summary score from baseline to 12-month follow-up - Polarity - Higher values are better

RRSO: risk-reducing salpingo-oophorectomy; RRS: risk-reducing salpingectomy. All women after RRS (with and without HRT) and only the women using HRT after RRSO are included in HRT user groups

Composite outcome: vasomotor outcomes and sexual function in premenopausal women

Outcome	HRT user after RRSO, N = 79	HRT non-user after RRSO, N = 40	HRT user after RRS, N = 302	HRT non-user after RRS, N = 296
Mean change in GCS from baseline to 12-month follow-up Mean (SD)	4.6 (7.7)	7.7 (8.3)	0.8 (6.4)	0.7 (6.3)

Mean change in GCS from baseline to 12-month follow-up - Polarity - Lower values are better
GCS: Greene Climacteric Scale in which 21 symptoms are rated on a 4-point Likert scale (domains: depression/anxiety, somatic, vasomotor, and sexual problems). A higher sum represents more climacteric symptoms (range, 0-63).; RRSO: risk-reducing salpingo-oophorectomy; RRS: risk-reducing salpingectomy. All women after RRS (with and without HRT) and only the women using HRT after RRSO are included in HRT user groups

Sexual function in premenopausal women

Outcome	HRT user after RRSO, N = 79	HRT non-user after RRSO, N = 40	HRT user after RRS, N = 302	HRT non-user after RRS, N = 296
Mean change in FSFI from baseline to 12-month follow-up Mean (SD)	-1.2 (10.7)	-5.1 (8.2)	0.3 (7)	0.3 (7.1)

Mean change in FSFI from baseline to 12-month follow-up - Polarity - Higher values are better
FSFI: Female Sexual Functioning Index. RRSO: risk-reducing salpingo-oophorectomy; RRS: risk-reducing salpingectomy All women after RRS (with and without HRT) and only the women using HRT after RRSO are included in HRT user groups

1 **Critical appraisal – NGA Critical appraisal - ROBINS I**

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 *(although the number of women with prior breast cancer was higher among women without HRT after RRSO than among women with HRT after RRSO)*
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	Directness	Directly applicable

2

Terra, 2022

Bibliographic Reference	Terra, Lara; Beekman, Maarten J; Engelhardt, Ellen G; Heemskerk-Gerritsen, Bernadette A M; van Beurden, Marc; Roeters van Lennep, Jeanine E; van Doorn, Helena C; de Hullu, Joanne A; Van Dorst, Eleonora B L; Mom, Constantijne H; Slangen, Brigitte F M; Gaarenstroom, Katja N; van der Kolk, Lizet E; Collee, J Margriet; Wevers, Marijke R; Ausems, Margreet G E M; Van Engelen, Klaartje; van de Beek, Irma; Berger, Lieke P V; van Asperen, Christi J; Gomez Garcia, Encarna B; Maas, Angela H E M; Hooning, Maartje J; Aaronson, Neil K; Mourits, Marian J E; van Leeuwen, Flora E; Sexual functioning more than 15 years after premenopausal risk-reducing salpingo-oophorectomy.; American journal of obstetrics and gynecology; 2022

Study details

Country/ies where study was carried out	The Netherlands
Study type	Cross-sectional a multicentre cross-sectional study, nested in a cohort of women at high familial risk of breast or ovarian cancer
Study dates	Between 2018 and 2021
Inclusion criteria	Women with: • a high familial risk of breast/ovarian cancer, • current age of >=55 years, and • having undergone risk-reducing salpingo-oophorectomy (RRSO) either before the age of 45 years or after the age of 54 years
Exclusion criteria	Women with: • ovarian cancer, • metastatic disease, • and therapy-induced menopause >5 years before RRSO. Breast cancer was not an exclusion criterion.

Patient characteristics	N=499 women with a high familial risk of breast/ovarian cancer having undergone RRSO n=127 HRT (tibolone 29.1%, oestradiol or progesterone 23.6%, oestradiol only 8.7%, vaginal oestrogen 1.6%, unknown 37%; 5.2% current user, 20% past user) n=332 no HRT **Age (mean (SD), years) at questionnaire completion:** 60 (3.5) **Time since RRSO (mean (SD), years):** 18.3 (4.1) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors: Education:** Primary school/lower level high school 27.6%, Middle level high school 33.1%, Advanced vocational/university 31.7% **Disabilities:** not reported **People with communication needs:** not reported ***BRCA* status:** *BRCA1* 49.2%, *BRCA2* 19.6%, non-carrier 31.2% **Age at surgery:** 41.7 (SD 2.8) years **Current use of HRT:** 26 (5.2%)
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Mean time since RRSO 18.3 (SD 4.1) years
Sample size	N=499 but n=459 included in the relevant analysis

Sources of funding	The Dutch Cancer Society (KWF) and the Maarten van der Weijden Foundation have provided funding for this project (registered under grant number 10164)

Study arms

HRT user (N = 26)

HRT non-user (N = 332)

Outcomes

Sexual function in premenopausal women

Outcome	HRT user, N = 26	HRT non-user, N = 332
SAQ-Pleasure Mean time since RRSO 18.3 years Mean (SD)	9.6 (4.5)	8.5 (3.6)
SAQ-Discomfort Mean time since RRSO 18.3 years Mean (SD)	1.1 (1.5)	2.2 (1.9)

SAQ-Pleasure - Polarity - Higher values are better
SAQ-Discomfort - Polarity - Lower values are better
SAQ: Sexual Activity Questionnaire. SD: standard deviation. RRSO: risk-reducing salpingo-oophorectomy

1 **Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies**

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns (not clear if adjusted for potential confounders for relevant outcomes)
Overall bias and directness	Directness	Directly applicable

2

Terra, 2023

Bibliographic Reference	Terra, Lara; Lee Meeuw Kjoe, Philippe R; Agelink Van Rentergem, Joost A; Beekman, Maarten J; Heemskerk-Gerritsen, Bernadette A M; Van Beurden, Marc; Roeters Van Lennep, Jeanine E; Van Doorn, Helena C; De Hullu, Joanna A; Mourits, Marian J E; Van Dorst, Eleonora B L; Mom, Constantijne H; Slangen, Brigitte F M; Gaarenstroom, Katja N; van der Kolk, Lizet E; Collee, J Margriet; Wevers, Marijke R; Ausems, Margreet G E M; Van Engelen, Klaartje; Van De Beek, Irma; Berger, Lieke P V; Van Asperen, Christi J; Gomez Garcia, Encarna B; Maas, Angela H E M; Hooning, Maartje J; Van Der Wall, Elsken; Van Leeuwen, Flora E; Schagen, Sanne B; Long-term effects of premenopausal risk-reducing salpingo-oophorectomy on cognition in women with high familial risk of ovarian cancer: A cross-sectional study.; BJOG : an international journal of obstetrics and gynaecology; 2023

Study details

Country/ies where study was carried out	The Netherlands
Study type	Cross-sectional A cross-sectional study with prospective follow-up, nested in a nationwide cohort
Study dates	Between 2018 and 2021
Inclusion criteria	• women were eligible if they had a risk-reducing salpingo-oophorectomy (RRSO) ≤ age 45 and were currently aged ≥55 years, resulting in at least 10 years since RRSO
Exclusion criteria	• ovarian carcinoma, • metastatic disease, • early-onset dementia and • insufficient understanding of the Dutch language A history of breast cancer was not an exclusion criterion.
Patient characteristics	N=406 women with a high familial risk of breast/ovarian cancer having undergone RRSO

	n=114 HRT (tibolone 23.1%, oestradiol or progestogen 17.6%, oestradiol only 5.6%, unknown 53.7%; current user 5.3%, past user 19.5%, unknown 9.4%) n=292 no HRT **Age (mean (SD), years) at questionnaire completion:** 60 (3.5) **Time since RRSO (mean (SD), years):** 18.1 (4.2) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors: Education:** Primary school/lower level high school 25.5%, Middle level high school 32.8%, Advanced vocational/university 32.8% **Disabilities:** not reported **People with communication needs:** not reported ***BRCA* status:** *BRCA1* 47.9%, *BRCA2* 19%, non-carrier 33% **Age at surgery:** 41.8 (SD 2.7) years
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Mean time since RRSO 18.1 (SD 4.2) years
Sample size	N=406
Sources of funding	The Dutch Cancer Society (KWF) granted funding for this project, registered under grant 10164. This study was peer-reviewed by the Dutch Cancer Society and several patient panels before granting funding

1

Study arms

HRT user (N = 114)

HRT non-user (N = 292)

Outcomes

Neurocognitive outcomes in premenopausal women

Outcome	HRT user, N = 114	HRT non-user, N = 292
Subjective cognition-Reasoning Mean time since RRSO 18.1 years Mean (95% CI)	2.33 (2.13 to 2.53) SD 1.1*	2.17 (2.06 to 2.29) SD 1*
Subjective cognition-Forgetful Mean time since RRSO 18.1 years Mean (95% CI)	2.68 (2.48 to 2.89) SD 1.1*	2.41 (2.29 to 2.53) SD 1*
Subjective cognition-Attention Mean time since RRSO 18.1 years Mean (95% CI)	2.42 (2.2 to 2.63) SD 1.2*	2.29 (2.16 to 2.41) SD 1.1*
Subjective cognition-Concentration Mean time since RRSO 18.1 years Mean (95% CI)	2.43 (2.24 to 2.63) SD 1.1*	2.3 (2.18 to 2.43) SD 1.1*
Subjective cognition-Multitasking Mean time since RRSO 18.1 years Mean (95% CI)	1.85 (1.65 to 2.05) SD 1.1*	1.84 (1.72 to 1.96) SD 1*

Outcome	HRT user, N = 114	HRT non-user, N = 292
Subjective cognition-Slow thinking Mean time since RRSO 18.1 years Mean (95% CI)	1.88 (1.71 to 2.04) SD 0.9*	1.76 (1.66 to 1.87) SD 0.9*

Subjective cognition-Reasoning - Polarity - Lower values are better
Subjective cognition-Forgetful - Polarity - Lower values are better
Subjective cognition-Attention - Polarity - Lower values are better
Subjective cognition-Concentration - Polarity - Lower values are better
Subjective cognition-Multitasking - Polarity - Lower values are better
Subjective cognition-Slow thinking - Polarity - Lower values are better
Subjective cognition assessed by the Medical Outcomes Study cognitive functioning scale (MOS-cog), measuring the frequency of self-reported cognitive problems in daily life (values based on Table S6)

Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes

Section	Question	Answer
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Low
Overall bias and directness	Directness	Directly applicable

1

2 **Tucker, 2016**

Bibliographic Reference	Tucker, Paige E; Bulsara, Max K; Salfinger, Stuart G; Tan, Jason Jit-Sun; Green, Helena; Cohen, Paul A; The effects of pre-operative menopausal status and hormone replacement therapy (HRT) on sexuality and quality of life after risk-reducing salpingo-oophorectomy.; Maturitas; 2016; vol. 85; 42-8

3

4 **Study details**

Country/ies where study was carried out	Australia
Study type	Cross-sectional
Study dates	Between 2009 and 2014
Inclusion criteria	• women who had undergone risk-reducing salpingo-oophorectomy
Exclusion criteria	• a suspected gynaecologic malignancy, • major psychiatric illness, • intellectual impairment or limited English language skills.
Patient characteristics	N=119 but analysed n=117 women who had RRSO

	n=24 current systemic HRT user n=9 current topical vaginal oestrogen user n=84 no HRT **Age (mean (SD), years) at surgery:** 50 (8) **Time since RRSO (mean (SD), years):** 24 months (16) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Breast cancer (n):** 60
Intervention(s)/control	• current systemic HRT user • current topical vaginal oestrogen user • HRT non-user
Duration of follow-up	Mean time since surgery 24 months (SD 16)
Sample size	N=117
Sources of funding	This study was funded by St John of God Subiaco Hospital, Perth, Western Australia

1

Study arms

Current systemic HRT user (N = 24)

Current topical vaginal oestrogen user (N = 9)

HRT non-user (N = 84)

Outcomes

Health related quality of life

Outcome	Systemic HRT user, N = 24	Topical vaginal oestrogen user, N = 9	HRT non-user, N = 84
SF-36 - Total score Mean time since RRSO 24 months. Adjusted breast cancer and menopause status at the time of surgery Mean (SD)	74.2 (19.58)	75.74 (13.05)	72.44 (19.76)

SF-36 - Total score - Polarity - Higher values are better
RRSO: risk-reducing salpingo-oophorectomy

Vasomotor symptoms

Outcome	Systemic HRT user, N = 24	Topical vaginal oestrogen user, N = 9	HRT non-user, N = 84
MENQOL-Vasomotor symptoms Mean time since RRSO 24 months. Adjusted for breast cancer and menopause status at the time of surgery Mean (SD)	2.96 (1.81)	3 (1.85)	4.04 (2.06)

Outcome	Systemic HRT user, N = 24	Topical vaginal oestrogen user, N = 9	HRT non-user, N = 84
MENQOL-Sexual symptoms Mean time since RRSO 24 months. Adjusted for breast cancer and menopause status at the time of surgery Mean (SD)	3.52 (2.12)	3.81 (1.92)	4.36 (2.2)

MENQOL-Vasomotor symptoms - Polarity - Lower values are better
MENQOL-Sexual symptoms - Polarity - Lower values are better
MENQOL: Menopause-specific quality of life questionnaire. RRSO: risk-reducing salpingo-oophorectomy

Sexual function

Outcome	Systemic HRT user, N = 24	Topical vaginal oestrogen user, N = 9	HRT non-user, N = 84
FSFI total score Mean time since RRSO 24 months. Adjusted for breast cancer and menopause status at the time of surgery Mean (SD)	21.62 (9.47)	23.87 (9)	16.26 (9.99)

FSFI total score - Polarity - Higher values are better
FSFI: Female Sexual Function Index. Higher score in the FSFI indicates a higher level of sexual functioning. RRSO: risk-reducing salpingo-oophorectomy

Critical appraisal - GDT Crit App - JBI Checklist for Analytical Cross Sectional Studies

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	No
Assessment questions	Were the study subjects and the setting described in detail?	No

Section	Question	Answer
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Partially applicable *(not sufficient details about the population reported)*

1

2 **Vermeulen, 2017**

Bibliographic Reference	Vermeulen, Ravi F M; Beurden, Marc van; Kieffer, Jacobien M; Bleiker, Eveline M A; Valdimarsdottir, Heiddis B; Massuger, Leon F A G; Mourits, Marian J E; Gaarenstroom, Katja N; van Dorst, Eleonora B L; van der Putten, Hans W H M; Aaronson, Neil K; Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: A prospective study.; European journal of cancer (Oxford, England : 1990); 2017; vol. 84; 159-167

3

1 Study details

Country/ies where study was carried out	The Netherlands
Study type	Prospective cohort study
Study dates	Between 2002 and 2004
Inclusion criteria	• age between 30 and 70 years; • member of a hereditary breast and ovarian cancer (HBOC) family with a risk estimated to exceed 10% or proven BReast CAncer susceptibility gene1 or gene2 (*BRCA1/2*) mutation carrier; and • referred to a gynaecologist to discuss the prevention of ovarian cancer
Exclusion criteria	• prior oophorectomy and • metastatic cancer or any other severe comorbidity
Patient characteristics	N=57 women at high risk of familiar breast/ovarian cancer after surgery n=27 HRT users n=30 HRT non-users If HRT was prescribed after surgery, this was a standard dosage of hormones (tibolone or oestrogen and progestin) administered either orally, transdermally or topically **Age (mean (SD), years):** HRT 39.2 (3.9), no HRT 43.8 (4.7) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors: Education:** HRT: Primary school/lower level high school 11%, Middle level high school 78%, Advanced vocational/university 11%; no HRT: Primary school/lower level high school 7%, Middle level high school 57%, Advanced vocational/university 37%

	Disabilities: not reported **People with communication needs:** not reported **Type of HRT:** oestrogen/progesterone 36%, tibolone 64% ***BRCA1/2* status:** *BRCA1/2* carrier HRT 89%, no HRT87%, No mutation, result not informative/known HRT 4%, no HRT 3%; not testes HRT 7%, no HRT 10% **History of breast cancer:** HRT 0%, no HRT 40%
Intervention(s)/control	• HRT user • HRT non-user
Duration of follow-up	Follow-up 3 and 9 months post surgery
Sample size	N=57
Sources of funding	This work was supported by a grant from the Dutch Cancer Society (grant number: NKI 2001-2382)

1

Study arms

HRT user (N = 27)

HRT non-user (N = 30)

Outcomes

Mood changes associated with menopause, vasomotor symptoms, genitourinary outcomes and sexual function in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = 30, N1 = 27
Difference in mean change in FACT-ES between baseline and 3 months post-surgery between HRT users and non-users Reported that difference is statistically significant Mean (95% CI)	-5.8 (-9.3 to -2.2)
Difference in mean change in FACT-ES between 3 and 9 months post-surgery between HRT users and non-users Reported that difference is statistically significant Mean (95% CI)	-7.3 (-11 to -3.5)

FACT-ES: The Functional Assessment of Cancer Treatment Endocrine Subscale; it includes hot flashes, cold/night sweats, vaginal discharge/itching/irritation/bleeding/dryness, pain/discomfort with intercourse, lost interest in sex, gained weight, lightheaded/dizzy, vomited, diarrhoea, headaches, fell bloated, breast sensitivity/tenderness, mood swings, irritable. Occurrence of each symptom in the past 4 weeks is scored on a 5-point scale, ranging from ‘not at all’ to ‘very much’. Analyses adjusted for age, mastectomy, and non-ignorable drop-out

Sexual function in premenopausal women

Outcome	HRT user vs HRT non-user, N2 = 30, N1 = 27
Change in mean SAQ-Pleasure from baseline to 9 months post surgery between HRT users and non-users Mean (95% CI)	HRT users: 2.7 (SD 6.2)* HRT non-users: -0.2 (SD 3.9)*
Change in mean SAQ-Discomfort from baseline to 9 months post surgery between HRT users and non-users Mean (95% CI)	HRT users: -1.2 (SD 1.8)* HRT non-users: 1 (1.2)*

Difference in mean change in SAQ-Pleasure between HRT users and non-users - Polarity - Higher values are better for pleasure but lower values are better for discomfort
SAQ: the Sexual Activity Questionnaire. Analyses adjusted for age, mastectomy, and non-ignorable drop-out. CI: confidence interval.
SD: standard deviation
*calculated by the NGA Technical Team

Critical appraisal – NGA Critical appraisal - ROBINS I

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

Section	Question	Answer
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	Directness	Directly applicable

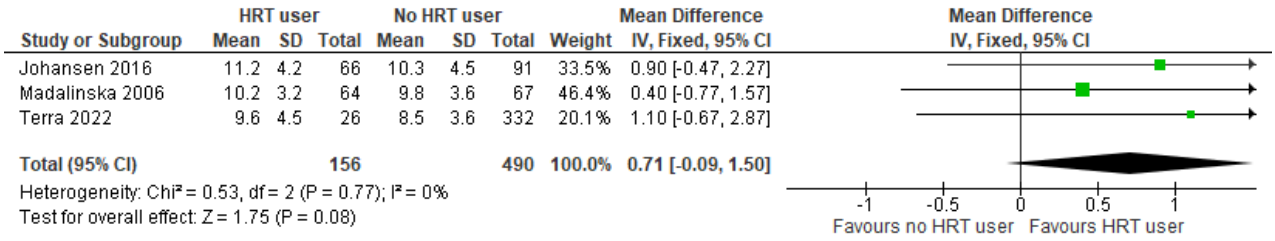
Appendix E Forest plots

Forest plots for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

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

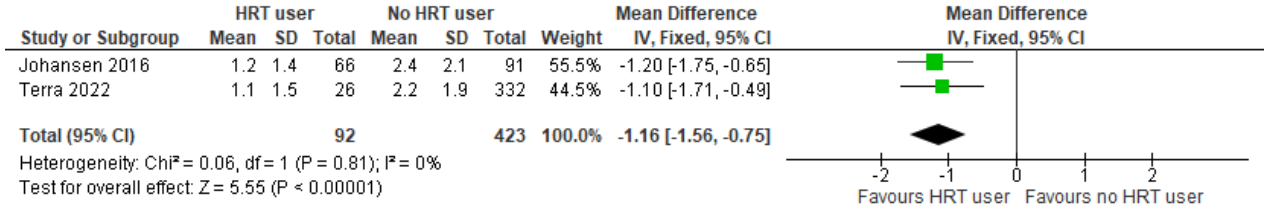
Comparison between HRT and no HRT after salpingo-oophorectomy

Figure 2: Sexual function – Pleasure (measured with the Sexual Activity Questionnaire)



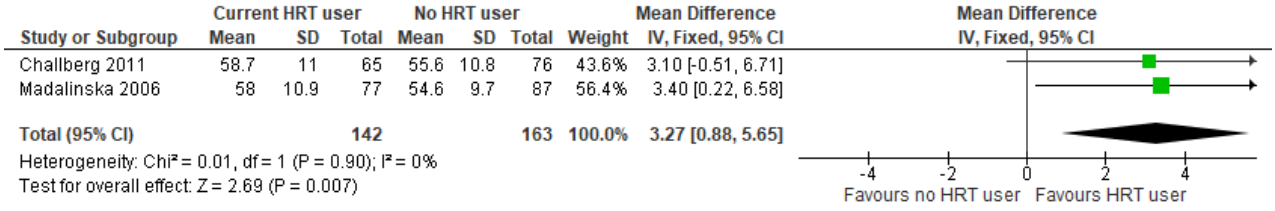
CI: confidence interval; HRT: hormone replacement therapy

Figure 3: Sexual function – Discomfort (measured with the Sexual Activity Questionnaire)



CI: confidence interval; HRT: hormone replacement therapy

Figure 4: Composite outcome (measured with the Functional Assessment of Cancer Therapy–Endocrine Symptoms scale)



CI: confidence interval; HRT: hormone replacement therapy

Appendix F GRADE tables

GRADE tables for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Breast cancer incidence

Table 4: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Breast cancer incidence (up to mean age of 58 years; mean age at surgical menopause was 42 years)												
Eisen 2008	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23 cases / 34 controls[2]	39 cases / 28 controls[2]	OR 0.48 (0.19 to 1.21)[3]	-	VERY LOW	CRITICAL
Breast cancer incidence (over the 10 years after oophorectomy)												
Kotsopoulos 2018	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	39/377 (10.3%)	53/496 (10.7%)	HR 0.97 (0.62 to 1.52)[5]	3 fewer per 1000 (from 39 fewer to 51 more)	LOW	CRITICAL
Breast cancer incidence (median follow-up after RRSO 6 years)												
Michaelson-Cohen 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	20/155 (12.9%)	16/148 (10.8%)	OR 1.4 (0.7 to 2.7)[6]	37 more per 1000 (from 30 fewer to 138 more)	LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; MID: minimally important difference; OR: odds ratio; RRSO: risk reducing salpingo-oophorectomy
1 95% CI crosses 1 MID
2 Case control study
3 Adjusted for parity, oral contraceptive use and country of residence
4 95% CI crosses 2 MIDs
5 Adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline
6 Adjusted for ager at surgery, ethnicity and gene mutated

Table 5: Evidence profile for comparison between combined (oestrogen plus progesterone) HRT vs no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral oophorectomy: Oestrogen plus progesterone user	HRT non-user	Relative (95% CI)	Absolute		
Breast cancer incidence (over the 10 years after oophorectomy)												
Kotsopoulos 2018	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	NR/66[2]	53/495 (10.7%)	HR 1.31 (0.66 to 2.57)[3]	-[2]	LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; MID: minimally important difference; NR: not reported
1 95% CI crosses 2 MIDs
2 Number of cancer cases not reported
3 Adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline

Table 6: Evidence profile for comparison between oestrogen alone HRT vs no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral oophorectomy: Oestrogen alone user	HRT non-user	Relative (95% CI)	Absolute		
Breast cancer incidence (over the 10 years after oophorectomy)												
Kotsopoulos 2018	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	NR/259[2]	53/495 (10.7%)	HR 0.73 (0.41 to 1.32)[3]	-[2]	LOW	CRITICAL

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; MID: minimally important difference; NR: not reported
1 95% CI crosses 2 MIDs
2 Number of cancer cases not reported
3 Adjusted for age at baseline, parity, period started age, first-degree relative with breast cancer, oral contraceptive use, country of residence, and HRT used at baseline

1 Health related quality of life

2 Table 7: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Overall health related quality of life (SF-36 total score) (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	84	-	MD 1.76 higher (7.14 lower to 10.66 higher)[3]	VERY LOW	IMPORTANT
Change in overall health related quality of life (measured with question "How do you rate your overall quality of life?"): mean change from baseline, mean follow-up 3.5 years (Better indicated by higher values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	37	50	-	MD 0.21 higher (3.97 lower to 4.39 higher)[5]	LOW	IMPORTANT
Change in health related quality of life - SF-36: Physical component summary score - mean change from baseline to 12-month follow-up (Better indicated by higher values)												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	79	40	-	MD 1.9 lower (6.02 lower to 2.22 higher)	LOW	IMPORTANT
Change in health related quality of life - SF-36: Mental component summary score - mean change from baseline to 12-month follow-up (Better indicated by higher values)												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	79	40	-	MD 6.6 lower (11.63 to 1.57 lower)	LOW	IMPORTANT
Change in health related quality of life - SF-36: Physical component summary score - mean change from baseline to 12-month follow-up (Better indicated by lower values) after salpingectomy												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	302	296	-	MD 0.6 higher (0.59 lower to 1.79 higher)	MODERATE	IMPORTANT
Change in health related quality of life - SF-36: Mental component summary score - mean change from baseline to 12-month follow-up (Better indicated by lower values) after salpingectomy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	302	296	-	MD 0 higher (2.02 lower to 2.02 higher)	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference
1 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist
2 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 19.76 = 9.88)
3 Adjusted breast cancer and menopause status at the time of surgery
4 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 1.2 = 0.6)
5 Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire
6 Optimal information size for imprecision: N<200
7 Optimal information size for imprecision: N<400

Cardiac events

Table 8: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Cardiac events (a composite of incident myocardial infarction, heart failure, and/or cerebrovascular disease (consisting of ischemic or haemorrhagic stroke, unspecified cerebrovascular disease, and occlusion of cerebral or precerebral arteries)); mean follow-up 7.34 years												
Do Valle 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/161 (6.8%)	14/199 (7%)	HR 1.24 (0.54 to 2.88)[2]	16 more per 1000 (from 32 fewer to 119 more)	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy
1 95% CI crosses 2 MIDs
2 Adjusted for age

1 Bone health and fracture

2 Table 9: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Bone health and fractures - Bone fractures												
Do Valle 2022	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17/153 (11.1%)	27/176 (15.3%)	HR 0.88 (0.43 to 1.81)[2]	17 fewer per 1000 (from 84 fewer to 107 more)	LOW	IMPORTANT
Bone health and fractures - Osteoporosis												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-[3]	-[3]	OR 0.72 (0.31 to 1.67)[4]	-	VERY LOW	IMPORTANT
Bone health and fractures - Osteoporosis in women who had DEXA scan												
Do Valle 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	5/153 (3.3%)	17/176 (9.7%)	HR 0.35 (0.13 to 0.95)[6]	62 fewer per 1000 (from 5 fewer to 83 fewer)	MODERATE	IMPORTANT
Mean annual change (%) in BMD in the lumbar spine from baseline to 22 months follow-up (Better indicated by lower values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	23	27	-	Annual change in BMD -2% vs -4.69%[9]	VERY LOW	IMPORTANT
Mean annual change (%) in BMD in the femoral neck from baseline to 22 months follow-up (Better indicated by lower values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	21	24	-	Annual change in BMD −2.32% vs −3.32%[9]	VERY LOW	IMPORTANT
Mean annual change (%) in BMD in the total hip from baseline to 22 months follow-up (Better indicated by lower values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	23	19	-	Annual change in BMD −1.38% vs −3.21%[9]	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Change in BMD T score in the lumbar spine from baseline to 22 months follow-up (Better indicated by higher values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[10]	none	23	27	-	MD 0.6 higher (0.16 to 1.04 higher)	LOW	IMPORTANT
Change in BMD T score in the femoral neck from baseline to 22 months follow-up (Better indicated by higher values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[11]	none	21	24	-	MD 0.2 higher (0.22 lower to 0.62 higher)	LOW	IMPORTANT
Change in BMD T score in the total hip from baseline to 22 months follow-up (Better indicated by higher values)												
Kotsopoulos 2019	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[12]	none	23	19	-	MD 0.3 higher (0.06 lower to 0.66 higher)	LOW	IMPORTANT
Mean change (g/cm2) in areal BMD in the lumbar spine from baseline to 24 months follow-up (Better indicated by lower values)												
Jiang 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	17	13	-	MD 0.06 higher (0.01 lower to 0.13 higher)	VERY LOW	IMPORTANT
Mean change (g/cm2) in areal BMD in the femoral neck from baseline to 24 months follow-up (Better indicated by lower values)												
Jiang 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	17	13	-	MD 0.05 higher (0.01 lower to 0.11 higher)	VERY LOW	IMPORTANT
Mean change (g/cm2) in areal BMD in the total hip from baseline to 24 months follow-up (Better indicated by lower values)												
Jiang 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	17	13	-	MD 0.05 higher (0.01 lower to 0.11 higher)	VERY LOW	IMPORTANT

CI: confidence interval; BMD: bone mineral density; HR: hazard ratio; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; OR: odds ratio
1 95% CI crosses 2 MIDs
2 Adjusted for age and breast cancer
3 Number of events and of those who used HRT not reported

4 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 1.2 = 0.6)
5 95% CI crosses 1 MID
6 Unadjusted due to low number of events
7 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS I
8 Optimal information size for imprecision: N<200
9 Reported that women who used HRT had significantly less annual change in BMD of the lumbar spine (−2.00% vs −4.69%; p =0.02) and total hip (−1.38% vs −3.21%; p =0.04) than those who did not use HRT; no difference for the femoral neck (−2.32% vs −3.32%; p=0.31)
10 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 1.1 = 0.6)
11 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 0.9 = 0.5)
12 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 0.7 = 0.4)
13 95%CI crosses 1 MID for continuous outcomes (0.5x control group SD 0.11 = 0.06)

Table 10: Evidence profile for comparison between different lengths of oestrogen deprivation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: length of oestrogen deprivation	Control	Relative (95% CI)	Absolute		
Osteopenia (defined as DXA T score -1.0 to -2.4) - Length of oestrogen deprivation 0 vs 1-23 months												
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/31 (12.9%)	3/10 (30%)	RR 0.43 (0.12 to 1.6)	171 fewer per 1000 (from 264 fewer to 180 more)	VERY LOW	IMPORTANT
Osteopenia (defined as DXA T score -1.0 to -2.4) - Length of oestrogen deprivation 0 vs >=24 months												
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/31 (12.9%)	26/78 (33.3%)	RR 0.39 (0.15 to 1.02)	203 fewer per 1000 (from 283 fewer to 7 more)	VERY LOW	IMPORTANT
Osteopenia (defined as DXA T score -1.0 to -2.4) - Length of oestrogen deprivation 1-23 months vs >=24 months												
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/10 (30%)	26/78 (33.3%)	RR 0.9 (0.33 to 2.44)	33 fewer per 1000 (from 223 fewer to 480 more)	VERY LOW	IMPORTANT
Osteoporosis (defined as DXA T score <-2.4) - Length of oestrogen deprivation 0 vs 1-23 months												
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/31 (3.2%)	1/10 (10%)	RR 0.32 (0.02 to 4.7)	68 fewer per 1000 (from 98 fewer to 370 more)	VERY LOW	IMPORTANT
Osteoporosis (defined as DXA T score <-2.4) - Length of oestrogen deprivation 0 vs >=24 months												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: length of oestrogen deprivation	Control	Relative (95% CI)	Absolute		
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/31 (3.2%)	10/78 (12.8%)	RR 0.25 (0.03 to 1.88)	96 fewer per 1000 (from 124 fewer to 113 more)	VERY LOW	IMPORTANT
Osteoporosis (defined as DXA T score <-2.4) - Length of oestrogen deprivation 1-23 months vs >24 months												
Challberg 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/10 (10%)	10/78 (12.8%)	RR 0.78 (0.11 to 5.47)	28 fewer per 1000 (from 114 fewer to 573 more)	VERY LOW	IMPORTANT

CI: confidence interval; DXA: dual-energy X-ray absorptiometry; HRT: hormone replacement therapy; MID: minimally important difference; RR: relative risk
1 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS I
2 95% CI crosses 2 MIDs

Mood changes associated with menopause and vasomotor symptoms

Table 11: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Mood changes associated with menopause - Mood alterations												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-[2]	-[2]	OR 1.05 (0.49 to 2.23)[3]	-	VERY LOW	IMPORTANT
Vasomotor symptoms - Hot flushes												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	-[2]	-[2]	OR 0.45 (0.19 to 1.02)[3]	-	VERY LOW	IMPORTANT
Vasomotor symptoms - Night sweats												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-[2]	-[2]	OR 0.78 (0.36 to 1.69)[3]	-	VERY LOW	IMPORTANT
Vasomotor symptoms (measured with MENQOL scale) (Better indicated by lower values)												
Tucker 2016	observational studies	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	24	84	-	MD 1.08 lower (1.93 to 0.23 lower)[7]	VERY LOW	IMPORTANT
Change in vasomotor symptoms (measured with MENQOL scale) from baseline to 3.5 years follow-up (Better indicated by lower values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	37	50	-	MD 0.14 lower (6.08 lower to 5.8 higher)[9]	LOW	IMPORTANT
Change in vasomotor symptoms (measured with MENQOL scale) from baseline to 1 year follow-up (Better indicated by lower values)												
Hickey 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	55	34	-	MD 1.1 lower (1.33 to 0.87 lower)	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; OR: odds ratio; MENQOL: Menopause-specific quality of life questionnaire; MID: minimally important difference

1 95% CI crosses 2 MIDs

2 Number of events and of those who used HRT not reported

3 Adjusted for marital status, ethnicity, education, income, family history of ovarian/breast cancer

4 95% CI crosses 1 MID

5 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist I

6 95% CI crosses 1 MID for continuous (0.5x control group SD 2.06 = 1.03)

7 Adjusted breast cancer and menopause status at the time of surgery

8 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 8.8 = 4.4)

9 Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up, baseline score and time between surgery and follow-up questionnaire

10 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 0.7 = 0.35)

1 Neurocognitive outcomes

2 Table 12: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Neurocognitive outcomes - Memory loss												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-[2]	-[2]	OR 1.14 (0.55 to 2.37)[3]	-	VERY LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Reasoning (Better indicated by lower values)												
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.16 higher (0.07 lower to 0.39 higher)	LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Forgetful (Better indicated by lower values)												
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.27 higher (0.04 to 0.5 higher)	LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Attention (Better indicated by lower values)												
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.13 higher (0.12 lower to 0.38 higher)	LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Concentration (Better indicated by lower values)												
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.13 higher (0.11 lower to 0.37 higher)	LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Multitasking (Better indicated by lower values)												
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.01 higher (0.22 lower to 0.24 higher)	LOW	IMPORTANT
Neurocognitive outcomes - Subjective Cognition-Slow thinking (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Terra 2023	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	292	-	MD 0.12 higher (0.07 lower to 0.31 higher)	LOW	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; OR: odds ratio
1 95% CI crosses 2 MIDs
2 Number of events and of those who used HRT not reported
3 Adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer

Genitourinary outcomes

Table 13: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Genitourinary outcomes - Vaginal dryness												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-[2]	-[2]	OR 0.4 (0.17 to 0.88)[3]	-	VERY LOW	IMPORTANT
Genitourinary outcomes - Urinary incontinence												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	-[2]	-[2]	OR 1.37 (0.58 to 3.29)[3]	-	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; OR: odds ratio
1 95% CI crosses 1 MID
2 Number of events and of those who used HRT not reported
3 Adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer
4 95% CI crosses 2 MIDs

1 Sexual function

2 Table 14: Evidence profile for comparison between HRT and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Sexual dysfunction												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-[2]	-[2]	OR 0.9 (0.41 to 1.94)[3]	-	VERY LOW	IMPORTANT
Sexual symptoms (measured with MENQOL scale) (Better indicated by lower values)												
Tucker 2016	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	24	84	-	MD 0.84 lower (1.81 lower to 0.13 higher)[6]	VERY LOW	IMPORTANT
Sexual function (measured with FSFI scale) (Better indicated by higher values)												
Tucker 2016	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	24	84	-	MD 5.36 higher (1.01 to 9.71 higher)[6]	VERY LOW	IMPORTANT
Change in sexual symptoms (measured with MENQOL scale) from baseline to 3.5 years follow-up (Better indicated by lower values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	34	39	-	MD 0.53 lower (8.06 lower to 7 higher)[9]	LOW	IMPORTANT
Change in sexual symptoms (measured with MENQOL scale) from baseline to 1 year follow-up (Better indicated by lower values)												
Hickey 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	none	55	34	-	MD 0.6 lower (3.41 lower to 2.21 higher)	LOW	IMPORTANT
Change in sexual function (measured with FSFI scale) from baseline to 12 months follow-up (Better indicated by higher values)												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	79	40	-	MD 3.9 higher (0.43 to 7.37 higher)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Change in sexual function (measured with FSFI scale) from baseline to 12 months follow-up (Better indicated by lower values) after salpingectomy												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	302	296	-	MD 0 higher (1.13 lower to 1.13 higher)	MODERATE	VERY LOW
Change in sexual function - Pleasure (measured with SAQ) from baseline to 3.5 years follow-up (Better indicated by higher values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	39	-	MD 0.7 lower (15.75 lower to 14.35 higher)[9]	HIGH	VERY LOW
Change in sexual function - Pleasure (measured with SAQ) from baseline to 9 months follow-up (Better indicated by higher values)												
Vermeulen 2017	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	27	30	-	MD 2.9 higher (0.18 to 5.62 higher)[13]	LOW	IMPORTANT
Change in sexual function - Discomfort (measured with SAQ) from baseline to 3.5 years follow-up (Better indicated by lower values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	none	34	39	-	MD 0.05 lower (5.28 lower to 5.18 higher)[9]	LOW	IMPORTANT
Change in sexual function - Discomfort (measured with SAQ) from baseline to 9 months follow-up (Better indicated by lower values)												
Vermeulen 2017	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	27	30	-	MD 2.2 lower (3 to 1.4 lower)[13]	LOW	IMPORTANT
Change in sexual function - Habit (measured with SAQ) from baseline to 3.5 years follow-up (Better indicated by higher values)												
Hall 2019	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	34	39	-	MD 0.06 lower (3.17 lower to 3.05 higher)[9]	LOW	IMPORTANT
Sexual function - Pleasure (measured with SAQ) (Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
3[16]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	490	-	MD 0.71 higher (-0.09 to 1.50 higher)[17]	MODERATE	IMPORTANT
Sexual function - Discomfort (measured with SAQ) (Better indicated by lower values)												
2[18]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[19]	none	156	490	-	MD 1.16 lower (1.56 to 0.75 lower)[20]	LOW	IMPORTANT
Sexual function - Discomfort (measured with SAQ) (Better indicated by lower values)												
Madalinska 2006	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[21]	none	0	-	-	MD 0.4 higher (0.15 lower to 0.95 higher)[22]	VERY LOW	IMPORTANT
Sexual function - Habit (measured with SAQ) (Better indicated by higher values)												
Madalinska 2006	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	67	-	MD 0.1 higher (0.09 lower to 0.29 higher)[22]	LOW	IMPORTANT
Composite outcome (FACT-ES scale): Mood changes associated with menopause, vasomotor symptoms, urogenital outcomes and sexual function (Better indicated by higher values)												
2[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[25]	none	142	163	-	MD 3.27 higher (0.88 to 5.65 higher)[26]	VERY LOW	IMPORTANT
Composite outcome: change from baseline to 3 months after surgery (FACT-ES scale): Mood changes associated with menopause, vasomotor symptoms, urogenital outcomes and sexual function (Better indicated by higher values)												
Vermeulen 2017	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	27	30	-	Change -5.8 (-9.3 to -2.2)[27]	LOW	IMPORTANT
Composite outcome: change between 3 and 9 months after surgery (FACT-ES scale): Mood changes associated with menopause, vasomotor symptoms, urogenital outcomes and sexual (Better indicated by higher values)												
Vermeulen 2017	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	27	30	-	Change -7.3 (-11 to -3.5)[27]	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: HRT user	HRT non-user	Relative (95% CI)	Absolute		
Composite outcome: change in GCS from baseline to 12 months follow-up (Better indicated by lower values)												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	79	40	-	MD 3.1 lower (6.18 to 0.02 lower)	LOW	IMPORTANT
Composite outcome: change in GCS from baseline to 12 months follow-up (Better indicated by lower values) after salpingectomy												
Steenbeek 2021	non-randomise controlled trial	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	302	296	-	MD 0.1 higher (0.92 lower to 1.12 higher)	MODERATE	IMPORTANT

CI: confidence interval; GCS: Greene Climacteric Scale; HRT: hormone replacement therapy; FACT-ES: Functional Assessment of Cancer Therapy–Endocrine Symptoms; FSFI: Female Sexual Functioning Index; MD: mean difference; MENQOL: Menopause-specific quality of life questionnaire; MID: minimally important difference; OR: odds ratio; SAQ: Sexual Activity Questionnaire

1 95% CI crosses 2 MIDs

2 Number of events and of those who used HRT not reported

3 Adjusted for marital status, ethnicity, education, income, family history of ovarian cancer and family history of breast cancer

4 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist

5 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.2 = 1.1)

6 Adjusted breast cancer and menopause status at the time of surgery

7 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 9.99 = 5)

8 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 12.3 = 6.2)

9 Adjusted for age at surgery, previous breast cancer diagnosis, HRT use at follow-up and time between surgery and follow-up questionnaire

10 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 0.8 = 0.4)

11 Optimal information size for imprecision: N<200 (no SD could be calculated)

12 Optimal information size for imprecision: N<400 (no SD could be calculated)

13 Adjusted for age, mastectomy and non-ignorable drop-out

14 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 9.3 = 4.7)

15 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 3.1 = 1.6)

16 Johansen 2016, Madalinska 2006, Terra 2022

17 Johansen 2016: adjusted for age and history of cancer; Madalinska 2006: adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy; Terra 2022: not clear if adjusted

18 *Johansen 2016, Terra 2022*

19 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2 = 1)

20 Johansen 2016: adjusted for age and history of cancer; Terra 2022: not clear if adjusted

21 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 1.7 = 0.9)

22 Adjusted for age, history of breast cancer, tamoxifen use and prophylactic mastectomy

23 Challberg 2011, Madalinska 2006

24 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS I and JBI checklist

25 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 10.25 = 5; as 2 studies meta-analysed, median of both baseline control groups SDs used)

26 Challberg 2011: not clear if adjusted for confounders; Madalinska 2006: not adjusted

27 reported that the difference between HRT users and HRT non-users was statistically significant, that is compared to the HRT users, the HRT non-users exhibited significant short- and longer-term increases in overall endocrine symptoms

Table 15: Evidence profile for comparison between oestrogen systemic HRT vs no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Oestrogen syst. HRT user	HRT non-user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25	91	-	MD 0.8 higher (1.05 lower to 2.65 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	25	91	-	MD 1.1 lower (1.8 to 0.4 lower)[2]	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4.5 = 2.25)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.1 = 1.05)

Table 16: Evidence profile for comparison between combined (oestrogen and progestin) HRT vs no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Combined HRT user	HRT non-user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20	91	-	MD 0.5 higher (1.68 lower to 2.68 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	20	91	-	MD 1.2 lower (1.91 to 0.49 lower)[2]	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4.5 = 2.25)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.1 = 1.05)

Table 17: Evidence profile for comparison between tibolone and no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Tibolone HRT user	HRT non-user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	91	-	MD 1.5 higher (0.44 lower to 3.44 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	21	91	-	MD 1.4 lower (2.17 to 0.63 lower)[2]	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4.5 = 2.25)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.1 = 1.05)

Vaginal oestrogen

Table 18: Evidence profile for comparison between topical vaginal oestrogen vs no topical vaginal oestrogen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Topical vaginal oestrogen user	HRT non-user	Relative (95% CI)	Absolute		
Health related quality of life: SF-36 total score (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9	84	-	MD 3.3 higher (6.22 lower to 12.82 higher)[3]	VERY LOW	IMPORTANT
Vasomotor symptoms (measured with MENQOL scale) (Better indicated by lower values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	9	84	-	MD 1.04 lower (2.33 lower to 0.25 higher)[3]	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Topical vaginal oestrogen user	HRT non-user	Relative (95% CI)	Absolute		
Sexual symptoms (measured with MENQOL scale) (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	9	84	-	MD 0.55 lower (1.89 lower to 0.79 higher)[3]	VERY LOW	IMPORTANT
Sexual function (measured with FSFI scale) (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	9	84	-	MD 7.61 higher (1.35 to 13.87 higher)[3]	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; FSFI: Female Sexual Functioning Index; MD: mean difference; MID: minimally important difference; MENQOL: Menopause-specific quality of life questionnaire
1 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist
2 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 19.76 = 9.9)
3 Adjusted for breast cancer and menopause status at the time of surgery
4 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.06 = 1)
5 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.2 = 1.1)
6 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 9.99 = 5)

Table 19: Evidence profile for comparison between local oestrogen HRT vs no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Local oestrogen user	HRT non-user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11	91	-	MD 1.5 lower (5.05 lower to 2.05 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Local oestrogen user	HRT non-user	Relative (95% CI)	Absolute		
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	11	91	-	MD 0.7 lower (1.96 lower to 0.56 higher)[2]	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4.5 = 2.25)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2.1 = 1.1)

Route of administration

Table 20: Evidence profile for comparison between HRT vs topical vaginal oestrogen HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Topical vaginal oestrogen user	Relative (95% CI)	Absolute		
Health related quality of life: SF-36 total score (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	9	-	MD 1.54 lower (13.12 lower to 10.04 higher)[3]	VERY LOW	IMPORTANT
Vasomotor symptoms (measured with MENQOL scale) (Better indicated by lower values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[4]	none	24	9	-	MD 0.04 lower (1.45 lower to 1.37 higher)[3]	VERY LOW	IMPORTANT
Sexual symptoms (measured with MENQOL scale) (Better indicated by lower values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	24	9	-	MD 0.29 lower (1.8 lower to 1.22 higher)[3]	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Topical vaginal oestrogen user	Relative (95% CI)	Absolute		
Sexual function (measured with FSFI scale) (Better indicated by higher values)												
Tucker 2016	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	24	9	-	MD 2.25 lower (9.24 lower to 4.74 higher)[3]	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; FSFI: Female Sexual Functioning Index; MD: mean difference; MID: minimally important difference; MENQOL: Menopause-specific quality of life questionnaire
1 Serious risk of bias in the evidence contributing to the outcomes as per JBI checklist
2 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 13.05 = 6.8)
3 Adjusted breast cancer and menopause status at the time of surgery
4 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 1.85 = 0.9)
5 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 1.92 = 0.96)
6 95% CI crosses 2 MIDs for continuous outcomes (0.5x control group SD 9 = 4.5)

Table 21: Evidence profile for comparison between systemic HRT vs local oestrogen HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Local oestrogen user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	66	11	-	MD 2.4 higher (1.17 lower to 5.97 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	66	11	-	MD 0.5 lower (1.73 lower to 0.73 higher)[2]	HIGH	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 5.8 = 2.9)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 2 = 1)

Table 22: Evidence profile for comparison between systemic HRT vs oestrogen HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Oestrogen sys. HRT user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	25	-	MD 0.1 higher (1.8 lower to 2 higher)[1]	HIGH	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	25	-	MD 0.1 lower (0.74 lower to 0.54 higher)[1]	HIGH	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 Adjusted for age and history of cancer

Table 23: Evidence profile for comparison between systemic HRT vs combined (oestrogen plus progestin) HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Combined HRT user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	66	20	-	MD 0.4 higher (1.82 lower to 2.62 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	20	-	MD 0 higher (0.66 lower to 0.66 higher)[2]	HIGH	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4.5 = 2.25)
2 Adjusted for age and history of cancer

Table 24: Evidence profile for comparison between systemic HRT vs tibolone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral salpingo-oophorectomy: Systemic HRT user	Tibolone user	Relative (95% CI)	Absolute		
Sexual function - pleasure (measured with SAQ) (Better indicated by higher values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	66	21	-	MD 0.6 lower (2.59 lower to 1.39 higher)[2]	MODERATE	IMPORTANT
Sexual function - discomfort (measured with SAQ) (Better indicated by lower values)												
Johansen 2016	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	66	21	-	MD 0.2 higher (0.53 lower to 0.93 higher)[2]	MODERATE	IMPORTANT

CI: confidence interval; HRT: hormone replacement therapy; MD: mean difference; MID: minimally important difference; SAQ: Sexual Activity Questionnaire
1 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 4 = 2)
2 Adjusted for age and history of cancer
3 95% CI crosses 1 MID for continuous outcomes (0.5x control group SD 1.5 = 0.8)

Appendix G Economic evidence study selection

Study selection for: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

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

Appendix I Economic model

Economic model for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

Excluded effectiveness studies

Table 25: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Abildgaard, Julie, Ahlstrom, Magnus Glindvad, Nielsen, Dorte Lisbeth et al. (2020) Use of antidepressants in women after prophylactic bilateral oophorectomy: A Danish national cohort study. Psycho-oncology 29(4): 655-662	- Outcomes in study do not match those specified in this review protocol
Armstrong, Katrina, Schwartz, J Sanford, Randall, Thomas et al. (2004) Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 22(6): 1045-54	- Study design does not match that specified in this review protocol
Atsma F, Bartelink ML, Grobbee DE et al. (2006) Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause (New York, N.Y.) 13(2): 265-279	- Systematic review used as source of primary studies
Birrer, N., Chinchilla, C., Del Carmen, M. et al. (2018) Is Hormone Replacement Therapy Safe in Women with a BRCA Mutation? American Journal of Clinical Oncology: Cancer Clinical Trials 41(3): 313-315	- Systematic review used as source of primary studies
Birrer, Nicole, Chinchilla, Carolina, Del Carmen, Marcela et al. (2018) Is Hormone Replacement Therapy Safe in Women With a BRCA Mutation? A Systematic Review of the Contemporary Literature. American journal of clinical oncology 41(3): 313-315	- Systematic review used as source of primary studies
Chan, Jessica L, Senapati, Suneeta, Johnson, Lauren N C et al. (2019) Risk factors for sexual dysfunction in BRCA mutation carriers after risk-reducing salpingo-oophorectomy. Menopause (New York, N.Y.) 26(2): 132-139	- Comparator in study does not match that specified in this review protocol
Chapman, Jocelyn S, Powell, C Bethan, McLennan, Jane et al. (2011) Surveillance of survivors: follow-up after risk-reducing salpingo-oophorectomy in BRCA 1/2 mutation carriers. Gynecologic oncology 122(2): 339-43	- Outcomes in study do not match those specified in this review protocol
Chen, L.-M., Blank, S.V., Burton, E. et al. (2019) Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine Evidence-Based Review. Fertility and Sterility 112(6): 1034-1042	- Systematic review used as source of primary studies
Cohen JV, Chiel L, Boghossian L et al. (2012) Non-cancer endpoints in BRCA1/2 carriers after risk-reducing salpingo-oophorectomy. Familial cancer 11(1): 69-75	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Domchek, Susan M and Rebbeck, Timothy R (2007) Prophylactic oophorectomy in women at increased cancer risk. Current opinion in obstetrics & gynecology 19(1): 27-30	- Narrative review
Domchek, Susan and Kaunitz, Andrew M (2016) Use of systemic hormone therapy in BRCA mutation carriers. Menopause (New York, N.Y.) 23(9): 1026-7	- Study design does not match that specified in this review protocol
Dominguez-Valentin, Mev, Seppala, Toni T, Engel, Christoph et al. (2020) Risk-Reducing Gynecological Surgery in Lynch Syndrome: Results of an International Survey from the Prospective Lynch Syndrome Database. Journal of clinical medicine 9(7)	- Study design not relevant to this review protocol
Fakkert, Ingrid E, Abma, Elske Marije, Westrik, Iris G et al. (2015) Bone mineral density and fractures after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer. European journal of cancer (Oxford, England: 1990) 51(3): 400-8	- Comparator in study does not match that specified in this review protocol
Finch, Amy; Evans, Gareth; Narod, Steven A (2012) BRCA carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations. Women's health (London, England) 8(5): 543-55	- Narrative review
Finch, Amy and Narod, Steven A (2011) Quality of life and health status after prophylactic salpingo-oophorectomy in women who carry a BRCA mutation: A review. Maturitas 70(3): 261-5	- Systematic review used as source of primary studies
Finch, A, Metcalfe, K A, Chiang, J K et al. (2011) The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecologic oncology 121(1): 163-8	- Secondary publication of an included study that does not provide any additional relevant information (Hall 2019 is included instead)
Gaba, Faiza and Manchanda, Ranjit (2020) Systematic review of acceptability, cardiovascular, neurological, bone health and HRT outcomes following risk reducing surgery in BRCA carriers. Best practice & research. Clinical obstetrics & gynaecology 65: 46-65	- Systematic review used as source of primary studies
Gabriel, C A, Tigges-Cardwell, J, Stopfer, J et al. (2009) Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk-reducing salpingo-oophorectomy. Familial cancer 8(1): 23-8	- Non-randomised study which does not adjust for differences between groups at baseline
Garcia, Christine, Lyon, Liisa, Conell, Carol et al. (2015) Osteoporosis risk and management in BRCA1 and BRCA2 carriers who undergo risk-reducing salpingo-oophorectomy. Gynecologic oncology 138(3): 723-6	- Outcomes in study do not match those specified in this review protocol
Garcia, Christine, Wendt, Jacqueline, Lyon, Liisa et al. (2014) Risk management options elected by women after testing positive for a BRCA mutation. Gynecologic oncology 132(2): 428-33	- Intervention in study does not match that specified in this review protocol
Garg, Nisha, Behbehani, Sadikah, Kosiorek, Heidi et al. (2020) Hormone Replacement Therapy Prescription after Premature Surgical Menopause.	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
Journal of minimally invasive gynecology 27(7): 1618-1623	
Gervais, Nicole J, Au, April, Almey, Anne et al. (2020) Cognitive markers of dementia risk in middle-aged women with bilateral salpingo-oophorectomy prior to menopause. Neurobiology of aging 94: 1-6	- Data not reported in an extractable format or a format that can be analysed
Gordhandas, Sushmita, Norquist, Barbara M, Pennington, Kathryn P et al. (2019) Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. Gynecologic oncology 153(1): 192-200	- Systematic review used as source of primary studies
Grandi, Giovanni, Sammarini, Margaret, Cortesi, Laura et al. (2021) Satisfaction with prophylactic risk-reducing salpingo-oophorectomy in BRCA mutation carriers is very high and little dependent on the participants' characteristics at surgery: a prospective study. Menopause (New York, N.Y.) 28(3): 263-270	- Outcomes in study do not match those specified in this review protocol
Heiniger, Louise, Butow, Phyllis N, Coll, Joseph et al. (2015) Long-term outcomes of risk-reducing surgery in unaffected women at increased familial risk of breast and/or ovarian cancer. Familial cancer 14(1): 105-15	- Comparator in study does not match that specified in this review protocol
Hickey, India; Jha, Swati; Wyld, Lynda (2021) The psychosexual effects of risk-reducing bilateral salpingo-oophorectomy in female BRCA1/2 mutation carriers: A systematic review of qualitative studies. Gynecologic oncology 160(3): 763-770	- Study design does not match that specified in in this review protocol
Hickey, Martha, Moss, Katrina M, Mishra, Gita D et al. (2021) What Happens After Menopause? (WHAM): A prospective controlled study of cardiovascular and metabolic risk 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. Gynecologic oncology 162(1): 88-96	- Outcomes in study do not match those specified in this review protocol
Hickey, Martha, Trainer, Alison, Braat, Sabine et al. (2017) What Happens After Menopause? (WHAM): protocol for a prospective, multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women. BMJ open 7(11): e018758	- Study design does not match that specified in in this review protocol
Huber, D, Seitz, S, Kast, K et al. (2021) Hormone replacement therapy in BRCA mutation carriers and risk of ovarian, endometrial, and breast cancer: a systematic review. Journal of cancer research and clinical oncology 147(7): 2035-2045	- Systematic review used as source of primary studies
Islam, RM, Davis, SR, Bell, RJ et al. A prospective controlled study of sexual function and sexually related personal distress up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. Menopause, 2021 Mar 15;28(7):748-755	- Comparator in study does not match that specified in this review protocol
Johansen, Nora, Liavaag, Astrid H, Iversen, Ole-Erik et al. (2017) Use of hormone replacement therapy after risk-reducing salpingo-oophorectomy. Acta obstetricia et gynecologica Scandinavica 96(5): 547-555	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Johansen, Nora, Liavaag, Astrid H, Morkrid, Lars et al. (2018) Hormone Levels and Sexual Functioning After Risk-Reducing Salpingo-Oophorectomy. Sexual medicine 6(2): 143-153	- Outcomes in study do not match those specified in this review protocol
Johansen, Nora, Tonstad, Serena, Liavaag, Astrid Helene et al. (2020) Risk of cardiovascular disease after preventive salpingo-oophorectomy. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 30(5): 575-582	- Outcomes in study do not match those specified in this review protocol
Kershaw, Victoria, Hickey, India, Wyld, Lynda et al. (2021) The impact of risk reducing bilateral salpingo-oophorectomy on sexual function in BRCA1/2 mutation carriers and women with Lynch syndrome: A systematic review and meta-analysis. European journal of obstetrics, gynecology, and reproductive biology 265: 7-17	- Systematic review used as source of primary studies
Kotsopoulos J, Lubinski J, Neuhausen SL et al. (2006) Hormone replacement therapy and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Gynecologic oncology 100(1): 83-88	- Population in study does not match that specified in in this review protocol
Kotsopoulos, Joanne, Gronwald, Jacek, Lubinski, Jan et al. (2020) Does preventive oophorectomy increase the risk of depression in BRCA mutation carriers? Menopause (New York, N.Y.) 27(2): 156-161	- Outcomes in study do not match those specified in this review protocol
Kotsopoulos, Joanne, Huzarski, Tomasz, Gronwald, Jacek et al. (2016) Hormone replacement therapy after menopause and risk of breast cancer in BRCA1 mutation carriers: a case-control study. Breast cancer research and treatment 155(2): 365-73	- Population in study does not match that specified in this review protocol
Kotsopoulos, Joanne, Shafrir, Amy L, Rice, Megan et al. (2015) The relationship between bilateral oophorectomy and plasma hormone levels in postmenopausal women. Hormones & cancer 6(1): 54-63	- Population in study does not match that specified in this review protocol
Manchanda, R, Gaba, F, Talaulikar, V et al. (2022) Risk-Reducing Salpingo-Oophorectomy and the Use of Hormone Replacement Therapy Below the Age of Natural Menopause: Scientific Impact Paper No. 66 October 2021: Scientific Impact Paper No. 66. BJOG: an international journal of obstetrics and gynaecology 129(1): e16-e34	- Narrative review
Marchetti, C, De Felice, F, Boccia, S et al. (2018) Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A meta-analysis. Critical reviews in oncology/hematology 132: 111-115	- More recent systematic review included that covers the same topic
Marchetti, Claudia, Iadarola, Roberta, Palaia, Innocenza et al. (2014) Hormone therapy in oophorectomized BRCA1/2 mutation carriers. Menopause (New York, N.Y.) 21(7): 763-8	- More recent systematic review included that covers the same topic
Mejia-Gomez, Javier, Gronwald, Jacek, Senter, Leigha et al. (2020) Factors associated with use of hormone therapy after preventive oophorectomy in BRCA mutation carriers. Menopause (New York, N.Y.) 27(12): 1396-1402	- Non-randomised study which does not adjust for differences between groups at baseline

Study	Reason for exclusion
Michelsen, T.M., Tonstad, S., Pripp, A.H. et al. (2010) Coronary heart disease risk profile in women who underwent salpingo-oophorectomy to prevent hereditary breast ovarian cancer. International Journal of Gynecological Cancer 20(2): 233-239	- Comparator in study does not match that specified in this review protocol
Michelsen, Trond M; Dorum, Anne; Dahl, Alv A (2009) A controlled study of mental distress and somatic complaints after risk-reducing salpingo-oophorectomy in women at risk for hereditary breast ovarian cancer. Gynecologic oncology 113(1): 128-33	- Outcomes in study do not match those specified in this review protocol
Pederson, Holly J and Batur, Pelin (2023) Use of exogenous hormones in those at increased risk for breast cancer: contraceptive and menopausal hormones in gene carriers and other high-risk patients. Menopause (New York, N.Y.)	- Narrative review
Perri, Tamar, Levin, Gabriel, Naor-Revel, Shani et al. (2022) Risk-reducing salpingo-oophorectomy and breast cancer incidence among Jewish BRCA1/BRCA2-mutation carriers-an Israeli matched-pair study. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 157(2): 431-436	- Comparator in study does not match that specified in this review protocol
Powell, C Bethan, Alabaster, Amy, Stoller, Nicole et al. (2018) Bone loss in women with BRCA1 and BRCA2 mutations. Gynecologic oncology 148(3): 535-539	- Comparator in study does not match that specified in this review protocol
Ramon Y Cajal, Teresa, Torres, Asuncion, Alonso, Carmen et al. (2011) Risk factors associated with the occurrence of breast cancer after bilateral salpingo-oophorectomy in high-risk women. Cancer epidemiology 35(1): 78-82	- Comparator in study does not match that specified in this review protocol
Rebbeck, T R, Levin, A M, Eisen, A et al. (1999) Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. Journal of the National Cancer Institute 91(17): 1475-9	- Outcomes in study do not match those specified in this review protocol
Rebbeck, Timothy R, Friebel, Tara, Wagner, Theresa et al. (2005) Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 23(31): 7804-10	- Comparator in study does not match that specified in this review protocol
Rettenmaier, M.A., Micha, J.P., Bohart, R. et al. (2020) Incidence and Risk Factors of Ovarian Cancer and Breast Cancer following Prophylactic Surgery: A Retrospective Cohort Study. Journal of Gynecologic Surgery 36(4): 189-193	- Comparator in study does not match that specified in this review protocol
Robson, Mark, Hensley, Martee, Barakat, Richard et al. (2003) Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. Gynecologic oncology 89(2): 281-7	- Outcomes in study do not match those specified in this review protocol
Rocca WA, Bower JH, Maraganore DM et al. (2007) Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 69(11): 1074-1083	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Rocca, Walter A, Grossardt, Brandon R, de Andrade, Mariza et al. (2006) Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. The Lancet. Oncology 7(10): 821-8	- Population in study does not match that specified in in this review protocol
Rocca, Walter A, Lohse, Christine M, Smith, Carin Y et al. (2021) Association of Premenopausal Bilateral Oophorectomy With Cognitive Performance and Risk of Mild Cognitive Impairment. JAMA network open 4(11): e2131448	- Population in study does not match that specified in this review protocol
Schrijver, Lieske H, Mooij, Thea M, Pijpe, Anouk et al. (2022) Oral Contraceptive Use in BRCA1 and BRCA2 Mutation Carriers: Absolute Cancer Risks and Benefits. Journal of the National Cancer Institute 114(4): 540-552	- Study design does not match that specified in in this review protocol
Segev, Yakir, Rosen, Barry, Lubinski, Jan et al. (2015) Risk factors for endometrial cancer among women with a BRCA1 or BRCA2 mutation: a case control study. Familial cancer 14(3): 383-91	- Comparator in study does not match that specified in this review protocol
Shifren JL, Braunstein GD, Simon JA et al. (2000) Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. The New England journal of medicine 343(10): 682-688	- Population in study does not match that specified in this review protocol
Siyam, Tasneem, Ross, Sue, Campbell, Sandra et al. (2017) The effect of hormone therapy on quality of life and breast cancer risk after risk-reducing salpingo-oophorectomy: a systematic review. BMC women's health 17(1): 22	- Systematic review used as source of primary studies
Stjepanovic, Neda, Lubinski, Jan, Moller, Pal et al. (2021) Breast cancer risk after age 60 among BRCA1 and BRCA2 mutation carriers. Breast cancer research and treatment 187(2): 515-523	- Population in study does not match that specified in in this review protocol
Stuursma, Annechien, Lanjouw, Lieke, Idema, Demy L et al. (2022) Surgical Menopause and Bilateral Oophorectomy: Effect of Estrogen-Progesterone and Testosterone Replacement Therapy on Psychological Well-being and Sexual Functioning; A Systematic Literature Review. The journal of sexual medicine 19(12): 1778-1789	- Population in study does not match that specified in this review protocol
Terry, Mary Beth, Daly, Mary B, Phillips, Kelly Anne et al. (2019) Risk-Reducing Oophorectomy and Breast Cancer Risk Across the Spectrum of Familial Risk. Journal of the National Cancer Institute 111(3): 331-334	- Outcomes in study do not match those specified in this review protocol
Tucker, Paige E, Bulsara, Max K, Salfinger, Stuart G et al. (2016) Prevalence of sexual dysfunction after risk-reducing salpingo-oophorectomy. Gynecologic oncology 140(1): 95-100	- Outcomes in study do not match those specified in this review protocol
Tucker, Paige E and Cohen, Paul A (2017) Review Article: Sexuality and Risk-Reducing Salpingo-oophorectomy. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 27(4): 847-852	- Systematic review used as source of primary studies
Vermeulen, R F M, Beurden, M van, Korse, C M et al. (2017) Impact of risk-reducing salpingo-oophorectomy in premenopausal women. Climacteric:	- Systematic review used as source of primary studies

Study	Reason for exclusion
the journal of the International Menopause Society 20(3): 212-221	
Vermeulen, R F M, Korse, C M, Kenter, G G et al. (2019) Safety of hormone replacement therapy following risk-reducing salpingo-oophorectomy: systematic review of literature and guidelines. Climacteric: the journal of the International Menopause Society 22(4): 352-360	- Systematic review used as source of primary studies

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: What are the benefits and risks of hormone replacement therapy after risk-reducing surgery for women at increased risk of familial ovarian cancer?

K.1.1. Research recommendation

What are the long-term benefits and risks of hormone replacement therapy (HRT) after risk-reducing surgery?

K.1.2 Why this is important

Women with an increased risk of familial ovarian cancer may have risk-reducing surgery before they reach natural menopause. Removal of both ovaries leads to an immediate surgical menopause. Some women suffer severe menopause symptoms, and early menopause may have long-term adverse health effects, such as osteoporosis, cardiovascular and neurocognitive health. HRT can be offered to reduce the impact of surgical menopause. While short term data are largely reassuring, there is currently little evidence on the long-term benefits and risks of HRT for women after surgery to reduce the risk of familial ovarian cancer. This is especially relevant for women who may be unable to take HRT after surgery because of having had breast cancer (for example, women with *BRCA/PALB2* gene mutations).

K.1.3 Rationale for research recommendation

Table 26: Research recommendation rationale

Research question	
Why is this needed	
Importance to 'patients' or the population	This research question is important to women undergoing risk-reducing surgery, to enable these women to make informed decisions on taking HRT after surgical menopause.
Relevance to NICE guidance	The lack of evidence regarding long-term outcomes of HRT currently restricts NICE guidance. On the balance of benefits and risks reported in this evidence review the committee made strong recommendations. However, if this balance would change related to long-term outcomes it is possible that recommendations may need to change..
Relevance to the NHS	Potential to relieve symptoms and long-term health outcomes associated with surgical menopause, symptomatology, sexual function and improved health-related quality of life. This aligns with the NHS Long Term Plan as one of the roles of the NHS is preventing deterioration of health and reducing symptoms to improve quality of life.
National priorities	Accessing high-quality, personalised menopause care is one of the 10-year ambitions in the Policy paper on Women's Health Strategy for England
Current evidence base	Current evidence is limited regarding the long-term risks and benefits of HRT after risk-reducing surgery
Equality	Access to information on menopause, and uptake of HRT, 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 of HRT vs no HRT after risk-reducing surgery would not be ethical or acceptable in this high-risk group. Longer term follow-up of cohort or observational surveillance studies may be possible.
Other comments	None

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2 ## K.1.4 Modified PICO table

3 **Table 27: Research recommendation modified PICO table**

Criterion	Explanation
Population	Premenopausal women at increased risk of familial ovarian cancer undergoing risk-reducing surgery
Intervention	HRT
Comparator	No HRT or different types of HRT
Outcomes	• Cancer incidence (breast, ovarian, endometrial, primary peritoneal) • Cardiovascular health • Bone health • Neurocognitive health • Sexual function • Health-related quality of life
Study design	Prospective or retrospective cohort studies
Timeframe	10 to 20 years follow-up
Additional information	None

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