National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[N] Risk-reducing surgery

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.8.1 to 1.8.5 and 1.8.9 to 1.8.20 (and information about risk-reducing surgery in Table 3) in the NICE guideline

September 2023

Draft for consultation

These evidence reviews were developed by NICE

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Risk-reducing surgery

Review question

How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Introduction

Women with a familial ovarian cancer risk are offered risk reducing surgery to help mitigate their personal risk of developing ovarian cancer. This surgery is normally in the form of surgical removal of their tubes and ovaries (bilateral salpingo-oophorectomy) and is often done by keyhole surgery. However, such surgery is not risk free with some women suffering surgical complications such as damage to internal organs, infection, or the need for repeat surgery. Rarely, these complications can have a lifelong impact. By removing the tubes and ovaries, a women's fertility is negatively impacted, and they would not be able to naturally conceive. Furthermore, by removing the ovaries before menopause, women are placed into a surgical menopause which can have serious implications on their bone and cardiovascular health along with leading to symptoms that impact negatively on their quality of life. Therefore, we need to be certain that risk-reducing surgery is effective and this review question addresses this question.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Women at increased risk of familial ovarian cancer
Intervention	Surgery: • bilateral salpingo-oophorectomy • bilateral salpingo-oophorectomy and hysterectomy • bilateral salpingectomy • bilateral salpingectomy and hysterectomy
Comparator	• in comparison with each other • usual care (no intervention) • surveillance (for example, no surgery)

Outcomes	**Critical**
	• Health related quality of life (measured using a validated scale)
	• Patient satisfaction
	• Surgery related adverse events such as:
	  ○ severe adverse events as defined by studies (for example, within 30 days, or 90 days as measured using the Clavien-Dindo classification of surgical complications)
	  ○ surgery related mortality
	  ○ long-term effects such as early menopause
	• Ovarian cancer related mortality
	Important

- Overall survival
- Disease-free survival (defined as time from surgical procedure to cancer diagnosis)
- Ovarian cancer detection rates

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

Included studies

Overall 21 studies were included in this review. These were 18 observational studies (Bogani 2017, Crosbie 2021, Domchek 2006, Domchek 2010, Evans 2009, Finch 2006, Finkelman 2012, Fry 2001, Gaba 2021, Ingham 2013, Kauff 2008, Madalinska 2007, Marchetti 2022, Marcinkute 2022, Metcalfe 2015, Nebgen 2018, Powell 2018, Rebbeck 2002), 1 non-randomised controlled trial (Steenbeck 2021) and 2 systematic reviews (Gaba 2020, Wei 2023). These are divided into the following categories:

- bilateral salpingo-oophorectomy vs surveillance (Evans 2009, Fry 2001, Kauff 2008, Madalinska 2007)
- bilateral salpingo-oophorectomy vs no bilateral salpingo-oophorectomy (Crosbie 2021, Finch 2006, Finkelman 2012, Marcinkute 2022, Metcalfe 2015, Powell 2018)
- bilateral salpingo-oophorectomy vs surveillance or no bilateral salpingo-oophorectomy (Domchek 2006, Domchek 2010, Ingham 2013, Rebbeck 2002)
- salpingectomy with delayed bilateral salpingo-oophorectomy vs surveillance (Nebgen 2018)
- salpingectomy with delayed bilateral salpingo-oophorectomy vs bilateral salpingo-oophorectomy (Steenbeek 2021)
- pre-menopausal bilateral salpingo-oophorectomy vs post-menopausal bilateral salpingo-oophorectomy (Gaba 2021)
- hysterectomy plus bilateral salpingo-oophorectomy vs bilateral salpingo-oophorectomy (Bogani 2017, Marchetti 2022)

One systematic review (Gaba 2020) was a descriptive review reporting on menopause-related outcomes in women *BRCA1/2* carriers who underwent risk-reducing surgery.

One systematic review and meta-analysis (Wei 2023 reported on health-related quality of life and menopause-related outcomes in women at increased-risk of breast or ovarian cancer.

The included studies are summarised in Table 2.

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Bogani 2017 Observational study Italy	N=85 women who were *BRCA2* mutation carriers or had a strong familial history of breast and/or ovarian cancer and underwent risk-reducing surgery Age (mean (SD), years): 47 (8.2)	Hysterectomy plus bilateral salpingo-oophorectomy	Bilateral salpingo-oophorectomy	• Surgery related adverse events
Crosbie 2021 Observational study UK	N=2193 women proven *BRCA1/2* carriers Age (median, years): surgery group 45.1, no surgery group 43.45	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Ovarian cancer related mortality • Overall mortality (survival) • Ovarian cancer detection rates (incidence)
Domchek 2006 Observational study International (US and Europe)	N=426 women with *BRCA1/2* mutations Age (mean (SD), years): surgery group 44.8 (8.5), no surgery group 42.6 (10)	Bilateral salpingo-oophorectomy	Surveillance or no bilateral salpingo-oophorectomy	• Ovarian cancer related mortality • Overall mortality (survival) • Ovarian cancer detection rates (incidence)
Domchek 2010 Observational study International (22 centres who were part of the PROSE consortium)	N=2482 women tested positive for *BRCA1/2* mutations Age (mean (range), years): surgery group: in those with no prior breast cancer 43.2 (20.5-79); in those with prior breast cancer 47.7 (29.7-75.2	Bilateral salpingo-oophorectomy	Surveillance or no bilateral salpingo-oophorectomy	• Ovarian cancer related mortality • Overall mortality (survival) • Ovarian cancer detection rates (incidence)
Evans 2009 Observational study UK	N=803 women at high-risk of ovarian cancer Age not reported	Bilateral salpingo-oophorectomy	Surveillance	• Ovarian cancer related mortality • Overall mortality (survival) • Ovarian cancer detection rates (incidence)

Study	Population	Intervention	Comparison	Outcomes
Finch 2006 Observational study International	N=1828 women with *BRCA1/2* mutations Age (mean (range), years): surgery group 51.1 (30-74) and 46.3 (30-74), no surgery group 45.1 (30-74)	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Ovarian cancer detection rates (incidence) • Disease-free survival
Finkelman 2012 Observational study International	N=3787 women with BRCA1/2 Age (mean (SD), years): 43.5 (12.7)	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Ovarian cancer detection rates (incidence) • Disease-free survival
Fry 2001 Observational study UK	N=57 women at high-risk of ovarian cancer Age not reported	Bilateral salpingo-oophorectomy	Surveillance	• Health related quality of life
Gaba 2020 Systematic review (descriptive synthesis) UK	N=67 studies (n=10 relate to bone and cardiovascular health following surgical intervention) Population: *BRCA1/2* carriers undergoing risk-reducing surgery	Bilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy with delayed oophorectomy	Not applicable as all women had risk-reducing surgery	• Long-term effects such as early menopause
Gaba 2021 Observational study UK	N=683 women at increased risk of ovarian cancer Age (mean (SD), years): surgery group 51.5 (9.56), no surgery group 38.25 (10.23)	Pre-menopausal salpingo-oophorectomy	Post-menopausal salpingo-oophorectomy	• Patient satisfaction
Ingham 2013 Observational study UK	N=565 women *BRCA1/2* mutation carriers Age (median (range), years): in *BRCA1* carriers 34.4 (2-87), in *BRCA2* carriers 37.4 (5-85)	Bilateral salpingo-oophorectomy	Surveillance or no bilateral salpingo-oophorectomy	• Overall mortality (survival) • Ovarian cancer detection rate (incidence)
Kauff 2008 Observational study International	N=792 women with *BRCA1/2* mutations Age (mean (range), years): surgery group 47.1 (31.1-	Bilateral salpingo-oophorectomy	Surveillance	• Disease-free survival • Ovarian cancer detection rate (incidence)

Study	Population	Intervention	Comparison	Outcomes
	79), no surgery group 42.9 (30-87.8)			
Madalinska 2007 Observational study The Netherlands	N=160 *BRCA1/2* mutation carriers Age (mean (SD), years): surgery group 48.3 (8.4), surveillance group 45.3 (8.1)	Bilateral salpingo-oophorectomy	Surveillance	• Health related quality of life
Marchetti 2022 Observational study Italy	N=132 women undergoing risk-reducing surgery Age (median (range), years): 46 (31-79)	Hysterectomy plus bilateral salpingo-oophorectomy	Bilateral salpingo-oophorectomy	• Surgery related adverse events
Marcinkute 2022 Observational study UK	N=887 women *BRCA1/2* carriers Age (mean (range), years): 44.6 (25.5-76.7)	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Disease-free survival
Metcalfe 2015 Observational study Canada	N=676 women with breast cancer and with *BRCA1/2* mutations Age (mean (range), years): surgery group 41.7 (25-65), no surgery group 42.6 (22-65)	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Ovarian cancer related mortality • Overall mortality (survival)
Nebgen 2018 Observational study US	N=43 pre-menopausal women with known *BRACA1/2* mutations Age (mean (range), years): BS/DO: *BRCA1* 35.7 (31-38), *BRCA2* 35.5 (30-43), salpingo oophorectomy *BRCA1* 40.2 (36-45), *BRCA2* 44.4 (40-47), surveillance *BRCA1* 35.5 (32-37), *BRCA2* 36.9 (32-43)	Bilateral salpingectomy with delayed oophorectomy	Surveillance	• Health related quality of life • Patient satisfaction • Long-term effects such as early menopause
Powell 2018 Observational study	N=244 women with *BRCA1/2* mutations	Bilateral salpingo-oophorectomy	No bilateral salpingo-oophorectomy	• Long-term effects such as early menopause

Study	Population	Intervention	Comparison	Outcomes
US	Age at scan (median (range), years): surgery group 57 (50-65), no surgery group 54.5 (44-60)			
Rebbeck 2002 Observational study International	N=551 women *BRCA1/2* mutation carriers Age (mean (range), years): surgery group 42 (21.2-74.8), no surgery group 40.9 (19.6-79.1)	Bilateral salpingo-oophorectomy	Surveillance/no bilateral salpingo-oophorectomy	• Disease-free survival
Steenbeek 2021 Non-randomised controlled trial The Netherlands	N=548 women with a documented *BRCA1/2* mutations Age (mean (SD), years): 37.2 (3.5)	Salpingectomy with delayed oophorectomy	Bilateral salpingo-oophorectomy	• Health related quality of life • Long-term effects such as early menopause
Wei 2023 Systematic review UK	n=3762 with surgery, n=3002 without surgery from n=34 studies (n=21 relevant studies) Population: women at increased-risk of breast/ovarian cancer, including diagnosis of pathogenic variants in cancer-susceptibility-genes or a strong family-history of breast/ovarian cancer	Bilateral salpingo-oophorectomy or or risk-reducing early-salpingectomy and delayed-oophorectomy	No bilateral salpingo-oophorectomy/surveillance	• Health related quality of life • Long-term effects such as early menopause

BS/DO: bilateral salpingectomy with delayed oophorectomy; SD: standard deviation

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

Summary of the evidence

Bilateral salpingo-oophorectomy versus surveillance

The evidence regarding health related quality of life is inconclusive. Some very low to low quality evidence showed that surgery has an important harm in terms of health related quality of life in women who underwent surgery as compared to those who did not. However, low quality evidence showed no important difference in terms of health related quality of life between the two groups.

In terms of ovarian cancer related mortality or overall mortality, there was no evidence of an important difference between the two groups (very low quality evidence).

Regarding disease free survival, high quality evidence showed an important benefit associated with surgery as the risk was reduced in those who underwent surgery. Similarly, moderate quality evidence also showed an important benefit associated with surgery in terms of ovarian cancer detection rate or incidence as fewer ovarian cancer cases were detected in those who underwent surgery as compared to those who did not.

Bilateral salpingo-oophorectomy versus no bilateral salpingo-oophorectomy

The overall health related quality of life evidence (very low to low quality) for this comparison is based on a systematic review which reported that the majority of the evidence showed no important difference between women who underwent bilateral salpingo-oophorectomy as compared to those who did not (including physical and mental components). The review also reported that the majority of the evidence showed increased menopause symptoms such as hot flashes, night sweats and sleep disturbance following surgery (very low quality evidence).

In terms of long-term menopause related outcomes such as bone health, very low to low quality evidence showed no important difference between the two groups. However, when comparing pre- and post-menopausal surgery, some low to moderate quality evidence showed an important benefit of pre-menopausal surgery as women who had pre-menopausal surgery reported fewer bone health related issues such as osteopenia or osteoporosis as compared to those who had post-menopausal surgery. However, after controlling for potential confounders timing of surgery showed no association with bone loss.

A descriptive systematic review in women who had risk-reducing surgery only also reported on long-term menopause related outcomes: the range for osteopenia reported varied between 23% and 61%, for osteoporosis between 6% to 20%, and for cardiovascular health between 1% and 4% (low quality evidence).

In terms of disease free survival, high quality evidence showed an important benefit associated with surgery as the risk was reduced in those who underwent surgery. Similarly, high quality evidence also showed that surgery had an important benefit in terms of ovarian cancer detection rates or incidence as it was lower in the surgery group as compared to no surgery group.

Bilateral salpingo-oophorectomy versus surveillance/no bilateral salpingo-oophorectomy

Low to high quality evidence showed an important benefit of surgery in terms of ovarian cancer related mortality and overall mortality as it was better in women who underwent bilateral salpingo-oophorectomy as compared to those who did not. However, there is some uncertainty around the estimate for ovarian cancer related mortality outcome measured as relative risk as the upper 95% confidence interval bound is at 1.

Regarding disease free survival, high quality evidence showed an important benefit associated with surgery as the risk was reduced in those who underwent surgery.

Similarly, high quality evidence showed an important benefit of surgery in terms of ovarian cancer detection rates or incidence as this was lower in the surgery group as compared to no surgery group.

Salpingectomy with delayed bilateral salpingo-oophorectomy versus surveillance

In terms of health related quality of life, patient satisfaction with their decision and menopause related outcomes, one study reported no difference between pre-menopausal

women who underwent salpingectomy with delayed bilateral salpingo-oophorectomy as compared to surveillance (very low quality evidence).

Salpingectomy with delayed bilateral salpingo-oophorectomy versus bilateral salpingo-oophorectomy

Two studies reported no difference in terms of health related quality of life or patient satisfaction with their decision in women who underwent salpingectomy with delayed bilateral salpingo-oophorectomy as compared to those who chose bilateral salpingo-oophorectomy (very low to moderate quality evidence). However, women who had bilateral salpingo-oophorectomy reported more climacteric symptoms 12 months after surgery as compared to women who had salpingectomy with delayed salpingo-oophorectomy (moderate quality evidence).

Pre-menopausal bilateral salpingo-oophorectomy versus post-menopausal bilateral salpingo-oophorectomy

The overall evidence regarding patient satisfaction or regret with their decision is inconclusive. Very low quality evidence showed an important harm associated with pre-menopausal surgery as more women who had it reported regretting their choice. However, there was no evidence of an important difference in terms of patients responding that the decision to undergo the surgery did them a lot of harm (very low quality evidence).

In terms of other satisfaction or regret aspects such as it was the right decision, making the same decision again and that the decision was a wise one, low quality evidence showed no important difference between the two groups.

Hysterectomy plus bilateral salpingo-oophorectomy versus bilateral salpingo-oophorectomy

Very low quality evidence showed no important difference in terms of surgery related severe adverse events (severe grade III or above complications) between women who underwent hysterectomy with bilateral salpingo-oophorectomy as compared to those who had bilateral salpingo-oophorectomy only. The evidence also showed that there was no evidence of an important difference between the two groups (low quality evidence).

See appendix F for full GRADE tables.

Economic evidence

Included studies

Five economic studies were identified which were relevant to this question (Bommer 2022, Manchanda 2015, Manchanda 2016, Muller 2018, Yamauchi 2018).

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

The systematic search of the economic literature undertaken for the guideline identified the following studies:

Risk-reducing strategies in BRCA-mutation carriers

- One Swiss study on the cost-utility of risk-reducing strategies to prevent breast and ovarian cancer in *BRCA*-mutation carriers (Bommer 2022);
- One German study on the cost-utility of different risk-reducing strategies to prevent breast and ovarian cancer in *BRCA* mutation carriers (Muller 2018);
- One Japanese study on the cost-utility of prevention strategies in *BRCA* mutation carriers (Yamauchi 2018).

Risk threshold for risk-reducing surgery for ovarian cancer prevention

- One UK study on the risk threshold for risk-reducing salpingo-oophorectomy for ovarian cancer prevention in premenopausal women with varying lifetime ovarian cancer risk levels (Manchanda 2016),
- One UK study on the risk threshold for risk-reducing salpingo-oophorectomy for ovarian cancer prevention in low-risk postmenopausal women with varying lifetime ovarian cancer risk levels (Manchanda 2015).

See Table 3 and Table 4 for the economic evidence profiles of the included studies.

Table 3: Economic evidence profiles for risk-reducing strategies in *BRCA* mutation carriers

Study	Limitations	Applicability	Other comments	Incremental Costs [1]	Incremental QALYs	Incremental Cost effectiveness	Uncertainty
Bommer 2022 Switzerland	Minor limitations [2]	Partially applicable [3]	-A cohort of female *BRCA1* or *BRCA2* mutation carriers aged 40 years -Modelling study (Markov) - Time horizon: 60 years (lifetime) Interventions: Risk reducing bilateral mastectomy (RRBM) plus risk reducing bilateral salpingo-oophorectomy (RRBSO) Comparators: Intensified surveillance (IS), RRBM, RRBSO, chemoprevention with Tamoxifen (CP)	*BRCA1* RRBM & RRBSO vs IS: -£64,654 CP: -£60,318 RRBM: -£39,163 RRBSO: -£36,175 *BRCA2* RRBM & RRBSO vs IS: -£41,475 CP: -£36,321 RRBM: -£17,708 RRBSO: -£9,792	*BRCA1* RRBM & RRBSO vs IS: 4.76 CP: 4 RRBM: 1.96 RRBSO: 2.45 *BRCA2* RRBM & RRBSO vs IS: 4.33 CP: 3 RRBM: 2.27 RRBSO: 0.61	RRBM & RRBSO dominant for both *BRCA1* and *BRCA2*	-At a willingness-to-pay (WTP) from £0 to £58,445 per QALY gained RRBM & RRBSO had 100% probability of being cost-effective (for both *BRCA1* and *BRCA2*) -Changes in ovarian cancer (OC) incidence after primary breast cancer, RRBSO costs, hazard ratio of RRBSO, RRBM costs with implant reconstruction, costs of implant replacement, utility values of IS and CP had the greatest impact on the ICERs. However, the conclusions were unchanged.
Muller 2018 Germany	Minor limitations [4]	Partially applicable [5]	-A cohort of 30-year-old female *BRCA* mutation carriers aged 30 years	RRBM and RRBSO at age 30 vs:	RRBM and RRBSO at age 30 vs:	RRBM and RRBSO at age 30: dominant	-At WTP of £45,447 per QALY the probability of RRBM and RRBSO at age 30 being cost-effective was 86%

Study	Limitations	Applicability	Other comments	Incremental Costs [1]	QALYs	Cost effectiveness	Uncertainty
			- Modelling study (Markov) - Time horizon: 75 years (lifetime) - Interventions: RRBM, RRBSO, RRBM and RRBSO at age 40, RRBM and RRBSO at age 30	-RRBM and RRBSO at age 40: - £1,251 -RRBSO: -£4,879 -RRBM: -£7,156 -IS: -£14,585	-RRBM and RRBSO at age 40: 0.38 -RRBSO: 0.95 -RRBM: 1.39 -IS: 2.7		-The results were robust, including to changes in cancer incidence, mortality, utility assumptions, the efficacy of surgical options, the discount rate, differentiating between 'OC' (<stage 4) and 'recurrent OC' (stage 4) states.
Yamauchi 2018 Japan	Potentially serious limitations [6]	Partially applicable [7]	-A cohort of female *BRCA1* and *BRCA2* mutation carriers aged 35 years - Modelling study (Markov) - Time horizon: 35 years -Interventions: RRBM at 35 years plus RRBSO at 45 years, IS from 35 years, RRBSO at 45 years, RRBM at 35 years Comparator: IS from 35 years	*BRCA1* RRBM at age 35, RRBSO at age 45 vs -IS from age 35: -£5,345 -IS from age 35, RRBSO at age 45: -£3,197 -RRBM at age 35: -£5,794 *BRCA2* RRBM at age 35 vs -IS from age 35: -£6,637	*BRCA1* RRBM at age 35, RRBSO at age 45 vs -IS from age 35: 1.49 -IS from age 35, RRBSO at age 45: 0.06 -RRBM at age 35: 0.45 *BRCA2*	For *BRCA1*: RRBM at age 35, RRBSO at age 45 was dominant For *BRCA2*: RRBM at age 35 was dominant	Findings robust to model inputs, including probabilities and costs. However, using lower values for some utilities for preventative surgical procedures resulted in changes in results that favoured IS, but results were not reported.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness	
			(annual mammogram, magnetic resonance imaging, biannual blood test, chemistry, transvaginal ultrasound, examination)	-RRBM at age 35, RRBSO at age 45: -£3,412 -IS from 35 years, RRBSO at age 45: -£10,793	RRBM at age 35 vs -IS from age 35: 1.82 -RRBM at age 35, RRBSO at age 45: 0.91 -IS from age 35, RRBSO at age 45: 1.17		

Abbreviations: CP: Chemoprevention; ICER: Incremental cost-effectiveness ratio; IS: Intensified surveillance; k: Thousand; OC: Ovarian cancer; QALY: Quality-adjusted life years; RRBM: Risk reducing bilateral mastectomy; RRBO: risk reducing bilateral oophorectomy; RRBS: Risk reducing bilateral salpingectomy; RRBSO: Risk reducing bilateral salpingo-oophorectomy; WTP: Willingness-to-pay

[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Some costs data supplemented with authors' assumptions, otherwise well conducted study with no notable methodological limitations
[3] Swiss study, 3% discount for costs and QALYs
[4] Some local unit cost data, otherwise well conducted study with no notable methodological limitations
[5] German study, 3% discount for costs and QALYs
[6] The time horizon for the study was 35 years and since individuals entered the model at the age of 35, the benefits and costs beyond the age of 70 were not taken into account. This may have resulted in an underestimation of the cost-effectiveness of risk-reducing surgeries. Resource use data from 2 centres in Japan and source of unit cost data unclear. No Probabilistic sensitivity analyses.
[7] Japanese study, 2% discount rate but unclear if applied to both costs and QALYs

Table 4: Economic evidence profiles for risk thresholds for risk-reducing surgery for ovarian cancer prevention

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness	
Manchanda 2016 UK	Minor limitations [1]	Directly applicable [2]	- Pre-menopausal women >40 years with varying lifetime ovarian cancer risk levels: 2%, 4%, 5%, 6%, 8% and 10% - Modelling study (Decision analysis model) - Time horizon: Lifetime) -Interventions: Risk-reducing bilateral salpingo-oophorectomy (RRBSO) at different lifetime risks of developing ovarian cancer -Comparator: No RRBSO -Results were stratified by lifetime ovarian cancer (OC) risk	RRBSO vs no RRBSO 10% lifetime OC risk: £1,530 8% lifetime OC risk: £3,1781 6% lifetime OC risk: £2,033 5% lifetime OC risk: £2,159 4% lifetime OC risk: £2,284 2% lifetime OC risk: £2,536	RRBSO vs no RRBSO 10% lifetime OC risk: 0.30 8% lifetime OC risk: 0.2 6% lifetime OC risk: 0.2 5% lifetime OC risk: 0.15 4% lifetime OC risk: 0.12 2% lifetime OC risk: 0.06	RRBSO vs no RRBSO £19,536 at 4% lifetime OC risk Other ICERs were: £5,031 - 10% lifetime OC risk £7,370 - 8% lifetime OC risk £11,337 - 6% lifetime OC risk £14,573 - 5% lifetime OC risk £46,480 - 2% lifetime OC risk	-At the NICE threshold of £20k per QALY, the probabilities of RRBSO being cost-effective were 23%, 46%, 60%, 72%, 91% and 98% at 2%, 4%, 5%, 6%, 8% and 10% lifetime OC risk levels, respectively -The results were more robust at higher levels of lifetime OC risk - There results were robust to various risk probabilities, costs of surgical prevention or treatment of ovarian and breast cancer and cardiovascular disease -The results were sensitive to RRBSO utility weight. -The results were also sensitive to hormone replacement therapy compliance. - The results were also sensitive to assumed reduction in breast cancer risk.
Manchanda 2015	Minor limitations [3]	Directly applicable [4]	-Low/intermediate risk postmenopausal	RRBSO vs no RRBSO	RRBSO vs no RRBSO	RRBSO vs no RRBSO	-At the NICE threshold of £20k per QALY the

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness	
UK			women ≥ 50 years with varying lifetime OC risk levels: 2%, 4%, 5%, 6, 8% and 10% - Modelling study (Decision analysis model) - Time horizon: Lifetime) -Interventions: RRBSO at different lifetime OC risk levels -Comparator: No RRBSO -Results were stratified by lifetime OC risk	10% lifetime OC risk: £412 8% lifetime OC risk: £762 6% lifetime OC risk: £1,113 5% lifetime OC risk: £1,288 4% lifetime OC risk: £1,464 2% lifetime OC risk: £1,815	10% lifetime OC risk: 0.22 8% lifetime OC risk: 0.17 6% lifetime OC risk: 0.11 5% lifetime OC risk: 0.08 4% lifetime OC risk: 0.057 2% lifetime OC risk: 0.0	£15,247 - 5% lifetime OC risk Other ICERs were: £1,864 - 10% lifetime OC risk £4,584 - 8% lifetime OC risk £9,958 - 6% lifetime OC risk £25,577 - 4% lifetime OC risk £674,656 - 2% lifetime OC risk	probabilities of RRBSO being cost-effective were 67%, 80%, 84%, 91% and 94% at risk thresholds of 4%, 5%, 6%, 8% and 10% -The results were not sensitive to treatment costs of RRBSO, ovarian cancer or cardiovascular event -The results were sensitive to excess cardiovascular deaths at the 5% threshold but not that sensitive at the 6% and 8% thresholds -The results were sensitive to the utility scores for RRBSO. For example, the model was not cost-effective at the lowermost limit of the utility score for RRBSO. -Generally, the impact of different variables on cost-effectiveness decreased as the lifetime OC risk increased.

Abbreviations: k: Thousand; NICE: National Institute for Health and Care Excellence; OC: Ovarian cancer; QALY: Quality-adjusted life years; RRBSO: Risk reducing bilateral salpingo-oophorectomy; UK: United Kingdom

[1] A well-conducted study in accordance with NICE reference case methods and no significant limitations were noted.
[2] UK study, QALYs
[3] A well-conducted study in accordance with NICE reference case methods and no significant limitations were noted.

1 *[4] UK study, QALYs*

Economic model

The committee prioritised this topic for economic modelling. However, there was existing economic evidence adequately addressing this question. They identified economic modelling on the cost-effectiveness of risk reducing surgery in individuals with pathogenic variants associated with increased ovarian cancer risk as an important area for economic modelling. The committee were made aware of an ongoing PhD research aiming to assess the cost-effectiveness of risk reducing surgery in women with increased ovarian cancer risk linked to pathogenic variants in *BRCA1*/*BRCA2*/*PALB2*/*RAD51C*/*RAD51D*/*BRIP1* cancer susceptibility genes. Consequently, the committee decided to invite the PhD researcher who is based in the Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine as an expert witness to present the findings of this research. A copy of the expert testimony form is provided in appendix L.

Evidence statements

Economic

Risk reducing surgery

- Evidence from a cost-utility analysis (Bommer 2022) using modelling indicates that combined risk reducing bilateral mastectomy (RRBM) and risk reducing bilateral salpingo-oophorectomy (RRBSO) is likely to be dominant when compared to intensified surveillance, chemoprevention with Tamoxifen, RRBM alone and RRBSO alone in adult women with *BRCA* pathogenic variants in Switzerland. The study is partially applicable to NICE's decision-making context and has minor limitations.
- Evidence from a cost-utility analysis (Müller 2018) using modelling suggests that combined RRBM and RRBSO at 30 years is likely to be the preferred option compared to intensified surveillance, RRBM alone, RRBSO alone, and RRBM and RRBSO at 40 years in adult women with *BRCA* pathogenic variants in Germany. The study is partially applicable to NICE's decision-making context and has minor limitations.
- Evidence from a cost-utility analysis (Yamauchi 2018) using modelling suggests that combined RRBM at 35 years and RRBSO at 45 years is likely to be the preferred option compared to intensified surveillance from 35 years and RRBSO at 45 years, and RRBM only at 35 years in adult women with *BRCA1* pathogenic variants in Japan. The study also found that in women with *BRCA2* pathogenic variants, RRBM only was the preferred option compared to all the other options. The study is partially relevant to NICE's decision-making context and it has potentially serious limitations.
- Evidence from a cost-utility analysis using modelling presented by an expert witness suggests that, for women with *BRCA1*/*BRCA2*, combined RRBM at 30 years and RRBSO at 35 years is likely to be cost-effective when compared to enhanced breast cancer screening and medical prevention alone from age 30, RRBM at age 30, and RRBSO at age 35 with high-risk breast cancer screening and tamoxifen from age 30. For women with *PALB2*, combined RRBM at 40 years and RRBSO at 45 years is the optimal strategy compared to high-risk breast cancer screening and tamoxifen from age 30, RRBM at age 40, and RRBSO at age 45 with high-risk breast cancer screening and tamoxifen from age 30. For women with *RAD51C* and *RAD51D*, RRBSO at 45 years with moderate-risk breast cancer screening and tamoxifen from age 40 is likely to be cost-effective when compared to moderate-risk breast cancer screening and medical prevention from age 40 only. For women with *BRIP1*, RRBSO at 45 years is likely to be cost-effective compared to no surgery. The study is directly relevant to the NICE's decision-making context and has minor limitations.

Thresholds for risk reducing surgery

- Evidence from a cost-utility analysis using modelling (Manchanda 2016) in the UK indicates that offering RRBSO to premenopausal women aged over 40 with at least a 4% lifetime ovarian cancer risk may potentially be cost-effective compared to not offering RRBSO at this lifetime ovarian cancer risk. The study is directly relevant to NICE's decision-making context and has minor limitations.
- Evidence from a cost-utility analysis using modelling (Manchanda 2015) in the UK suggests that offering RRBSO to low/intermediate risk postmenopausal women aged 50 or older with at least a 5% lifetime ovarian cancer risk may potentially be cost-effective compared to not offering RRBSO at this lifetime ovarian cancer risk. The study is directly relevant to NICE's decision-making context and has minor limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Health related quality of life and patient satisfaction were prioritised as critical outcomes by the committee as they may help to determine the burden of the risk-reducing surgery in women at increased risk of familial ovarian cancer. Also, because deferring risk reducing treatments in favour of surveillance or no treatment, may have a negative impact on overall survival – but this choice might be made for quality of life reasons for example preservation of fertility or an early menopause.

The committee agreed that surgery related adverse events should be critical outcomes as they may help to identify potential harm and distress to women choosing to undergo surgery.

Long-term effects such as an early menopause were chosen as critical outcomes as usually women, undergoing risk-reducing surgery will experience an early menopause, and therefore it is important to identify health risks associated with it after the surgery.

Ovarian cancer related mortality was chosen as a critical outcome and overall survival, disease-free survival as well as ovarian cancer detection rates were prioritised as important outcomes as the committee was especially interested in the effectiveness of risk-reducing surgery on ovarian cancer related mortality. Additionally, all the above outcomes provide a measure of the impact of ovarian cancer and the effectiveness of risk-reducing surgery in women with increased risk of familial ovarian cancer.

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 a very low or low quality. This was predominately due to serious risk of bias for a few outcomes and serious or very serious imprecision around the effect estimates.

Benefits and harms

Factors to take into account when considering risk-reducing surgery

The committee discussed that there are a number of general factors that need to be considered in relation to risk-reducing surgery. They based their recommendations on the effectiveness evidence of improved outcomes such as disease-free survival and cancer incidence which showed an important benefit of surgery as well as economic evidence. The quality of the effectiveness evidence was mainly high and the majority of the economic evidence had only minor limitations. They also noted the fact that ovarian cancer starts in the organs that are removed and so the committee agreed that surgery is clearly the most effective risk-reduction option (and clearly more effective than surveillance – see evidence review K for details). Based on experience they noted that it does not completely remove the

risk of cancer because there is a small risk of peritoneal cancer. They discussed that bilateral salpingo-oophorectomy has direct consequences, for example the person can no longer become pregnant and enters menopause. On the balance of benefits and risks the committee decided that completion of family should be one of the deciding factors when risk-reducing surgery is offered because the incidence of ovarian cancer in people younger than 35 is relatively small (which is consistent with the findings of the economic model). Due to surgically induced menopause as a life changing consequence of salpingo-oophorectomy the committee also agreed that the risk level would need to be high enough to balance risks and benefits. They considered lifetime risk and noted that the economic evidence (such analyses weigh up the benefits, risks and costs) showed that a threshold level of 4% lifetime risk in people who are premenopausal would be cost-effective and 5% cost effective for people post menopause. The difference in lifetime risk is due to the risk of ovarian cancer decreasing after menopause due to hormonal changes and also that postmenopausal people can no longer through natural conception pass genetic risk on to their children. Such lifetime risk calculations would depend on whether they have a pathogenic variant or whether there is a verified family history of ovarian cancer for them or a family member. The committee agreed that this level of risk would minimise people having unnecessary surgery.

The committee recognised, based on experience, that decisions around risk-reducing surgery can be distressing for people because for premenopausal women it would mean that they would become menopausal and can no longer have children and for postmenopausal women it is a surgical procedure associated with some risks. This could influence their ability to come to a decision about having surgery which could potentially be lifesaving for them and the committee emphasised that psychological factors (such as distress and anxiety) should be taken into account, including what psychological support may be available. The committee also noted, based on experience, that sometimes a referral for psychological support may be needed (because of the level of distress and anxiety and the level of the person's risk) so that the person is supported in decision making and psychological distress is addressed.

The committee discussed early menopause as a consequence of risk-reducing surgery for premenopausal women. They decided that it was important that the person would receive specialist menopause counselling before (to be prepared for what to expect in relation to the menopause), and after surgery (to discuss potential menopause symptoms and associated treatments). They also recommended that information is provided (see section below on information provision).

The committee noted, based on their knowledge and experience, that decisions about risk-reducing surgery for people who are carriers of bi-allelic pathogenic variants in mismatch repair genes (for example, homozygous PMS2) are complex. However, they are also very rare so the committee agreed that a referral to a specialist multidisciplinary team would be needed for discussions about potential risk-reducing surgery.

Types of risk-reducing surgery and timing in relation to the person's specific pathogenic variant

The committee discussed the evidence of an important benefit of bilateral salpingo-oophorectomy in terms, that is that bilateral salpingo-oophorectomy improves disease-free survival as well as the detection rate of early-stage ovarian cancer. They noted that most of the evidence came from studies with carriers of the *BRCA1* or *BRCA2* variants. Based on the evidence, they recommended bilateral salpingo-oophorectomy for people at increased risk of ovarian cancer with *BRCA1* and *BRCA2*, and also *RAD51C*, *RAD51D*, *BRIP1* or *PALB2*, which are also associated with an increased risk of ovarian cancer.

The *MLH1*, *MSH2* or *MSH6* pathogenic variants are associated with Lynch syndrome, which is associated with an increased risk of endometrial as well as ovarian cancer. Although there was no evidence identified related to different types of surgery within this specific group, the committee decided that total hysterectomy as well as bilateral salpingo-oophorectomy should

be recommended to prevent both of these types of cancers. In terms of the specific criteria related to pathogenic variant and age, the committee recommended it based on the UK Cancer Genetics Group and the economic analysis. The UK Cancer Genetics Group (UKCGG) base their age ranges for each pathogenic variant on the difference between the general population risk of cancer (which they took from Cancer Research UK) and the risk of cancer for the specific variant (ascertained from specific related publications – see relevant UKCGG information). For example, for *BRCA1* the risk increases to above population risk from age 31 onwards and then increases at a faster rate from that age onwards. The economic model presented to the committee by an expert witness (which was specifically designed to address variant and age) used the UKCGG data and started from age 30 to clarify at which age risk-reducing surgery would be most cost effective. This was done for each pathogenic variant most associated with ovarian cancer. The model was set up in this way to avoid risk-reducing surgeries taking place earlier than necessary given a particular risk level (see 'cost effectiveness and resource use' below and appendix L for the expert testimony).

PMS2 is a pathogenic variant that is also associated with Lynch syndrome, but it is not associated with ovarian cancer compared to *MLH1*, *MLH2* and *MSH2* but with endometrial cancer only. They decided to not include it in the table of types of risk-reducing surgery alongside the other Lynch pathogenic variants, because PMS2 increases the risk of endometrial cancer alone rather than endometrial as well as ovarian cancer. The committee decided that it should be mentioned because of its connection to Lynch syndrome which is included in the scope of the guideline and because it is on the gene panel for Lynch syndrome. Therefore, the committee agreed, base on expertise that total hysterectomy can be considered (weaker recommendation) in people with this pathogenic variant (no earlier than age 45). This is in line with UKCGG but was not something that was specifically modelled in the economic analysis because of it being linked to endometrial rather than ovarian cancer. When a person with a *PMS2* pathogenic variant also has a family history of ovarian cancer the committee decided that a total hysterectomy as well as a bilateral salpingo oophorectomy should be considered because both the risk of endometrial and ovarian cancer would be increased.

Whilst the committee agreed that the earliest ages they selected for risk-reducing surgery were those with the best balance of risks and benefits, they discussed that there could be exceptional circumstances where risk-reducing surgery may be relevant and appropriate at a younger age (for example when the risk is very high).

The committee discussed that delayed oophorectomy would avoid surgical menopause and could therefore be a preferred option. They noted that some of the evidence related to this showed promise, for example, moderate quality evidence showed that women who had salpingectomy with delayed salpingo-oophorectomy reported fewer climacteric symptoms 12 months after surgery as compared to women who had bilateral salpingo-oophorectomy. However, the evidence for this comparison mainly relates to quality of life and patient satisfaction outcomes, and there was no evidence identified for the critical outcomes such as disease-free survival and ovarian cancer detection. They therefore only recommended this in the context of a clinical trial. They did not recommend research into this because they were aware that a trial was currently in progress which was large enough and with a long enough follow-up to address this (the PROTECTOR trial).

They noted that for most pathogenic variants associated with ovarian cancer (apart from those associated with Lynch syndrome) the risk of endometrial cancer was not significantly increased above population level, so they recommended against total hysterectomy unless a personalised risk assessment shows a high risk of endometrial cancer (due to other reasons) or there is another gynaecological indication for hysterectomy.

Tests before risk-reducing surgery, referral to the gynaecology oncology multidisciplinary team, and what to consider during surgery

Based on experience and expertise, the committee, decided that transvaginal ultrasound and a serum CA125 tests should be performed before risk-reducing salpingo-oophorectomy surgery because they are tests that can identify asymptomatic tubal or ovarian cancer. If only a total hysterectomy is planned, then the test should be an endometrial biopsy which can detect asymptomatic cancer in the womb. Whilst this was not part of the evidence that was looked for, the committee based on expertise, agreed that it is crucial to do this because the type of management would be different if a person is shown to have cancer.

There was high quality evidence that bilateral salpingo-oophorectomy improves detection rates for asymptomatic cancer. Based on this evidence the committee recommended referral to the gynaecology oncology multidisciplinary team if asymptomatic cancer is identified so that cancer treatment can be planned.

In terms of surgical techniques, the committee noted that most of the studies used minimal access surgery. Whilst there was no direct comparison between minimal access and open surgery the committee agreed, based on experience, that this is generally the preferred and safer option. They also discussed that some of the evidence included peritoneal washing, but the study included this in both arms of the comparison. It was therefore unclear whether this would be more effective than not using it. Despite this uncertainty in the evidence, the committee were aware that cancerous cells can spread to the peritoneal cavity and recommended to take peritoneal washings to prevent missing cancerous cells which could be spreading. The committee noted, based on expertise, that early detection of cancerous cells and timely intervention are essential to improving outcomes.

The committee noted that it is general good practice to investigate any lesions that are noticed during surgery even if they are found outside the organs that are being removed, to increase the likelihood of finding any asymptomatic cancers.

Information about risk-reducing surgery

The committee agreed that, when discussing a potential risk-reducing surgery, there are some key issues that the woman will need to know about to be able to make an informed decision. They acknowledged that people affected by this condition reported that they were not always satisfied with the information that they were receiving (see evidence review A) and that it would therefore be important to list the minimum information that should be given related to risk-reducing surgery so that this is standard practice.

Not all people may be aware of what risk-reducing surgery is and how it would be carried out so in the shared decision-making process this information should form the starting point for the discussion. Based on the clinical evidence and reasons described above, advice should be given about the effectiveness of risk-reducing surgery as the most reliable way to reduce the likelihood of developing ovarian cancer. The committee noted, based on experience, that there is a misconception that risk-reducing surgery would eliminate the risk completely and they therefore recommended that it should be explained that there will still be a small risk that remains.

There is information to be provided about risk levels associated with different pathogenic variants and the timing around risk-reducing surgery that would be important for the woman to know about.

As described above there could be psychological distress and symptoms of the menopause that may have an impact on the person’s sex life (genitourinary symptoms) and any other ways that an early menopause could affect them.

There are some pathogenic variants that also increase the risk of other cancers, such as increased risk of breast cancer associated with BRCA1 and BRCA2 and to be able to make informed choices the person needs to be aware of these risks.

It was discussed that people may not know which local or national organisations could support them and may also not know that there are peer support groups. They discussed that there are a number of support organisation and that people ought to be made aware that they exist (for example The Eve Appeal, BRCA Umbrella and ovarian cancer action).

Other factors the committee took into account

The committee acknowledged the BRCA1 and BRCA2 not only increase the risk of ovarian cancer but also the risk of breast cancer. Risk-reducing surgery for breast cancer therefore also needs to be considered. The committee therefore cross referred to the NICE guideline on familiar breast cancer so that the relevant recommendations on risk reducing mastectomy are taken into account.

Cost effectiveness and resource use

There was evidence, which was presented by an expert witness, on the cost-effectiveness of risk-reducing surgery in individuals with pathogenic variants that increase ovarian cancer risk. The committee discussed the findings which indicated that risk reducing bilateral mastectomy at age 30 and risk reducing bilateral salpingo-oophorectomy at age 35 were the optimal strategies for *BRCA1*/*BRCA2*. For *PALB2*, combined risk reducing bilateral mastectomy at age 40 and risk reducing bilateral salpingo-oophorectomy at age 45 were deemed optimal, while risk reducing bilateral salpingo-oophorectomy at age 45 was optimal for *RAD51C*, *RAD51D* and *BRIP1*.

The committee found it encouraging that probabilistic sensitivity analysis demonstrated that, at the NICE cost-effectiveness threshold of £20,000 per QALY, the combined risk reducing bilateral mastectomy and risk reducing bilateral salpingo-oophorectomy strategy was the most cost-effective in a high percentage of simulations: 95.9% for *BRCA1*, 88.5% for *BRCA2* and 84.7% for *PALB2*. Risk reducing bilateral salpingo-oophorectomy at age 45 was the optimal and cost-effective strategy in 100% of simulations for *RAD51C*/*RAD51D*/*BRIP1*.

Furthermore, the committee found it reassuring that even when varying parameters at the extremes of their confidence intervals or ranges, the ICERs for risk-reducing surgeries remained below the lower NICE cost-effectiveness threshold of £20,000 per QALY gained.

The committee acknowledged the direct applicability of the evidence to NICE's decision-making process, noting only minor methodological limitations. They explained that the findings were as expected and aligned with the current practice.

The committee also considered other existing economic evidence, comprising three non-UK studies focusing on *BRCA* carriers. All these studies evaluated slightly different risk-reducing strategies and age thresholds for risk-reducing surgeries. Three studies concluded that risk reducing bilateral mastectomy and risk reducing bilateral salpingo-oophorectomy were optimal for individuals with *BRCA*, with varying risk-reducing surgery initiation ages ranging from 30 to 45 years.

The committee noted that this non-UK evidence was partially applicable to the NICE decision-making context. Also, even though these studies were well conducted and had only minor methodological limitations the committee discussed the difficulty of generalising from these studies due to potential differences in cost inputs. For example, cancer management and risk-reducing surgery costs in the NHS are likely to be different.

The committee queried whether the modelling presented by the expert witness could be utilised to examine thresholds for risk-reducing surgery, specifically determining the carrier

risk at which risk-reducing surgery would be cost-effective. However, conducting such analysis was beyond the scope of the research presented. Nevertheless, the committee was able to refer to two existing UK economic evaluations to inform their lifetime ovarian cancer risk thresholds for risk-reducing surgery.

The committee highlighted that before risk-reducing surgery, information provision and support are crucial and recommendations reflect good practice that should be already undertaken by services. The decision to undergo risk-reducing surgery is complex and psychological support is essential, which should already be available. However, they recognised the potential strain on specialist psychological services due to the lack of such services.

Risk-reducing surgery can induce surgical menopause in premenopausal people. Therefore, comprehensive menopause counselling is essential to ensure people understand the surgery's implications and their treatment options, including associated risks and benefits. The committee noted that these recommendations reflect current practice across services. Furthermore, they acknowledged the complexity of managing risk-reducing surgery decisions in people with bi-allelic pathogenic variants in mismatch repair genes, such as homozygous PMS2, and expect such decisions to be currently undertaken by specialist tertiary teams.

The committee explained that hysterectomy is standard practice for endometrial cancer. In people over 45 with a confirmed family history of ovarian cancer, it would be rare to leave the ovaries if a hysterectomy is being performed. Undertaking these procedures simultaneously could lead to cost savings due to reduced need for separate pre- and post-operative care, shorter overall hospital stays and earlier quality of life improvements. The recommendation not to perform hysterectomies in people with certain pathogenic variants unless, for example, there is a high endometrial cancer risk should align with most services' current practices. However, making this explicit could potentially reduce the number of unnecessary risk-reducing hysterectomies.

All other recommendations reinforce current practice, including preoperative testing before risk-reducing surgery, referring asymptomatic individuals to the gynaecology oncology multidisciplinary team if cancer is, for example, detected during preoperative investigation, and procedures during risk-reducing surgery. However, it was acknowledged that where such care is currently suboptimal, there could be some additional resource implications.

The committee also noted that widening the genetic testing criteria may lead to an increase in the number of people undergoing risk-reducing surgery, requiring expansion of services. However, they highlighted that any additional costs associated with this expansion will be outweighed by a decrease in cancer risk and its associated costs.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.1 to 1.8.5 and 1.8.9 to 1.8.20 (and information about risk-reducing surgery in Table 3) in the NICE guideline.

References – included studies

Effectiveness

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Appendices

Appendix A Review protocol

Review protocol for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Table 5: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022360523
1.	Review title	Effectiveness of risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)
2.	Review question	How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?
3.	Objective	To establish the effectiveness of risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)
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 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 Exclusion: women with bilateral salpingo-oophorectomy, ovarian cancer
7.	Intervention	Surgery: • bilateral salpingo-oophorectomy • bilateral salpingo-oophorectomy and hysterectomy • bilateral salpingectomy • bilateral salpingectomy and hysterectomy
8.	Comparator	• in comparison with each other • usual care (no intervention) • surveillance (for example, no surgery)
9.	Types of study to be included	• Randomised controlled trials (RCTs)

		• Systematic reviews/meta-analyses of RCTs In the absence of RCTs comparative non-randomised studies will be included
10.	Other exclusion criteria	**Inclusion criteria**: • Full text papers • 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	Effectiveness of risk-reducing surgery in women at increased risk of familiar ovarian cancer in primary, secondary or tertiary care

12.	Primary outcomes (critical outcomes)	• Health related quality of life (measured using a validated scale)
		• Patient satisfaction
		• Surgery related adverse events such as:
		  ○ severe adverse events as defined by studies (for example, within 30 days, or 90 days as measured using the Clavien-Dindo classification of surgical complications)
		  ○ surgery related mortality
		  ○ long-term effects such as early menopause
		• Ovarian cancer related mortality

13.	Secondary outcomes (important outcomes)	• Overall survival • Disease-free survival (defined as time from surgical procedure to cancer diagnosis) • Ovarian cancer detection rates
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated.

		Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records (or 300 records, whichever is smaller); 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer

16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: 0.8 and 1.25 for all relative dichotomous outcomes, for continuous outcomes any published validated MIDs, if none are available then +/- 0.5x control group SD.
17.	Analysis of sub-groups	Evidence will be stratified by: • Risk threshold (risk of ovarian cancer) • Type of surgery • Menopause status (pre-/post-menopause) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Groups identified in the equality considerations section of the scope

		• socioeconomic and geographical factors • age • ethnicity • disabilities • people for whom English is not their first language or who have other communication needs • trans people (particularly trans men) • non-binary people Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is 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	February 2023		
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	☐	☐
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
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=360523
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	Genetic testing, 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
36.	Details of final publication	www.nice.org.uk

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: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Database: Ovid MEDLINE ALL

Date of last search: 15/12/2022

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

#	Searches
35	Ataxia Telangiectasia Mutated Proteins/
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	Checkpoint Kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
42	exp Sertoli-Leydig Cell Tumor/
43	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
48	or/9-47
49	8 and 48
50	exp Salpingectomy/
51	exp Ovariectomy/
52	(oophorectom* or salping* or ovar??ctom* or ovar??tom* or BSO or RRSO* or RRBSO or RRSDO or RRESDO).tw,kf.
53	(((fallopian* or ovar* or tubal) adj4 (amputat* or resect* or excis* or surg* or remov* or extirpat*)) or tubectom*).tw,kf.
54	Hysterectomy, Vaginal/ or Hysterectomy/
55	(colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*).tw,kf.
56	((supervaginal or supravaginal or uterus* or uteri*) adj3 (amputat* or resect* or excis* or surg* or remov* or extirpat*)).tw,kf.
57	(gyn?ecolog* adj2 surg*).tw,kf.
58	exp Prophylactic Surgical Procedures/
59	(((risk* adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
60	risk reduction behavior/
61	(risk* adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
62	or/50-61
63	49 and 62
64	letter/
65	editorial/
66	news/
67	exp historical article/
68	Anecdotes as Topic/
69	comment/
70	case report/
71	(letter or comment*).ti.
72	or/64-71
73	randomized controlled trial/ or random*.ti,ab.
74	72 not 73
75	animals/ not humans/
76	exp Animals, Laboratory/
77	exp Animal Experimentation/
78	exp Models, Animal/
79	exp Rodentia/
80	(rat or rats or mouse or mice or rodent*).ti.
81	or/74-80

#	Searches
82	63 not 81
83	limit 82 to English language
84	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
85	drug therapy.fs.
86	(groups or placebo or randomi#ed or randomly or trial).ab.
87	Clinical Trials as Topic/
88	trial.ti.
89	or/84-88
90	Meta-Analysis/
91	Meta-Analysis as Topic/
92	(meta analy* or metanaly* or metaanaly*).ti,ab.
93	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
94	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
95	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
96	(search* adj4 literature).ab.
97	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
98	cochrane.jw.
99	or/90-98
100	83 and (89 or 99)
101	Observational Studies as Topic/
102	Observational Study/
103	Epidemiologic Studies/
104	exp Case-Control Studies/
105	exp Cohort Studies/
106	Cross-Sectional Studies/
107	Controlled Before-After Studies/
108	Historically Controlled Study/
109	Interrupted Time Series Analysis/
110	Comparative Study.pt.
111	case control$.tw.
112	case series.tw.
113	(cohort adj (study or studies)).tw.
114	cohort analy$.tw.
115	(follow up adj (study or studies)).tw.
116	(observational adj (study or studies)).tw.
117	longitudinal.tw.
118	prospective.tw.
119	retrospective.tw.
120	cross sectional.tw.
121	or/101-120
122	83 and 121

1 **Database: Ovid Embase**

2 **Date of last search: 15/12/2022**

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	exp breast cancer/

#	Searches
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
7	or/4-6
8	3 or 7
9	exp genetic predisposition/
10	pedigree/
11	exp hereditary tumor syndrome/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
21	((hereditary breast and ovarian cancer) or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
23	risk factor/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,kf.
26	tumor suppressor gene/
27	exp tumor suppressor protein/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	Fanconi anemia protein/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
33	("breast cancer gene 1" or "breast cancer gene 2").tw.
34	Rad51 protein/
35	ATM protein/
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	checkpoint kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	small cell carcinoma/
40	genetics/
41	39 and 40
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	androblastoma/ or Sertoli cell tumor/ or 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/

#	Searches
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/9-38,41-49
51	8 and 50
52	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	exp 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	prophylactic surgical procedure/
61	(((risk* adj2 reduc*) or prevent* or prophyla*) adj2 surg*).tw,kf.
62	risk reduction/
63	(risk* adj2 reduc* adj2 (behavio?r* or choice* or strateg* or decision*)).tw,kf.
64	or/52-63
65	51 and 64
66	letter.pt. or letter/
67	note.pt.
68	editorial.pt.
69	case report/ or case study/
70	(letter or comment*).ti.
71	or/66-70
72	randomized controlled trial/ or random*.ti,ab.
73	71 not 72
74	animal/ not human/
75	nonhuman/
76	exp Animal Experiment/
77	exp Experimental Animal/
78	animal model/
79	exp Rodent/
80	(rat or rats or mouse or mice or rodent*).ti.
81	or/73-80
82	65 not 81
83	limit 82 to English language
84	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
85	83 not 84
86	random*.ti,ab.
87	factorial*.ti,ab.
88	(crossover* or cross over*).ti,ab.
89	((doubl* or singl*) adj blind*).ti,ab.
90	(assign* or allocat* or volunteer* or placebo*).ti,ab.
91	crossover procedure/
92	single blind procedure/
93	randomized controlled trial/
94	double blind procedure/
95	or/86-94
96	systematic review/

#	Searches
97	meta-analysis/
98	(meta analy* or metanaly* or metaanaly*).ti,ab.
99	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
100	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
101	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
102	(search* adj4 literature).ab.
103	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
104	((pool* or combined) adj2 (data or trials or studies or results)).ab.
105	cochrane.jw.
106	or/96-105
107	85 and (95 or 106)
108	Clinical study/
109	Case control study/
110	Family study/
111	Longitudinal study/
112	Retrospective study/
113	comparative study/
114	Prospective study/
115	Randomized controlled trials/
116	114 not 115
117	Cohort analysis/
118	cohort analy$.tw.
119	(Cohort adj (study or studies)).tw.
120	(Case control$ adj (study or studies)).tw.
121	(follow up adj (study or studies)).tw.
122	(observational adj (study or studies)).tw.
123	(epidemiologic$ adj (study or studies)).tw.
124	(cross sectional adj (study or studies)).tw.
125	case series.tw.
126	prospective.tw.
127	retrospective.tw.
128	or/108-113,116-127
129	85 and 128

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

Date of last search: 15/12/2022

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* 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 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,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

#	Searches
#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 tumo?r* 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 tumo?r* 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 tumo?r* 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	((tumo?r* or cancer* or metastas?s or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	(Fanconi NEXT An?emia NEAR/3 protein*):ti,ab,kw
#32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#34	MeSH descriptor: [Rad51 Recombinase] this term only
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	("Ataxia telangiectasia" NEAR/1 mutated NEXT (protein* or kinase*)):ti,ab,kw
#37	(ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#38	MeSH descriptor: [Checkpoint Kinase 2] this term only
#39	((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)):ti,ab,kw
#40	(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] explode all trees 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 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#46	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H4?8 LIKE"):ti,ab,kw
#47	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#48	Epithelial NEXT cell NEXT 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 KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1):ti,ab,kw
#50	{OR #9-#49}
#51	#8 AND #50
#52	MeSH descriptor: [Salpingectomy] explode all trees
#53	MeSH descriptor: [Ovariectomy] explode all trees

#	Searches
#54	(oophorectom* or salping* or ovar??ctom* or ovar??tom* 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	(gyn?ecolog* 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 (behavio?r* or choice* or strateg* or decision*)):ti,ab,kw
#65	{OR #52-#64}
#66	#51 AND #65
#67	conference:pt or (clinicaltrials or trialsearch):so
#68	#66 NOT #67

1 Database: Epistemonikos

2 Date of last search: 15/12/2022

#	Searches
1	(advanced_title_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR advanced_abstract_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)))
2	(advanced_title_en:((oophorectom* OR salping* OR ovariectom* OR ovariotom* OR BSO OR RRSO* OR RRBSO OR RRSDO OR RRESDO OR colpohysterectom* OR panhysterectom* OR hysterocolpectom* OR hysterectom*)) OR advanced_abstract_en:((oophorectom* OR salping* OR ovariectom* OR ovariotom* OR BSO OR RRSO* OR RRBSO OR RRSDO OR RRESDO OR colpohysterectom* OR panhysterectom* OR hysterocolpectom* OR hysterectom*)))
3	1 AND 2
4	[Filters: protocol=no, classification=systematic-review, cochrane=missing]

3 Database: INAHTA International HTA Database

4 Date of last search: 15/12/2022

#	Searches
1	"Ovarian Neoplasms"[mhe]
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]
3	#1 OR #2
4	"Breast Neoplasms"[mhe]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]
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]
7	#4 OR #5 OR #6
8	#3 OR #7
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]
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]
11	((MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((MUTYH or MYH or FAP or AFAP or APC))[abs]

#	Searches
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]
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]
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]
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]
16	(((carrier* or gene*) AND mutat*))[Title] OR (((carrier* or gene*) AND mutat*))[abs]
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]
18	((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	((("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	(((((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	(("small cell"AND (cancer* or carcinoma*) AND gene*))[Title] OR (("small cell"AND (cancer* or carcinoma*) AND gene*))[abs]
22	((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	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	"Salpingectomy"[mhe]
25	"Ovariectomy"[mhe]
26	(((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]
27	"Hysterectomy"[mh]
28	"Hysterectomy, Vaginal"[mh]
29	((colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*))[Title] OR ((colpohysterectom* or panhysterectom* or hysterocolpectom* or hysterectom*))[abs]
30	(((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]
31	(((gynecolog* or gynaecolog*) AND surg*))[Title] OR (((gynecolog* or gynaecolog*) AND surg*))[abs]
32	(((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]
33	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
34	#8 AND #23
35	#33 AND #34
36	Limit 35 to English language

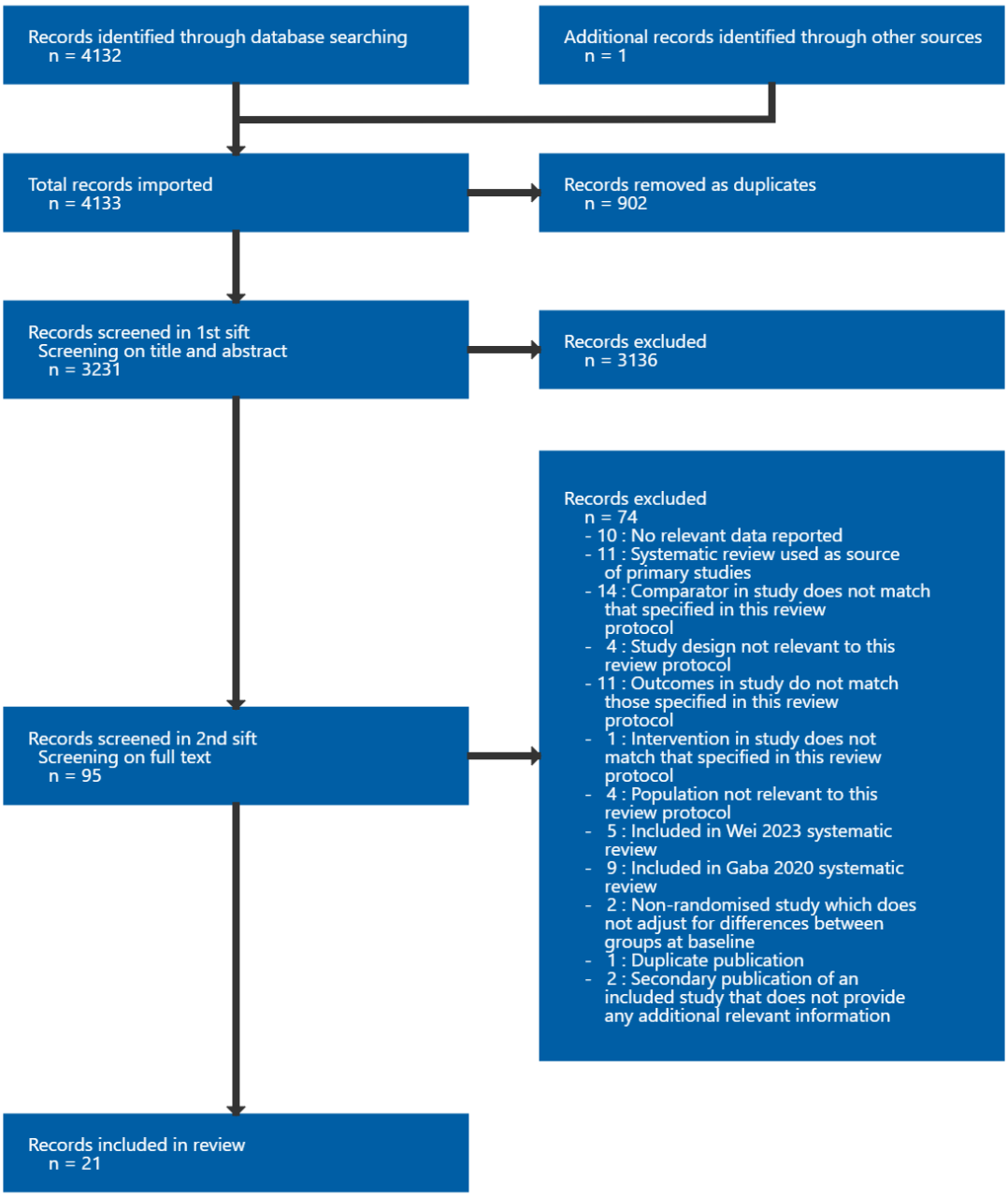
1

2

Appendix C Effectiveness evidence study selection

Study selection for: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Bogani, 2017

Bibliographic Reference	Bogani, G.; Tagliabue, E.; Signorelli, M.; Chiappa, V.; Carcangiu, M.L.; Paolini, B.; Casarin, J.; Scaffa, C.; Gennaro, M.; Martinelli, F.; Borghi, C.; Ditto, A.; Lorusso, D.; Raspagliesi, F.; Assessing the Risk of Occult Cancer and 30-day Morbidity in Women Undergoing Risk-reducing Surgery: A Prospective Experience; Journal of Minimally Invasive Gynecology; 2017; vol. 24 (no. 5); 837-842

Study details

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Between June 2014 and January 2017
Inclusion criteria	• age >=18 years, • *BRCA1* and *BRCA2* mutation carriers or a strong familial history of beast and/or ovarian cancer (BRCAX), • the execution of risk-reducing surgery (BSO with or without hysterectomy), • 30 days of follow-up
Exclusion criteria	• suspicious neoplastic lesions of the genital tract diagnosed before surgery • consent withdrawal
Patient characteristics	N=85 women who were *BRCA2* mutation carriers or had a strong familial history of breast and/or ovarian cancer and underwent risk-reducing surgery n=30 had hysterectomy plus bilateral salpingo-oophorectomy

	n=55 had bilateral salpingo-oophorectomy **Age (mean (SD), years):** 47 (8.2) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Previous breast cancer (n):** 60 (70.5%) ***BRCA1/2* mutation (n):** *BRCA1* 32 (37.6%), *BRCA2* 25 (29.4%), BRCAX (with a strong familial history of beast and/or ovarian cancer) 28 (33%)
Intervention(s)/control	**Intervention** • hysterectomy plus bilateral salpingo-oophorectomy **Control** • bilateral salpingo-oophorectomy
Duration of follow-up	1 month
Sample size	N=85
Sources of funding	Not reported

1

Study arms

Hysterectomy plus bilateral salpingo-oophorectomy (N = 30)

Bilateral salpingo-oophorectomy (N = 55)

Outcomes

Surgery related adverse events

Outcome	Hysterectomy plus bilateral salpingo-oophorectomy, N = 30	Bilateral salpingo-oophorectomy, N = 55
Severe (grade 3 or more) surgery-related complications Measured at 1 month follow-up after surgery No of events	n = 0; % = 0	n = 0; % = 0

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 there were any significant baseline differences between the groups; not clear if the analysis was adjusted for any of these differences)*
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	Moderate *(not reported if there were any significant baseline differences between the groups; not clear if the analysis was adjusted for any of these differences)*
Overall bias	Directness	Directly applicable

1

2 **Crosbie, 2021**

Bibliographic Reference	Crosbie, E.J.; Flaum, N.; Harkness, E.F.; Clayton, R.D.; Holland, C.; Martin-Hirsch, P.; Wood, N.; Keating, P.; Woodward, E.R.; Lalloo, F.; Donnai, P.; Edmondson, R.J.; Evans, D.G.; Specialist oncological surgery for removal of the ovaries and fallopian tubes in BRCA1 and BRCA2 pathogenic variant carriers may reduce primary peritoneal cancer risk to very low levels; International Journal of Cancer; 2021; vol. 148 (no. 5); 1155-1163

3

4 **Study details**

Country/ies where study was carried out	UK

Study type	Retrospective cohort study
Study dates	1980 to 2019
Inclusion criteria	• women were eligible if they had undergone risk-reducing bilateral salpingo-oophorectomy (RRBSO) without any evidence on CA125 and ultrasound of the prior presence of ovarian cancer
Exclusion criteria	Not reported
Patient characteristics	N=2193 women proven *BRCA1/2* carriers n=891 had bilateral salpingo-oophorectomy n=1302 had no bilateral salpingo-oophorectomy **Age (median, years):** surgery group 45.1, no surgery group 43.45 **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors** **Education (n):** not reported **Disabilities:** not reported **People with communication needs:** not reported **Previous/prospective breast cancer (n):** surgery group: *BRCA1* group 236 (50.4%), *BRCA2* group 230 (54.4%); no surgery group: *BRCA1* group 60.1%, *BRCA2* group 60.4% ***BRCA1/2* mutation (n):** *BRCA1* = 468, *BRCA2* = 423
Intervention(s)/control	**Intervention**

	• bilateral salpingo-oophorectomy **Control** • no bilateral salpingo-oophorectomy From 1980 to 2008, the predominant RRBSO procedure was a total abdominal hysterectomy and RRBSO. Since 2009, the predominant procedure has been laparoscopic RRBSO without hysterectomy.
Duration of follow-up	There were 7815.1 women-years (mean = 8.7; median = 7.1) of follow-up to censoring from RRBSO date but only 7261.1 risk eligible years (mean = 8.15 years). Cases were followed from date of RRBSO to date of death, PPC or date of last follow-up, whichever was earlier. Controls were followed from date of personal mutation report to date of death, ovarian/peritoneal cancer or date of last follow-up, whichever was earlier. Cases were censored at date of surgery if ovarian cancer was identified as an occult lesion.
Sample size	N=2193
Sources of funding	Some authors were supported by a National Institute for Health Research grant to the Biomedical Research Centre, Manchester (IS-BRC-1215-20007) or by CRUK via the funding to Cancer Research UK Manchester Cancer Research Centre (C147/ A18083 and C147/A25254)

1

1 **Study arms**

2 **Bilateral salpingo-oophorectomy (N = 891)**

3 **No bilateral salpingo-oophorectomy (N = 1853)**

4 **Outcomes**

5 **Mortality**

Outcome	Bilateral salpingo-oophorectomy, N = 891	No bilateral salpingo-oophorectomy, N = 1302
Ovarian/peritoneal cancer related mortality Mean years follow-up in surgery group 8.15 years, in no surgery group 2.3 years No of events	n = 14; % = 1.6	n = 15; % = 2

6 **Overall mortality (survival)**

Outcome	Bilateral salpingo-oophorectomy, N = 891	No bilateral salpingo-oophorectomy, N = 1302
Overall mortality Mean years follow-up: 8.15 and 2.3, respectively No of events	n = 64; % = 7.2	n = 136; % = 17.8

Ovarian/peritoneal cancer detection rate (incidence)

Outcome	Bilateral salpingo-oophorectomy, N = 891	No bilateral salpingo-oophorectomy, N = 763
Ovarian/peritoneal cancer incidence Mean years follow-up in surgery group 8.15 years, in no surgery group 2.3 years No of events	n = 3; % = 0.34	n = 32; % = 4.2

N=763 in no surgery group for mortality outcomes (some women went on to have surgery during follow-up)

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(not clear if there were any baseline differences between the two groups)*
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	Moderate *(not clear if there were any baseline differences between the two groups)*
Overall bias	Directness	Directly applicable

1

2 **Domchek, 2006**

Bibliographic Reference	Domchek, S.M.; Friebel, T.M.; Neuhausen, S.L.; Wagner, T.; Evans, G.; Isaacs, C.; Garber, J.E.; Daly, M.B.; Eeles, R.; Matloff, E.; Tomlinson, G.E.; Van't Veer, L.; Lynch, H.T.; Olopade, O.I.; Weber, B.L.; Rebbeck, T.R.; Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: A prospective cohort study; Lancet Oncology; 2006; vol. 7 (no. 3); 223-229

3

4 **Study details**

Country/ies where study was carried out	International
Study type	Prospective cohort study controls were matched within 5 years of age to the corresponding surgery participant's age at the surgery
Study dates	Not reported
Inclusion criteria	• women with germline, disease-associated mutations in *BRCA1* or *BRCA2* • surgery group participants and controls: cancer free (had never had a cancer diagnosis) at enrolment and did not have a cancer diagnosis within 6 months after enrolment • surgery group participants: cancer-free before surgery; matched controls were cancer-free at the time of the surgical participant's procedure; no previous prophylactic surgery, including mastectomy and oophorectomy
Exclusion criteria	• women with *BRCA1* or *BRCA2* variants of unknown functional importance

	• women who ever underwent bilateral prophylactic mastectomy—either before enrolment or during follow-up
Patient characteristics	N=426 women with germline, disease-associated mutations in *BRCA1/2* n=155 had bilateral salpingo-oophorectomy n=271 had no bilateral salpingo-oophorectomy **Age (mean (SD), years):** surgery group 44.8 (8.5), no surgery group 42.6 (10) **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* mutation (n):** surgery group 155, no surgery group 271 **Use of hormone-replacement therapy (n) (ever use):** surgery group 94 (61%), no surgery group 38 (14%)
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy **Control** • surveillance or no bilateral salpingo-oophorectomy Both the BPSO group and control group had various cancer-surveillance programmes that were not controlled for in this study.

Duration of follow-up	In the surgery group 3.1 years (SD 2.4), in the no surgery group 2.1 (SD 2); from the time of centre ascertainment (the point at which a participant was first identified) to censoring or death due to: any cause, breast cancer, or primary peritoneal cancer or primary ovarian cancer
Sample size	N=426
Sources of funding	Supported by grants from the US Public Health Service (R01-CA83855 to TRR; CA74415 to SLN); the University of Pennsylvania Cancer Centre (to TRR and BLW); the US Breast Cancer Research Foundation (to BLW); QVC Network and the Fashion Footwear Association of New York (to BLW and SMD); the Dana-Farber Women's Cancers programme (to JEG); the US Department of Defense (DAMD17-96-I-6088 to AKG; DAMD-17-94-J-4340 and DAMD-17-97-I-7112 to HTL; DAMD-17-03-1-0619 to SMD); the Utah Cancer registry (funded by Public Health Service Grant NO1-CN-6700); the Utah State Department of Health; and the Nebraska State Cancer and Smoking-Related Diseases research programme (LB595 to HTL).

Study arms

Bilateral salpingo-oophorectomy (N = 155)

Surveillance or no bilateral salpingo-oophorectomy (N = 271)

Outcomes

Mortality

Outcome	**Bilateral salpingo-oophorectomy, N = 155**	**Surveillance or no bilateral salpingo-oophorectomy, N = 271**
Ovarian/peritoneal cancer related mortality Mean years follow-up (SD) in surgery group 4 years (3.1), in no surgery group 2.7 (2.5) years No of events	n = 1; % = 0.6	n = 3; % = 1.1

Overall mortality (survival)

Outcome	Bilateral salpingo-oophorectomy, N = 155	Surveillance or no bilateral salpingo-oophorectomy, N = 271
Overall mortality Mean years follow-up (SD) in surgery group 3.1 years (2.4), in no surgery group 2.1 (2) No of events	n = 4; % = 3	n = 12; % = 4

Ovarian/peritoneal cancer related mortality (Cox proportional-hazards model)

Outcome	Bilateral salpingo-oophorectomy vs Surveillance or no bilateral salpingo-oophorectomy, N2 = 271, N1 = 155
Ovarian/peritoneal cancer related mortality Mean years follow-up (SD) in surgery group 4 years (3.1), in no surgery group 2.7 (2.5) years. HR adjusted for birth year, gene (*BRCA1* vs *BRCA2*), and centre Hazard ratio/95% CI	0.05 (0.01 to 0.46)

HR: hazard ratio

Overall mortality (survival, Cox proportional-hazards model)

Outcome	Bilateral salpingo-oophorectomy vs Surveillance or no bilateral salpingo-oophorectomy, N2 = 271, N1 = 155
Overall mortality Mean years follow-up (SD) in surgery group 4 years (3.1), in no surgery group 2.7 (2.5) years. HR adjusted for birth year and gene (*BRCA1* vs *BRCA2*), and stratified by centre Hazard ratio/95% CI	0.24 (0.08 to 0.71)

HR: hazard ratio

Ovarian/peritoneal cancer detection rate (incidence)

Outcome	Bilateral salpingo-oophorectomy, N = 155	Surveillance or no bilateral salpingo-oophorectomy, N = 271
Ovarian/peritoneal cancer incidence Mean years follow-up (SD) in surgery group 3.1 years (2.4), in no surgery group 2.1 (2) years No of events	n = 2; % = 1	n = 16; % = 6

Data from the primary analysis were included (a matched design that selected controls who had not undergone surgery at any time during follow-up, and who were matched within 5 years of age to the corresponding surgery participant's age at surgery)

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

1 **Domchek, 2010**

Bibliographic Reference	Domchek, S.M.; Friebel, T.M.; Singer, C.F.; Gareth Evans, D.; Lynch, H.T.; Isaacs, C.; Garber, J.E.; Neuhausen, S.L.; Matloff, E.; Eeles, R.; Pichert, G.; Van T'veer, L.; Tung, N.; Weitzel, J.N.; Couch, F.J.; Rubinstein, W.S.; Ganz, P.A.; Daly, M.B.; Olopade, O.I.; Tomlinson, G.; Schildkraut, J.; Blum, J.L.; Rebbeck, T.R.; Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality; JAMA; 2010; vol. 304 (no. 9); 967-975

2

3 **Study details**

Country/ies where study was carried out	International
Study type	Prospective cohort study non-matching design
Study dates	Participants were ascertained between 1974 and 2008 (Median: 1999)
Inclusion criteria	• women with inherited, disease-associated *BRCA1/2* mutations were identified from 22 centres in the PROSE consortium • no ovarian cancer diagnosis and no RRSO at the time of ascertainment • a minimum of 6 months of follow-up
Exclusion criteria	• if they had a cancer diagnosis within the first six months of follow-up to avoid including cancers that would have been minimally influenced by RRSO • women were excluded if they were diagnosed with an occult ovarian at RRSO
Patient characteristics	N=2482 women tested positive for *BRCA1/2* mutations n=993 had salpingo-oophorectomy (n=257 had risk-reducing masctecomy) n=1232 had surveillance or no salpingo-oophorectomy

	Age (mean (range), years): surgery group: in those with no breast cancer prior 43.2 (20.5-79); in those with breast cancer prior 47.7 (29.7-75.2); no surgery group: mean start age in those with no breast cancer prior 36.7 (18.1-90.4), in those with breast cancer prior 45.5 (21.9-86.2) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported
Intervention(s)/control	**Intervention** • salpingo-oophorectomy **Control** • increased surveillance or no salpingo-oophorectomy women were offered increased surveillance at all centres according to established guidelines
Duration of follow-up	Median date of follow up: 2005. The median follow up for women was 3.65 years (range: 0.52-27.4 years) among those who underwent surgery, and 4.29 years (range: 0.5-27.9 years) in controls who did not undergo surgery
Sample size	N=2482
Sources of funding	This study was supported by grants from the Public Health Service (R01-CA83855 and R01-CA102776 to TRR), the University of Pennsylvania Cancer Center (to TRR), the Cancer Genetics Network (HHSN21620074400C to SMD and CI), the Marjorie Cohen Research Fund (to SMD) the Dana-Farber/Harvard Cancer Center SPORE in BC P50 CA-089393 (to JEG), the Department of Defense (DAMD-17-96-I-6088 to AKG; DAMD-17-94-J-4340 and DAMD-17-97-I-7112 to HTL; DAMD-17-03-1-0619 to SMD), P30-CA51008-15 (to Georgetown University), The Utah Cancer registry (funded by Public Health Service Grant NO1-CN-6700) and the Utah State Department of Health, the Nebraska State Cancer and Smoking-Related Diseases Research Program (LB595 to HTL), P30- CA-16042 (to PAG), Cancer Research UK Grant Number C5047/A7357 (to RE), and NCI P30 CA51008-12 (to CI). OIO is Doris Duke Distinguished Clinical

	Scientist. RE acknowledges The Support of the NIHR to The Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust

Study arms

Salpingo-oophorectomy (N = 966)

Surveillance or no salpingo-oophorectomy (N = 1377)

Outcomes

Ovarian cancer related mortality

Outcome	Salpingo-oophorectomy, N = 966	Surveillance or no salpingo-oophorectomy, N = 1377
Ovarian cancer related mortality Median follow up 3.65 years (range: 0.52-27.4 years) in surgery group and 4.29 years (range: 0.5-27.9 years) in control group No of events	n = 4; % = 0.4	n = 34; % = 2.5

Ovarian cancer related mortality (Cox proportional hazards model)

Outcome	Salpingo-oophorectomy vs Surveillance or no salpingo-oophorectomy, N2 = 1377, N1 = 966
Ovarian cancer related mortality Median follow up 3.65 years (range: 0.52-27.4 years) in surgery group and 4.29 years (range: 0.5-27.9 years) in control group. HR adjusted for year of birth, oral contraceptive use Hazard ratio/95% CI	0.21 (0.06 to 0.8)

HR: hazard ratio

Overall mortality (survival)

Outcome	Salpingo-oophorectomy, N = 993	Surveillance or no salpingo-oophorectomy, N = 1489
Overall mortality Median follow up 3.65 years (range: 0.52-27.4 years) in surgery group and 4.29 years (range: 0.5-27.9 years) in control group No of events	n = 31; % = 3	n = 146; % = 9.8

Overall mortality (survival, Cox proportional hazards model)

Outcome	Salpingo-oophorectomy vs Surveillance or no salpingo-oophorectomy, N2 = 1489, N1 = 993
Overall mortality Median follow up 3.65 years (range: 0.52-27.4 years) in surgery group and 4.29 years (range: 0.5-27.9 years) in control group. HR adjusted for year of birth Hazard ratio/95% CI	0.4 (0.26 to 0.61)

HR: hazard ratio

Ovarian cancer detection rate (incidence)

Outcome	Salpingo-oophorectomy, N = 465	Surveillance or no salpingo-oophorectomy, N = 1092
Ovarian cancer incidence in women with no prior breast cancer Median follow up 3.65 years (range: 0.52-27.4 years) in surgery group and 4.29 years (range: 0.5-27.9 years) in control group No of events	n = 6; % = 1.3	n = 63; % = 5.8

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

Evans, 2009

Bibliographic Reference	Evans, DG; Clayton, R; Donnai, P; Shenton, A; Lalloo, F; Risk-reducing surgery for ovarian cancer: outcomes in 300 surgeries suggest a low peritoneal primary risk; European journal of human genetics; 2009; vol. 17 (no. 11); 1381-1385

Study details

Country/ies where study was carried out	UK

Study type	Retrospective cohort study
Study dates	Not clear
Inclusion criteria	• Women attending the cancer genetic clinic at St Mary's Hospital had their risk of ovarian cancer evaluated from empiric epidemiological data or from estimates of the likelihood of a *BRCA1/2*-associated risk
Exclusion criteria	Not reported
Patient characteristics	N=803 women at high-risk of ovarian cancer n=300 had bilateral salpingo-oophorectomy (n=265 had full hysterectomies, n=35 laparoscopic salpingo-oophorectomy surgical procedures) n=503 had annual screening **Age (mean (SD), years):** not reported **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* mutation (n):** surgery group 160, no surgery group 160
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy **Control**

	• annual screening Women were on annual screening with ovarian ultrasound and serum CA125 All surgeries before 2003 were full abdominal hysterectomies, including BSO. After 2003 many women have opted for laparoscopic BSO.
Duration of follow-up	Follow-up was considered from the date of risk-reducing surgery to last known follow-up, death or 01/03/2008 for the intervention group; and from first scan to time of most recent scan, cancer detection or death in the control group. There were 2400.37 person-years of follow-up (range 0 –27 years; mean 8.17 years median 7.27) in the intervention group and 3444.25 person-years follow-up (range 1 – 17 years; mean 6.8 years; median 7.18, 94 women >10 years) in the control group.
Sample size	N=803
Sources of funding	Not reported

Study arms

Salpingo-oophorectomy (N = 300)

Annual screening (N = 503)

Outcomes

Mortality

Outcome	**Salpingo-oophorectomy, N = 300**	**Annual screening, N = 503**
Ovarian cancer related mortality Mean years follow-up (range) in surgery group 8.17 years (0-27), in no screening group 6.8 (1-17) years No of events	n = 1; % = 0.3	n = 6; % = 1.2

Outcome	Salpingo-oophorectomy, N = 300	Annual screening, N = 503
Overall mortality (survival) Mean years follow-up (range) in surgery group 8.17 years (0-27), in no screening group 6.8 (1-17) years No of events	n = 0; % = 0	n = 4; % = 0.8

1 **Ovarian cancer incidence**

Outcome	Salpingo-oophorectomy, N = 300	Annual screening, N = 503
Ovarian cancer incidence Mean years follow-up (range) in surgery group 8.17 years (0-27), in no screening group 6.8 (1-17) years No of events	n = 0; % = 0	n = 15; % = 3

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

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(the surgery group contained a substantial group of women with lower overall predicted risk. This accounts for the 0.46% annual risk compared with the 0.66% risk predicted in the surgery group; no adjustment 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

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	Moderate *(the surgery group contained a substantial group of women with lower overall predicted risk; no adjustment for potential confounders)*
Overall bias	Directness	Directly applicable

1

2 **Finch, 2006**

Bibliographic Reference	Finch, A; Beiner, M; Lubinski, J; Lynch, HT; Moller, P; Rosen, B; Murphy, J; Ghadirian, P; Friedman, E; Foulkes, WD; et, al.; Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation; JAMA; 2006; vol. 296 (no. 2); 185-192

3

4 **Study details**

Country/ies where study was carried out	International

Study type	Prospective cohort study
Study dates	Between 1992 and 2003
Inclusion criteria	• women at 1 of 32 centres in Canada, the United States, Europe, and Israel who carry a deleterious *BRCA1* or *BRCA2* mutation
Exclusion criteria	• women diagnosed with ovarian, fallopian tube, or peritoneal cancer prior to the baseline questionnaire
Patient characteristics	N=1828 women with *BRCA1/2* n=555 had bilateral salpingo-oophorectomy prior to study entry and n=490 had the surgery after entering the study n=783 had no bilateral salpingo-oophorectomy (n=490 (38.5%) underwent an oophorectomy during the follow-up period) **Age (mean (range), years):** surgery group 51.1 (30-74) and 46.3 (30-74), no surgery group 45.1 (30-74) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Previous breast cancer (n):** surgery group 331 (59.6%) and 366 (54.4%), no surgery group 421 (53.8%) ***BRCA1/2* mutation:** with *BRCA1* mutation 75.5%, with *BRCA2* mutation 24.1%, 0.4% with both mutations
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy

	Control • no bilateral salpingo-oophorectomy
Duration of follow-up	Mean follow-up 3.5 years Participants were followed from the date of completion of the baseline questionnaire or age 30 (whichever was later). They were followed from study entry to: (1) the date of completion of the follow-up questionnaire; (2) the development of ovarian, peritoneal, or fallopian tube cancer; (3) age 75 years; or (4) death
Sample size	N=1828
Sources of funding	Supported by a grant from the Canadian Breast Cancer Research Alliance and from National Institutes of Health grant RO1 CA63678

Study arms

Bilateral salpingo-oophorectomy (N = 1045)

No bilateral salpingo-oophorectomy (N = 783)

Outcomes

Ovarian, fallopian tube, peritoneal cancer detection rate (incidence)

Outcome	**Bilateral salpingo-oophorectomy, N = 1045**	**No bilateral salpingo-oophorectomy, N = 783**
Ovarian, fallopian tube, peritoneal cancer incidence Mean follow-up 3.5 years No of events	n = 7; % = 0.7	n = 32; % = 4.1

Disease-free survival

Outcome	Bilateral salpingo-oophorectomy vs No bilateral salpingo-oophorectomy, N2 = 546, N1 = 825
Disease-free survival Mean follow-up 3.5 years. HR adjusted for age, gene, country of origin, past history of breast cancer, oral contraceptive use, breast-feeding, parity Hazard ratio/95% CI	0.2 (0.07 to 0.58)

HR: hazard ratio

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

1 **Finkelman, 2012**

Bibliographic Reference	Finkelman, B.S.; Rubinstein, W.S.; Friedman, S.; Friebel, T.M.; Dubitsky, S.; Schonberger, N.S.; Shoretz, R.; Singer, C.F.; Blum, J.L.; Tung, N.; et, al.; Breast and ovarian cancer risk and risk reduction in Jewish BRCA1/2 mutation carriers; Journal of Clinical Oncology; 2012; vol. 30 (no. 12); 1321-1328

2

3 **Study details**

Country/ies where study was carried out	International
Study type	Prospective cohort study
Study dates	Between 1973 and 2010
Inclusion criteria	• women with disease-associated *BRCA1/2* mutations
Exclusion criteria	• women who did not have a confirmed disease-associated *BRCA1/2* mutation or if they had mutations in both *BRCA/2*.
Patient characteristics	N=3787 women with *BRCA1/2* mutations n=1701 had bilateral salpingo-oophorectomy n=2086 had no bilateral salpingo-oophorectomy **Age (mean (SD), years):** 43.5 (12.7) **Gender (n):** women 100% **Ethnicity (n):** Jewish n=488 **Socioeconomic and geographical factors:** more than high school education: 81%

	Disabilities: not reported **People with communication needs:** not reported
Intervention(s)/control	**Intervention** • risk-reducing salpingo-oophorectomy **Control** • no risk-reducing salpingo-oophorectomy
Duration of follow-up	Mean follow-up 5.4 years
Sample size	N=3787
Sources of funding	Supported by National Institutes of Health (NIH) Grants No. R01-CA083855 and R01-CA102776 (T.R.R.) and by Medical Scientist Training Program Grant No. T32-GM07170 from the NIH, as well as institutional funds from the University of Pennsylvania School of Medicine (B.S.F.). C.I. is supported by the Cancer Genetics Network and by National Cancer Institute Grant No. P30-CA051008-17. R.E. also receives support from the National Institute for Health Research to The Biomedical Research Centre at The Institute of Cancer Research and Royal Marsden National Health Service (NHS) Foundation Trust. Part of the Carrier Clinic at The Institute of Cancer Research and Royal Marsden NHS Foundation Trust receives support from Cancer Research United Kingdom Grant No. C5047/A8385

1

Study arms

Bilateral salpingo-oophorectomy (N = 1701)

No bilateral salpingo-oophorectomy (N = 2086)

Outcomes

Ovarian cancer incidence

Outcome	Bilateral salpingo-oophorectomy, N = 1701	No bilateral salpingo-oophorectomy, N = 2086
Ovarian cancer incidence Mean follow-up 5.4 years No of events	n = 12; % = 0.7	n = 139; % = 6.7

Disease free survival

Outcome	Bilateral salpingo-oophorectomy vs No bilateral salpingo-oophorectomy, N2 = 2086, N1 = 1701
Disease free survival Mean follow-up 5.4 years. HR adjusted for age at ascertainment, parity and oral contraceptive use Hazard ratio/95% CI	0.08 (0.04 to 0.16)

HR: hazard ratio

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

Fry, 2001

Bibliographic Reference	Fry, A; Busby-Earle, C; Rush, R; Cull, A; Prophylactic oophorectomy versus screening: psychosocial outcomes in women at increased risk of ovarian cancer.; Psycho-oncology; 2001; vol. 10 (no. 3); 231-41

Study details

Country/ies where study was carried out	UK
Study type	Case-control
Study dates	Not reported
Inclusion criteria	• women who had undergone prophylactic oophorectomy between 1 and 5 years previously

	• women at increased risk of ovarian cancer (by virtue of their family history) who had not undergone prophylactic surgery and continued to attend a Familial Ovarian Cancer Clinic (FOCC) for annual screening: (i) significantly increased risk of ovarian cancer (lifetime risk at least twice that of the general population); (ii) current age within the range 35–66 years, which was determined from the mean age of the surgical sample 2 standard deviations (mean(S.)=50.1(7.7))
Exclusion criteria	• women who had developed cancer of the breast or intra-abdominal cancer since her operation • women who had not clearly elected to have surgery, but had undergone oophorectomy during the course of an investigative procedure • women who were under investigation for or currently diagnosed with breast cancer or ovarian cancer
Patient characteristics	N=57 women at high-risk of ovarian cancer n=29 had salpingo-oophorectomy n=28 were on the ovarian screening programme **Age (mean (SD), years):** not reported **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Past history of breast cancer (n):** surgery group 9, no surgery group 2
Intervention(s)/control	• **Intervention**

	prophylactic oophorectomy • **Control** ovarian screening programme 62.1% in the surgery group had undergone hysterectomy at the same time as oophorectomy or at some time previously.
Duration of follow-up	None
Sample size	N=55
Sources of funding	Not reported

Study arms

Prophylactic oophorectomy (N = 29)

Regular screening (N = 28)

Outcomes

Health related quality of life

Outcome	**Prophylactic oophorectomy, N = 29**	**Regular screening, N = 28**
QOL (SF-36 short form) - mental health Mean (SD)	69.3 (17.1)	77.1 (11.3)
QOL (SF-36 short form) - role-emotional Mean (SD)	69.1 (41.3)	90.1 (22.3)
QOL (SF-36 short form) - social functioning Mean (SD)	79.2 (22)	96 (8.3)

Outcome	Prophylactic oophorectomy, N = 29	Regular screening, N = 28
QOL (SF-36 short form) - bodily pain Mean (SD)	66.2 (28.9)	84.5 (17.1)

QOL (SF-36 short form) - mental health - Polarity - Higher values are better
QOL (SF-36 short form) - role-emotional - Polarity - Higher values are better
QOL (SF-36 short form) - social functioning - Polarity - Higher values are better
QOL (SF-36 short form) - bodily pain - Polarity - Higher values are better
QOL: quality of life

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

Section	Question	Answer
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Not reported
(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?	Can't tell
(B) What are the results?	7. What are the results of this study?	Women who had undergone prophylactic surgery reported greater interference with work and social activities due to physical or emotional problems (as measured with the SF-36) as compared to those who were on the ovarian screening programme
(B) What are the results?	8. How precise are the results?	Based on the standard deviation, it can be assumed that some results are more precise than the others
(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 OC risk either due to pathogenic variants in an OC gene (*BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1*) or strong family history (FH) of ovarian cancer (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	• non-UK residents or women with a personal history of OC
Patient characteristics	N=683 at increased risk of ovarian cancer n=346 had risk-reducing surgery n=337 had no surgery **Age (mean (SD), years):** surgery group 51.5 (9.56), no surgery group 38.25 (10.23) **Gender (n):** women 100% **Ethnicity (n):** Caucasian: surgery group 300, no surgery group 301; non-Caucasian: surgery group 41, no surgery group 33 **Socioeconomic and geographical factors:** Education: PhD, Masters, Bachelor's degree: surgery group 141, no surgery group 199; NVQ4, A-level/NVQ3, NVQ1/NVQ2, GCSE/O-level/CSE, no formal qualification: surgery group 195, no surgery group 130 **Disabilities:** not reported

	People with communication needs: not reported **Personal history of breast cancer (n):** surgery group 160, no surgery group 77 ***BRCA1/2* mutation (n):** surgery group 7, no surgery group 5
Intervention(s)/control	**Intervention** • Pre-menopausal salpingo-oophorectomy **Control** • Post-menopausal salpingo-oophorectomy
Duration of follow-up	None reported
Sample size	N=683
Sources of funding	This work underwent peer-review and was supported by Rosetrees Trust (grant number M779). The UK PROTECTOR study into early salpingectomy in high-risk women is supported by The Barts Charity (grant MRC0167).

1

Study arms

Pre-menopausal salpingo-oophorectomy (N = 161)

Post-menopausal salpingo-oophorectomy (N = 84)

Outcomes

Patient satisfaction according to menopausal status following salpingo-oophorectomy

Outcome	Pre-menopausal salpingo-oophorectomy, N = 161	Post-menopausal salpingo-oophorectomy, N = 84
It was the right decision (agree and strongly agree) No of events	n = 143; % = 88.8	n = 80; % = 95.2
I regret the choice that was made (agree and strongly agree) n=160 and n=81 respectively No of events	n = 15; % = 9.4	n = 1; % = 1.2
I would make the same decision if I had to do it over again (agree and strongly agree) No of events	n = 141; % = 87.6	n = 79; % = 94
The decision did me a lot of harm (agree and strongly agree) n=160 and n=80 respectively No of events	n = 18; % = 11.3	n = 4; % = 5
The decision was a wise one (agree and strongly agree) n=158 and n=83 respectively No of events	n = 147; % = 93	n = 77; % = 92.8

Measured using Likert scale: strongly disagree, disagree, neither agree nor disagree, agree, strongly agree

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	Low
Overall bias and directness	Directness	Directly applicable

Gaba, 2020

Bibliographic Reference	Gaba, F.; Manchanda, R.; Systematic review of acceptability, cardiovascular, neurological, bone health and HRT outcomes following risk reducing surgery in BRCA carriers; Best Practice and Research: Clinical Obstetrics and Gynaecology; 2020; vol. 65; 46-65

Study details

Country/ies where study was carried out	UK
Study type	Systematic review Qualitative synthesis
Study dates	From inception to January 2019
Inclusion criteria	Studies: • human studies • English-language • population: *BRCA1/2*-carriers undergoing RRSO or RRESDO
Exclusion criteria	Studies: • that included participants with a personal history of OC, mismatch-repair mutation-carriers (MLH1/MSH2/MSH6) and individuals at population level OC-risk
Patient characteristics	Total N not reported, n=67 studies included (n=10 relate to bone and cardiovascular health following surgical intervention)
Intervention(s)/control	• risk-reducing salpingo-oophorectomy • risk-reducing early salpingectomy with delayed oophorectomy No evidence identified for early salpingectomy with delayed oophorectomy
Duration of follow-up	Highest mean follow-up 6.5 years
Sample size	Overall N not reported
Sources of funding	No funding was received for this review

Outcomes

Menopause related outcomes in women who had surgery

Outcome	Study, N = NR
Bone loss: osteopenia (%) Range	23 to 61
Bone loss: osteoporosis (%) Range	6 to 20
Cardiovascular health: coronary heart disease/myocardial infarction (%) Range	1 to 4

NR: not reported

Critical appraisal – NGA Critical appraisal - ROBIS tool

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

1 **Ingham, 2013**

Bibliographic Reference	Ingham, SL; Sperrin, M; Baildam, A; Ross, GL; Clayton, R; Lalloo, F; Buchan, I; Howell, A; Evans, DG; Risk-reducing surgery increases survival in BRCA1/2 mutation carriers unaffected at time of family referral; Breast cancer research and treatment; 2013; vol. 142 (no. 3); 611-618

2

3 **Study details**

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Between February 1980 and December 2011
Inclusion criteria	• women were identified from the Genetic Medicine Database, Manchester Regional Genetics Service, St. Mary's Hospital, UK. • female *BRCA1/2* mutation carriers • if they were alive at the date of family ascertainment and did not have a diagnosis of breast or ovarian cancer
Exclusion criteria	None reported
Patient characteristics	N=565 *BRCA1/2* mutation carriers n=108 had bilateral salpingo-oophorectomy n=457 general surveillance / no surgery **Age (median (range), years):** in *BRAC1* carriers 34.4 (2-87), in *BRCA2* carriers 37.4 (5-85) **Gender (n):** women 100% **Ethnicity (n):** not reported

	Socioeconomic and geographical factors: not reported **Disabilities:** not reported **People with communication needs:** not reported **Mutation status (n):** 346 *BRCA1*, 345 *BRCA2*
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy **Control** • general surveillance / no bilateral salpingo-oophorectomy Prior to 2005 nearly all RRBSO involved a full abdominal hysterectomy. Since 2005, the vast majority have been offered laparoscopic BSO only.
Duration of follow-up	The median duration of follow-up (from ascertainment to death or loss to follow-up) was 13.3 years and median age at last follow-up (or death) was 48.4 years
Sample size	N=565
Sources of funding	Unfunded research

1

Study arms

Bilateral salpingo-oophorectomy (N = 108)

Surveillance or no bilateral salpingo-oophorectomy (N = 457)

Outcomes

Overall mortality (survival)

Outcome	Bilateral salpingo-oophorectomy, , N = 108	General surveillance or no bilateral salpingo-oophorectomy, , N = 457
Overall mortality Median duration of follow-up 13.3 years No of events	n = 4; % = 3.7	n = 71; % = 15.5

Overall mortality (survival, Cox proportional hazard model)

Outcome	Bilateral salpingo-oophorectomy vs General surveillance or no bilateral salpingo-oophorectomy, N2 = 457, N1 = 108
Overall mortality Median duration of follow-up 13.3 years. A multivariate Cox proportional hazard model was fit with explanatory variables: BRRM and BRRSO (indicating whether and when either procedure was carried out post-cancer diagnosis) Hazard ratio/95% CI	0.22 (0.08 to 0.61)

1 **Ovarian cancer detection rate (incidence)**

Outcome	Bilateral salpingo-oophorectomy, N = 108	General surveillance or no bilateral salpingo-oophorectomy, N = 457
Ovarian cancer incidence Median duration of follow-up 13.3 years No of events	n = 1; % = 0.93	n = 37; % = 8.1

2 **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

3

1 **Kauff, 2008**

Bibliographic Reference	Kauff, N.D.; Domchek, S.M.; Friebel, T.M.; Robson, M.E.; Lee, J.; Garber, J.E.; Isaacs, C.; Evans, D.G.; Lynch, H.; Eeles, R.A.; Neuhausen, S.L.; Daly, M.B.; Matloff, E.; Blum, J.L.; Sabbatini, P.; Barakat, R.R.; Hudis, C.; Norton, L.; Offit, K.; Rebbeck, T.R.; Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: A multicenter, prospective study; Journal of Clinical Oncology; 2008; vol. 26 (no. 8); 1331-1337

2

3 **Study details**

Country/ies where study was carried out	International
Study type	Prospective cohort study
Study dates	Between November 1994 and December 2004
Inclusion criteria	• women who had a documented deleterious mutation in *BRCA1/2*; • have at least one ovary in situ at time of genetic testing; • have no personal history of *BRCA*-associated gynaecologic cancer before genetic testing; • were older than 30 years of age at the time of genetic testing because participation in ovarian cancer risk-reduction strategies is not generally recommended prior to this age. Participants with a personal history of breast cancer without evidence of distant metastatic disease at time of genetic testing were eligible for enrollment • Participants were included in the RRSO cohort if they had bilateral salpingo-oophorectomy for reasons other than known or suspected cancer after the receipt of genetic test results
Exclusion criteria	• participants (n=4) with mutations in both *BRCA1* and *BRCA2*
Patient characteristics	N=792 women with BRCA1/2 n=509 had surgery n=283 no surgery **Age (mean (range), years):** in surgery group 47.1 (31.1-79), in no surgery group 42.9 (30-87.8)

	Gender (n): women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Personal history of breast cancer (n):** in surgery group 303, in no surgery group 133 **Mutation status (n):** 325 with *BRCA1*, 184 with *BRCA2*
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy **Control** • surveillance Surveillance group included all women with mutations who did not elect to undergo RRSO
Duration of follow-up	Mean (range) follow-up: surgery group 40.3 months (6-114.6), no surgery group 37.6 (6.2-119.3) For women in the salpingo-oophorectomy group, the duration of follow-up was calculated from the date of surgery to the date of diagnosis of new breast or *BRCA*-associated gynaecologic cancer, the date of last contact, or the date of death. For women in the surveillance group, the duration of follow-up was calculated from the date of receipt of genetic test results to the date of diagnosis of new breast or *BRCA*-associated gynaecologic cancer, the date of last contact, or the date of death.
Sample size	N=792
Sources of funding	Supported in part by the Department of Defense Breast Cancer Research Program (DAMD17-03-1-0375 to N.D.K., DAMD-17-03-1-0619 to S.M.D.), the US Public Health Service (R01-CA83855 to T.R.R., R01-CA102776 to T.R.R., R01-

	CA74415 to S.L.N.), Cancer Research UK (C5047/A3354 to R.A.E.) the Lucius N. Littauer Foundation, the Frankel Foundation, the Genet Fund, the Koodish Fellowship Fund, the Project Hope Fund for Ovarian Cancer Research and Education, QVC Network, the Fashion Footwear Association of New York, the Edward Spiegel Memorial Fund, revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services, the Charles F. and Mary C. Heider Chair in Cancer Research at Creighton University, the University of Pennsylvania Cancer Center, and the Prevention, Control, and Population Research Program of Memorial Sloan-Kettering Cancer Center.

Study arms

Bilateral salpingo-oophorectomy (N = 509)

Surveillance (N = 283)

Outcomes

Disease-free survival

Outcome	**Bilateral salpingo-oophorectomy vs Surveillance, N2 = 283, N1 = 509**
Disease-free survival Mean (range) follow-up: surgery group 40.3 months (6-114.6), no surgery group 37.6 (6.2-119.3). HR adjusted for age at start of follow-up, parity, personal history of breast cancer, and history of prior use of hormone-replacement therapy Hazard ratio/95% CI	0.12 (0.03 to 0.41)

HR: hazard ratio

1 **Invasive epithelial carcinoma of the ovary, fallopian tube, or peritoneum cancer detection rate (incidence)**

Outcome	Bilateral salpingo-oophorectomy, N = 509	Surveillance, N = 283
Invasive epithelial carcinoma of the ovary, fallopian tube, or peritoneum cancer incidence Mean (range) follow-up: surgery group 40.3 months (6-114.6), no surgery group 37.6 (6.2-119.3) No of events	n = 3; % = 0.6	n = 12; % = 4.2

2 **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

3

1 **Madalinska, 2007**

Bibliographic Reference	Madalinska, J.B.; Van Beurden, M.; Bleiker, E.M.A.; Valdimarsdottir, H.B.; Lubsen-Brandsma, L.; Massuger, L.F.; Mourits, M.J.E.; Gaarenstroom, K.N.; Van Dorst, E.B.L.; Van Der Putten, H.; Boonstra, H.; Aaronson, N.K.; Predictors of prophylactic bilateral salpingo-oophorectomy compared with gynecologic screening use in BRCA1/2 mutation carriers; Journal of Clinical Oncology; 2007; vol. 25 (no. 3); 301-307

2

3 **Study details**

Country/ies where study was carried out	The Netherlands
Study type	Prospective cohort study
Study dates	Between 2002 and 2004
Inclusion criteria	• *BRCA1/2* carriers older than 35 years who had completed their childbearing
Exclusion criteria	Not reported
Patient characteristics	N=160 *BRCA1/2* mutation carriers (12-month follow-up) n=118 had surgery n=42 screening **Age (mean (SD), years):** in surgery group 48.3 (8.4), in screening group 45.3 (8.1) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:**

	Education level: Primary school/lower level high school: in surgery group 26%, in screening group 12%, Middle level high school: in surgery group 54%, screening group 50%, Advanced vocational/university: 20%, in screening group38% **Disabilities:** not reported **People with communication needs:** not reported **Personal history of breast cancer:** in surgery group 53%, in screening group 38%
Intervention(s)/control	**Intervention** • bilateral salpingo oophorectomy **Control** • periodic gynaecologic screening
Duration of follow-up	12 months
Sample size	N=160
Sources of funding	None reported

1

Study arms

Bilateral salpingo-oophorectomy (N = 118)

Screening (N = 42)

Outcomes

Health related quality of life

Outcome	Bilateral salpingo-oophorectomy, N = 118	Screening, N = 42
QOL (short form SF-36) - global health status Measured at 12 months after baseline Mean (SD)	76 (20.6)	79.8 (17.9)

QOL (short form SF-36) - global health status - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(some significant differences between the intervention and screening group, for example, women who opted for surgery were older, were more likely to be married, had lower educational levels, and were more likely to be postmenopausal than those who chose screening)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low

Section	Question	Answer
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 *(some differences in the characteristics between the surgery and screening groups)*
Overall bias	Directness	Directly applicable

Marchetti, 2022

Bibliographic Reference	Marchetti, C.; Arcieri, M.; Vertechy, L.; Ergasti, R.; Russo, G.; Zannoni, G.F.; Minucci, A.; Ercoli, A.; Scambia, G.; Fagotti, A.; Risk reducing surgery with peritoneal staging in BRCA1-2 mutation carriers. A prospective study; European Journal of Surgical Oncology; 2022

1 **Study details**

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Between January 2019 until March 2021
Inclusion criteria	• the presence of known pathogenic germline mutation in a *BRCA1/2* genes
Exclusion criteria	• Women were excluded if the surgery primary aim was other than risk-reducing surgery and if there was a high preoperative suspicion for ovarian or endometrial cancer.
Patient characteristics	N=132 women undergoing risk-reducing surgery n=91 had bilateral salpingo-oophorectomy and hysterectomy n=41 had bilateral salpingo-oophorectomy **Age (median (range), years):** 46 (31-79) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors** **Education (n):** not reported **Disabilities:** not reported **People with communication needs:** not reported **Previous breast cancer (n):** 96 (73%)

	***BRCA1/2* mutation (n):** *BRCA1* 74 (56.1%), *BRCA2* 58 (43.9%)
Intervention(s)/control	**Intervention** • bilateral salpingo-oophorectomy, total hysterectomy and PeS (peritoneal washing and peritoneal/omental biopsies) **Control** • bilateral salpingo-oophorectomy and PeS Almost all the procedures (99.2%), were performed by minimally invasive surgery, while 1 patient underwent laparotomy (due to the presence of severe post-surgical adhesions after a hemicolectomy for a previous colon cancer)
Duration of follow-up	90 months from surgery
Sample size	N=132
Sources of funding	Not reported

Study arms

Bilateral salpingo-oophorectomy, total hysterectomy and PeS (peritoneal washing and peritoneal/omental biopsies) (N = 91)

Bilateral salpingo-oophorectomy and PeS (N = 41)

Outcomes

Surgery related adverse events

Outcome	**Bilateral salpingo-oophorectomy, total hysterectomy and PeS, N = 91**	**Bilateral salpingo-oophorectomy and PeS, N = 41**
Grade IIIA events based on Clavien-Dindo classification system	n = 0; % = 0	n = 0; % = 0

Outcome	Bilateral salpingo-oophorectomy, total hysterectomy and PeS, N = 91	Bilateral salpingo-oophorectomy and PeS, N = 41
No of events		
Grade IIIB events based on Clavien-Dindo classification system; Cases reported within 90 months from surgery No of events	n = 4; % = 4.4	n = 0; % = 0
Grade IV events based on Clavien-Dindo classification system No of events	n = 0; % = 0	n = 0; % = 0

1 PeS: peritoneal washing and peritoneal/omental biopsies

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

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(not clear as no patients' characteristics according to surgery type reported)*
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	Moderate *(not clear as no patients' characteristics according to surgery type reported)*
Overall bias	Directness	Directly applicable

1

2 **Marcinkute, 2022**

Bibliographic Reference	Marcinkute, R.; Woodward, E.R.; Gandhi, A.; Howell, S.; Crosbie, E.J.; Wissely, J.; Harvey, J.; Highton, L.; Murphy, J.; Holland, C.; Edmondson, R.; Clayton, R.; Barr, L.; Harkness, E.F.; Howell, A.; Lalloo, F.; Evans, D.G.; Uptake and efficacy of bilateral risk reducing surgery in unaffected female BRCA1 and BRCA2 carriers; Journal of Medical Genetics; 2022; vol. 59 (no. 2); 133-140

3

4 **Study details**

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Between November 1994 and March 2019
Inclusion criteria	• The individuals were identified from the prospectively maintained Manchester Genetic Medicine Database (North Manchester Research Ethics Committee (reference 08/H1006/77)) • women with a positive pre-symptomatic test for *BRCA1/2* gene path variants

	• women without previous BC/OC diagnoses
Exclusion criteria	None reported
Patient characteristics	N=887 women *BRCA1/2* carriers n=414 had salpingo-oophorectomy (14/887 women underwent surgery after breast cancer diagnosis) n=473 had no surgery **Age (mean (range), years):** 44.6 (25.5-76.7) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors** **Education (n):** not reported **Disabilities:** not reported **People with communication needs:** not reported
Intervention(s)/control	**Intervention** • salpingo-oophorectomy **Control** • no salpingo-oophorectomy
Duration of follow-up	The mean period of time from positive predictive genetic test result or 25th birthday (whichever was later) to the censor date (DOD, BC, OC or last follow-up, whichever was earliest) was 6.26 years (range=0.01–24.3).
Sample size	N=887

Sources of funding	EJC is a National Institute for Health Research (NIHR) Clinician Scientist (NIHR-CS-012–009) and DGE is an NIHR Senior Investigator (NF-SI-0513–10076). DGE, EJC, EFH and ERW are supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215–20007).

Study arms

Salpingo-oophorectomy (N = 414)

No salpingo oophorectomy (N = 473)

Outcomes

Disease-free survival

Outcome	**Salpingo-oophorectomy vs No salpingo oophorectomy, N2 = 473, N1 = 414**
Disease-free survival Mean follow-up (range) 6.26 years (0.01–24.3) Hazard ratio/95% CI	0.02 (0 to 5.9)

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(not clear as no patients' characteristics according to study groups reported)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low

Section	Question	Answer
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 *(not clear as no patients' characteristics according to study groups reported)*
Overall bias	Directness	Directly applicable

1

2 **Metcalfe, 2015**

Bibliographic Reference	Metcalfe, Kelly; Lynch, Henry T; Foulkes, William D; Tung, Nadine; Kim-Sing, Charmaine; Olopade, Olufunmilayo I; Eisen, Andrea; Rosen, Barry; Snyder, Carrie; Gershman, Shelley; Sun, Ping; Narod, Steven A; Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers.; JAMA oncology; 2015; vol. 1 (no. 3); 306-13

3

4 **Study details**

Country/ies where study was carried out	Canada

Study type	Retrospective cohort study
Study dates	Between 1978 and 2008
Inclusion criteria	• families where a *BRCA1/2* mutation was documented in the family and at least 1 case of invasive breast cancer was recorded • women from these families who received a diagnosis of stage I or II breast cancer at age 65 years or younger
Exclusion criteria	• affected women who were known to be non-carriers • women who had undergone oophorectomy prior to breast cancer diagnosis
Patient characteristics	N=676 with breast cancer and with *BRCA1/2* mutations (the majority of oophorectomies were performed for prevention of ovarian cancer and not for the treatment of breast cancer) n=345 had oophorectomy n=331 had no oophorectomy **Age (mean (range), years):** surgery group 41.7 (25-65), no surgery group 42.6 (22-65) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors** **Education (n):** not reported **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* mutation (n):** surgery group *BRCA1* 219 and *BRCA2* 121, no surgery group *BRCA1* 192 and *BRCA2* 133
Intervention(s)/control	**Intervention**

	• oophorectomy **Control** • no oophorectomy
Duration of follow-up	Mean (range) follow-up after breast cancer diagnosis 12.5 (0.7-20)
Sample size	N=676
Sources of funding	Funded by the Canadian Breast Cancer Foundation (Ontario Chapter). Dr Metcalfe is supported by the Canadian Institutes of Health Research and the Ontario Women's Health Council.

Study arms

Oophorectomy (N = 345)

No oophorectomy (N = 331)

Outcomes

Ovarian cancer related mortality

Outcome	**Oophorectomy, N = 345**	**No oophorectomy, N = 331**
Ovarian cancer related mortality Mean (range) follow-up after breast cancer diagnosis 12.5 (0.7-20) No of events	n = 1 ; % = 0.3	n = 9 ; % = 2.7

Overall mortality (survival)

Outcome	Oophorectomy vs No oophorectomy, N2 = 331, N1 = 345
Overall mortality Mean (range) follow-up after breast cancer diagnosis 12.5 (0.7-20); HR adjusted for mutation status, age at diagnosis, oestrogen receptor status, tumour size, lymph node status, receipt of chemotherapy, and receipt of oophorectomy Hazard ratio/95% CI	0.35 (0.22 to 0.56)

HR: hazard ratio

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

1

2 **Nebgen, 2018**

Bibliographic Reference	Nebgen, D.R.; Hurteau, J.; Holman, L.L.; Bradford, A.; Munsell, M.F.; Soletsky, B.R.; Sun, C.C.; Chisholm, G.B.; Lu, K.H.; Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: A pilot study in women with BRCA1/2 mutations; Gynecologic Oncology; 2018; vol. 150 (no. 1); 79-84

3

4 **Study details**

Country/ies where study was carried out	US
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	• Premenopausal women, aged 30 to 47 years with known deleterious *BRCA* mutations but no personal history of OC
Exclusion criteria	• medical comorbidities making surgery unsafe as determined by the patient's surgeon; pregnancy; abnormal CA125 levels; diagnosis of ovarian, fallopian tube, or primary peritoneal carcinoma during the study period; development of new malignancy; recurrence of prior malignancy; or request by the participant to be excluded
Patient characteristics	N=43 women with known BRACA1/2 mutations n=19 women had bilateral salpingectomy with delayed oophorectomy (BS/DO) n=12 had salpingo-oophorectomy n=12 no surgery

	Age (mean (range), years): BS/DO: *BRCA1* 35.7 (31-38), *BRCA2* 35.5 (30-43), salpingo oophorectomy *BRCA1* 40.2 (36-45), *BRCA2* 44.4 (40-47), screening *BRCA1* 35.5 (32-37), *BRCA2* 36.9 (32-43) **Gender (n):** women 100% **Ethnicity (n):** 41 White **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Personal history of breast cancer (n):** BS/DO 3, salpingo oophorectomy 7, screening 6
Intervention(s)/control	**Intervention** • bilateral salpingectomy with delayed oophorectomy (BS/DO) • salpingo-oophorectomy **Control** • screening
Duration of follow-up	12 months
Sample size	N=43
Sources of funding	The University of Texas MD Anderson Cancer Center is supported in in part by the National Institutes of Health through Cancer Center Support Grant P30CA016672.

1

Study arms

Bilateral salpingectomy with delayed oophorectomy (BS/DO) (N = 19)

Salpingo-oophorectomy (N = 12)

Screening (N = 12)

Outcomes

Health related quality of life bilateral salpingectomy with delayed oophorectomy vs salpingo-oophorectomy

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = 12	Screening, N = NR
QOL (RAND36) - total Difference of 12 month and 0-month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	2.3	1.9	*empty data*

QOL: quality of life; Scores range from 0 to 100 for each of the health states. Higher scores reflect a more favourable health state; nr: not relevant

Patient satisfaction with decision bilateral salpingo-oophorectomy with delayed oophorectomy vs salpingo-oophorectomy

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = 12	Screening, N = NR
SWD - total Difference of 12 month and 0-month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	0	1.5	*empty data*

SWD: Satisfaction with Decision; Total score ranges from 6 to 30. Higher scores indicate more satisfaction with a decision; nr: not relevant

Menopause related outcomes: menopause symptoms bilateral salpingo-oophorectomy with delayed oophorectomy vs salpingo-oophorectomy

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = 12	Screening, N = NR
MRS - total Difference of 12 month and 0-month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	0	1.5	*empty data*

MRS: Menopause Rating Scale; Total scores range from 0 to 44. The range of scores for psychological, somatic, and urogenital symptom dimension scores are 0 to 16, 0 to 16, and 0 to 12, respectively. Higher scores indicate worse menopausal symptoms; nr: not relevant

Health related quality of life bilateral salpingo-oophorectomy with delayed oophorectomy vs screening

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = NR	Screening, N = 12
QOL (RAND36) - total Difference of 12 month and 0-month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	2.3	*empty data*	-0.2

QOL: quality of life; Scores range from 0 to 100 for each of the health states. Higher scores reflect a more favourable health state; nr: not relevant

Patient satisfaction with decision bilateral salpingectomy with delayed oophorectomy vs screening

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = NR	Screening, N = 12
SWD - total Difference of 12 month and 0 month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	0	*empty data*	-1

SWD: Satisfaction with Decision; Total score ranges from 6 to 30. Higher scores indicate more satisfaction with a decision; nr: not relevant

Menopause related outcomes: menopause symptoms bilateral salpingectomy with delayed oophorectomy vs screening

Outcome	Bilateral salpingectomy with delayed oophorectomy, N = 19	Salpingo-oophorectomy, N = NR	Screening, N = 12
MRS - total Difference of 12 month and 0 month median scores, no 95%CI reported; no statistical difference in the change of score over time between arms Custom value	0	*empty data*	1

MRS: Menopause Rating Scale; Total scores range from 0 to 44. The range of scores for psychological, somatic, and urogenital symptom dimension scores are 0 to 16, 0 to 16, and 0 to 12, respectively. Higher scores indicate worse menopausal symptoms; NR: not relevant

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 there were any baseline differences between the arms; salpingo-oophorectomy group women appear to be older)*
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 *(not clear if there were any baseline differences between the arms; salpingo-oophorectomy group women appear to be older)*
Overall bias	Directness	Directly applicable

2

1 **Powell, 2018**

Bibliographic Reference	Powell CB; Alabaster A; Stoller N; Armstrong MA; Salyer C; Hamilton I; Raine-Bennett T; Bone loss in women with BRCA1 and BRCA2 mutations.; Gynecologic oncology; 2018; vol. 148 (no. 3)

2

3 **Study details**

Country/ies where study was carried out	US
Study type	Prospective cohort study
Study dates	December 2015 and November 2016
Inclusion criteria	• women aged 40 and older with *BRCA1* or *BRCA2* deleterious mutation documented in the medical record and had current Kaiser Permanente Northern California membership.
Exclusion criteria	• pregnant women • with a diagnosis of ovarian cancer, • and contact for another open study for ovarian cancer surveillance in *BRCA* mutation carriers who had ovaries
Patient characteristics	N=244 women with *BRCA1/2* mutations n=218 had salpingo-oophorectomy n=20 had no salpingo-oophorectomy **Age at scan (median (range), years):** surgery group 57 (50-65), no surgery group 54.5 (44-60) **Gender (n):** women 100% **Ethnicity (n):** White 165

	Socioeconomic and geographical factors: Education (n): high school: 19, some college 83, 4yr degree or more 134 **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* mutation:** with *BRCA1* mutation 47.5%, with *BRCA2* mutation 51.2%, 0.4% with both mutations **Hysterectomy (n)**: surgery group 90 (41.5%), no surgery group 0
Intervention(s)/control	**Intervention** • salpingo-oophorectomy **Control** • no salpingo-oophorectomy
Duration of follow-up	The time from menopause to index (DXA) was 7.5 years in women without RRSO and 9 years in women with RRSO (P = 0.63)
Sample size	N=244
Sources of funding	Funded by an unrestricted grant from Julie and Ronald Tipps in honour of Lee Caudill.

1

Study arms

Salpingo-oophorectomy (N = 218)

No salpingo-oophorectomy (N = 20)

Pre-menopausal surgery (N = 112)

Post-menopausal surgery (N = 106)

Outcomes

Menopause related outcomes

Outcome	Salpingo-oophorectomy, N = 218	No salpingo-oophorectomy, N = 20	Pre-menopausal surgery, N = NR	Post-menopausal surgery, N = NR
Bone loss/fractures: Osteopenia or osteoporosis (DXA) No of events	n = 158; % = 72.5	n = 11; % = 55	*empty data*	*empty data*
Bone loss/fractures: Osteoporosis (DXA) No of events	n = 30; % = 13.8	n = 1; % = 5	*empty data*	*empty data*
Bone loss/fractures: Osteopenia or osteoporosis (self-reported) No of events	n = 53; % = 24.3	n = 2; % = 10	*empty data*	*empty data*

NR: not relevant. Bone loss defined as presence of osteopenia or osteoporosis on the most recent DXA scan. Osteoporosis defined based on the WHO standard of a T- score ≤ −2.5, osteopenia as a T-score of between −2.5 and −1.0, and normal if the T-score was ≥ −1.0. DXA scans were categorized and in the same order: osteoporosis (T score of less than or equal to minus 2. 5) osteopenia (T score -1.0 to -2.5) and normal (T score greater than -1.0)

Menopause related outcomes in pre-menopausal vs post-menopausal surgery

Outcome	Salpingo-oophorectomy, N = NR	No salpingo-oophorectomy, N = NR	Pre-menopausal surgery, N = 112	Post-menopausal surgery, N = 106
Bone loss/fractures: Osteopenia or osteoporosis (DXA) No of events	*empty data*	*empty data*	n = 71; % = 63.4	n = 87; % = 82.1
Bone loss/fractures: Osteoporosis (DXA) No of events	*empty data*	*empty data*	n = 13; % = 11.6	n = 17; % = 16
Bone loss/fractures: Osteopenia or osteoporosis (self-reported) No of events	*empty data*	*empty data*	n = 17; % = 15.2	n = 36; % = 34

pre-menopausal women at the time of surgery were 45 (median) years, post-menopausal women were 57 (median) years; pre-menopausal women at the time of DXA scan were 51 (median) years, post-menopausal women were 62.5 (median) years (significant difference for both)
NR: not relevant. Bone loss defined as presence of osteopenia or osteoporosis on the most recent DXA scan. Osteoporosis defined based on the WHO standard of a T- score ≤ −2.5, osteopenia as a T-score of between −2.5 and −1.0, and normal if the T-score was ≥ −1.0. DXA scans were categorized and in the same order: osteoporosis (T score of less than or equal to minus 2. 5) osteopenia (T score -1.0 to -2.5) and normal (T score greater than -1.0)

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(women who were pre-menopausal at the time of surgery were significantly younger at surgery and at DXA than women who were post-menopausal (median 45 versus 57 years of age, and 51 versus 62.5 years of age, respectively). Women who were pre-menopausal at surgery also had less time*

Section	Question	Answer
		since menopause to the index DXA compared to women who were postmenopausal at surgery (median 5 years versus 14 years))
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

Rebbeck, 2002

Bibliographic Reference	Rebbeck, TR; Lynch, HT; Neuhausen, SL; Narod, SA; Van't Veer, L; Garber, JE; Evans, G; Isaacs, C; Daly, MB; Matloff, E; et, al.; Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations; New England journal of medicine; 2002; vol. 346 (no. 21); 1616-1622

1 **Study details**

Country/ies where study was carried out	International
Study type	Retrospective cohort study matched design
Inclusion criteria	Intervention: • Women with germ-line, disease-associated *BRCA1/2* mutations who reported having undergone prophylactic oophorectomy • and only if their surgery was not performed to treat ovarian cancer Controls: • if woman had a disease-associated *BRCA1/2* mutation, was alive with both ovaries intact at the time the woman with whom she was matched underwent prophylactic oophorectomy, and had no history of ovarian cancer at the time of the matched subject's prophylactic oophorectomy
Exclusion criteria	• women who had undergone unilateral oophorectomy or had a history of ovarian cancer (including borderline tumours or tumours of low malignant potential) before undergoing prophylactic oophorectomy
Patient characteristics	N=551 *BRCA1/2* mutation carriers n=259 had salpingo-oophorectomy n=292 had no salpingo-oophorectomy **Age (mean (range), years):** surgery group 42 (21.2-74.8), no surgery group 40.9 (19.6-79.1) **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* mutation (n):** surgery group *BRAC1* 219 and *BRCA2* 42, no surgery group *BRCA1* 240 and *BRCA2* 52
Intervention(s)/control	**Intervention** • bilateral oophorectomy **Control** • no bilateral oophorectomy
Duration of follow-up	The average length of follow-up after the subject underwent prophylactic oophorectomy was 8.2 years for those undergoing surgery and 8.8 years for the controls. Participants who had undergone prophylactic oophorectomy and controls were followed from the date of the participant's prophylactic oophorectomy until the occurrence of the first cancer or until censoring.
Sample size	N=551
Sources of funding	Supported by grants from the Public Health Service (R01-CA83855, to Dr. Rebbeck; CA57601, to Dr. Weber; and CA74415, to Dr. Neuhausen), the University of Pennsylvania Cancer Center (to Drs. Rebbeck and Weber), the Breast Cancer Research Foundation (to Dr. Weber), the Dana– Farber Women's Cancers Program (to Dr. Garber), the Department of Defense (DAMD-17-96-I-6088, to Dr. Daly; and DAMD-17-94-J-4340 and DAMD-17-97-I-7112, to Dr. Lynch), the Utah Cancer registry (funded by Public Health Service grant NO1-CN-6700) and the Utah State Department of Health, and the Nebraska State Cancer and Smoking-Related Diseases Research Program (LB595, to Dr. Lynch).

1

Study arms

Salpingo-oophorectomy (N = 259)

Surveillance or no salpingo-oophorectomy (N = 292)

Outcomes

Disease-free survival

Outcome	Salpingo-oophorectomy vs Surveillance or no salpingo-oophorectomy, N2 = 292, N1 = 259
Disease-free survival Mean follow-up after the surgery 8.2 years and 8.8 years for the controls Hazard ratio/95% CI	0.04 (0.01 to 0.16)

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

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Low
Overall bias	Directness	Directly applicable

1

2 **Steenbeek, 2021**

Bibliographic Reference	Steenbeek, M.P.; Harmsen, M.G.; Hoogerbrugge, N.; De Jong, M.A.; Maas, A.H.E.M.; Prins, J.B.; Bulten, J.; Teerenstra, S.; Van Bommel, M.H.D.; Van Doorn, H.C.; Mourits, M.J.E.; Van Beurden, M.; Zweemer, R.P.; Gaarenstroom, K.N.; Slangen, B.F.M.; Brood-Van Zanten, M.M.A.; Vos, M.C.; Piek, J.M.J.; Van Lonkhuijzen, L.R.C.W.; Apperloo, M.J.A.; Coppus, S.F.P.J.; Massuger, L.F.A.G.; Inthout, J.; Hermens, R.P.M.G.; De Hullu, J.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

3

4 **Study details**

Country/ies where study was carried out	The Netherlands
Study type	Non-randomised controlled trial
Study dates	Between January 16, 2015, and November 7, 2019
Inclusion criteria	• women with a documented *BRCA1/2* mutation • aged 25 to 40 years (*BRCA1*-PV) or 25 to 45 years (*BRCA2*-PV), • premenopausal, • and capable of reading and speaking Dutch, • to have completed childbearing
Exclusion criteria	• women when they 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	N=548 women with a documented BRCA1/2 mutation n=394 had salpingectomy (RRS) with delayed oophorectomy n=154 had salpingo-oophorectomy **Age (mean (SD), years):** 37.2 (3.5) **Gender (n):** women 100% **Ethnicity (n):** not reported **Socioeconomic and geographical factors:** **Education (n):** low 62, medium 194, high 285, unknown 7 **Disabilities:** not reported **People with communication needs:** not reported ***BRCA1/2* mutation (n):** *BRCA1* 297, *BRCA2* 280 **Personal breast cancer history (n):** 79 (14.4%)
Intervention(s)/control	**Intervention** • salpingectomy (RRS) with delayed oophorectomy Consisted of RRS after the completion of childbearing and RRO at the age of 40 to 45 years (*BRCA1*-PV) or 45 to 50 years (*BRCA2*-PV)

	Control • salpingo-oophorectomy
Duration of follow-up	12 months
Sample size	N=548
Sources of funding	Not reported

Study arms

Salpingectomy (RRS) with delayed oophorectomy (N = 394)

Salpingo-oophorectomy (N = 154)

Outcomes

Health related quality of life

Outcome	**Salpingo-oophorectomy vs Salpingectomy (RRS) with delayed oophorectomy, N2 = 296, N1 = 40**
QOL (SF-36 short form) - physical component summary Mean refers to adjusted mean difference at 12 months from baseline between arms; adjusted for the baseline score of the questionnaire, baseline age, type of *BRCA* Mean (95% CI)	-1.9 (-4.2 to 0.5)
QOL (SF36 short form) - mental component summary Mean refers to adjusted mean difference at 12 months from baseline between arms; adjusted for the baseline score of the questionnaire, baseline age, type of *BRCA* Mean (95% CI)	2.4 (-1.8 to 6.6)

QOL: quality of life

Menopause related outcomes: menopause symptoms

Outcome	Salpingo-oophorectomy vs Salpingectomy (RRS) with delayed oophorectomy, N2 = 296, N1 = 40
GCS Mean refers to adjusted mean difference at 12 months from baseline between arms; adjusted for the baseline score of the questionnaire, baseline age, type of *BRCA* Mean (95% CI)	6.7 (5 to 8.4)

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)

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

1 **Wei, 2023**

Bibliographic Reference	Wei, X; Oxley, S; Sideris, M; Kalra, A; Brentnall, A; Sun, L; Yang, L; Legood, R; Manchanda R; Quality of life after risk-reducing surgery for breast and ovarian cancer prevention: a systematic review and meta-analysis; Am J Obstet Gynecol; Apr 12; S0002-9378(23)00240-5, 2023

2

3 **Study details**

Country/ies where study was carried out	UK
Study type	Systematic review
Study dates	Search was done to February 2023
Inclusion criteria	Studies • where the population included women at increased-risk of breast or ovarian cancer, including diagnosis of pathogenic variants in cancer-susceptibility-genes (CSGs) or a strong family-history of the above cancers • in English • human studies using a predefined search strategy Women at increased-risk of OC definition: a diagnosis of pathogenic-variants (PV) in BC or OC cancer-susceptibility-genes (CSGs) or documented FH of BC or OC, which would translate to a >30-40% or >5% lifetime-risk of BC or OC respectively
Exclusion criteria	Studies included women who: • underwent RRM with a personal-history of BC • underwent RRSO/RRESDO with a personal-history of OC • are at population-risk (not at increased-risk) of BC or OC Study designs: • case-reports

	• review articles
Patient characteristics	34 studies, n=3762 with surgery, n=3002 without surgery)
Intervention(s)/control	**Intervention** • risk-reducing salpingo-oophorectomy (RRSO) or risk-reducing early-salpingectomy and delayed-oophorectomy (RRESDO) for ovarian cancer (OC) prevention **Control** • no surgery/surveillance
Duration of follow-up	The post-surgery follow-up duration ranged 1-6 years for RRSO and 1-year for RRESDO
Sample size	From n=34 studies relevant n=19 studies (N=2247) which reported outcomes after the salpingo-oophorectomy and n=2 studies (N=413) after risk-reducing early-salpingectomy and delayed-oophorectomy (PRESDO)
Sources of funding	Supported by grants from The Rosetrees Trust, China Medical Board (No.19-336), National Key R&D Program of China (2021YFC2500400 and 2021YFC2500405), and National Natural Science Foundation of China (No. 71911530221 and No. 72174010)

Study arms

Salpingo-oophorectomy (N = NR)
NR: not reported

No salpingo-oophorectomy (N = NR)
NR: not reported

<1 year (N = NR)
nr: not reported

>1 year (N = NR)
NR: not reported

Post-menoause (N = NR)
NR: not reported

Pre-menopause (N = NR)
NR: not reported

Outcomes

Health related quality of life

Outcome	Salpingo-oophorectomy vs No salpingo-oophorectomy, N2 = NR, N1 = NR
QOL (SF36) - physical component summary 7 studies (N=1050); I2 86% Mean (95% CI)	-0.75 (-2.01 to 0.5)
QOL (SF36) - mental component summary 7 studies (N=1050); I2 0% Mean (95% CI)	-0.14 (-1.33 to 1.04)

QOL: quality of life; Mean refers to mean difference between surgery vs no surgery group; NR: not reported

Menopause related outcomes: menopause symptoms

Outcome	Salpingo-oophorectomy vs No salpingo-oophorectomy, N2 = NR, N1 = NR
MRS - overall score 2 studies (N=184); I2 0% Mean (95% CI)	2.08 (-0.21 to 4.37)

MRS: Menopause Rating scale; Mean refers to mean difference between surgery vs no surgery group; NR: not reported

Health related quality of life the first year after surgery vs. after

Outcome	>1 year vs <1 year, N2 = NR, N1 = NR
QOL (SF36) - physical component summary 2 studies (N=351); I2 0% Mean (95% CI)	0.64 (-0.69 to 1.98)
QOL (SF36) - mental component summary 2 studies (N=351); I2 0% Mean (95% CI)	1.19 (-0.15 to 2.52)

QOL: quality of life; Mean refers to mean difference between surgery vs no surgery group >1 year after surgery vs <1 year; NR: not reported

Health related quality of life according to menopausal status

Outcome	Post-menopause vs Pre-menopause, N2 = NR, N1 = NR
QOL (SF36) - physical component summary 1 study (N=90) Mean (95% CI)	-3.19 (-7.54 to 1.16)
QOL (SF36) - mental component summary 1 study (N=90) Mean (95% CI)	-0.6 (-4.95 to 3.75)

QOL: quality of life; Mean refers to mean difference between surgery vs no surgery group in post-menopausal vs. pre-menopausal women; NR: not reported

Critical appraisal – NGA Critical appraisal - ROBIS tool

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low

Section	Question	Answer
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

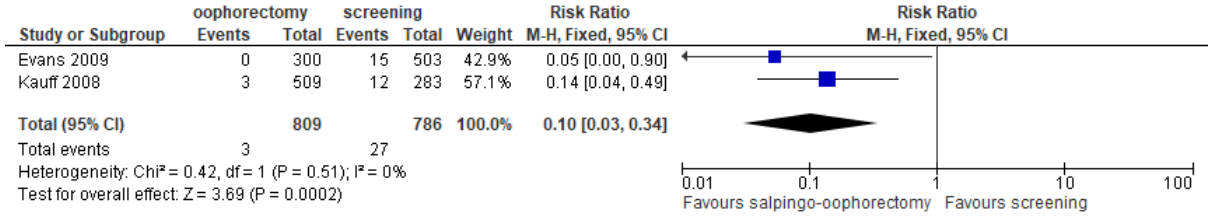
Appendix E Forest plots

Forest plots for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

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.

Bilateral salpingo-oophorectomy vs surveillance

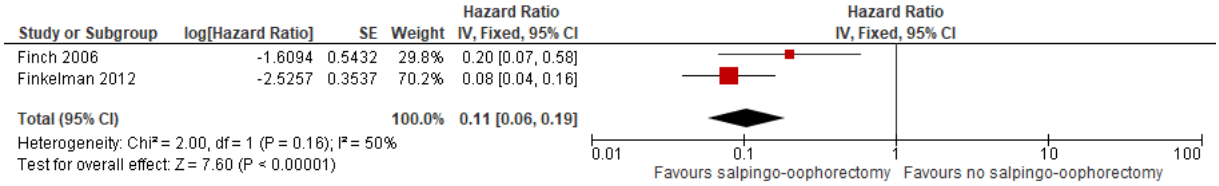
Figure 2: Ovarian cancer detection rates (incidence)



CI: confidence interval

Bilateral salpingo-oophorectomy vs no bilateral salpingo-oophorectomy

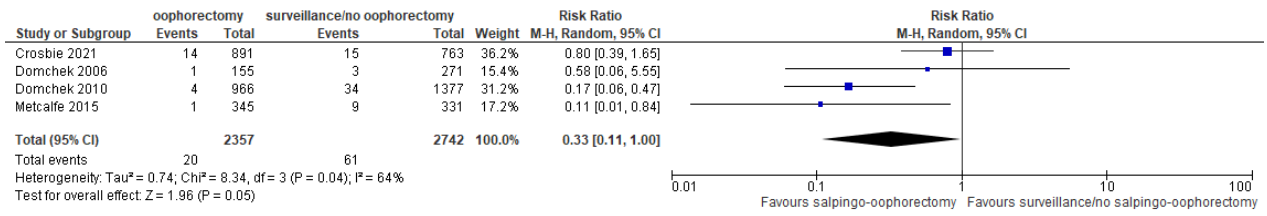
Figure 3: Disease-free survival



CI: confidence interval

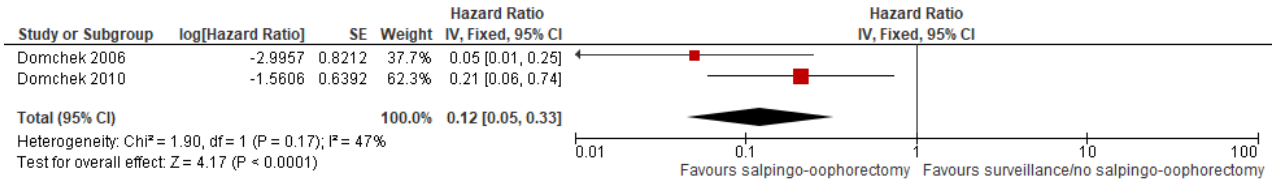
Bilateral salpingo-oophorectomy vs surveillance/no bilateral salpingo-oophorectomy

Figure 4: Ovarian cancer related mortality



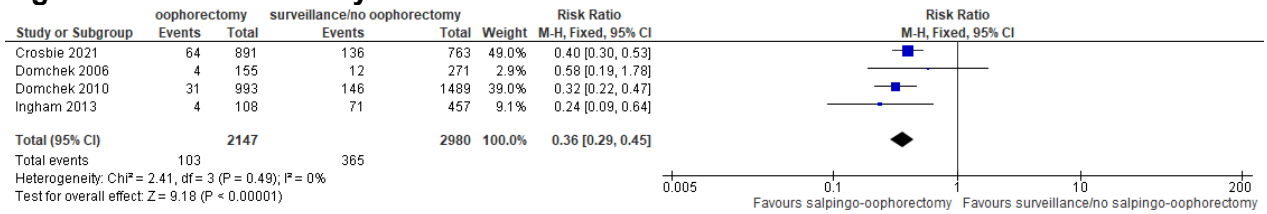
CI: confidence interval

Figure 4: Ovarian cancer related mortality as hazard ratios



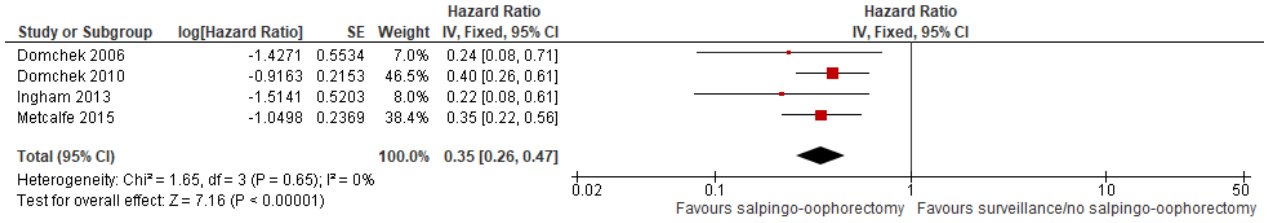
CI: confidence interval

Figure 5: Overall mortality



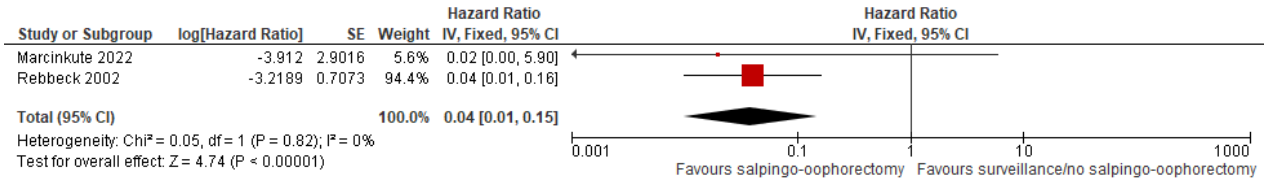
CI: confidence interval

Figure 6: Overall mortality reported as hazard ratios



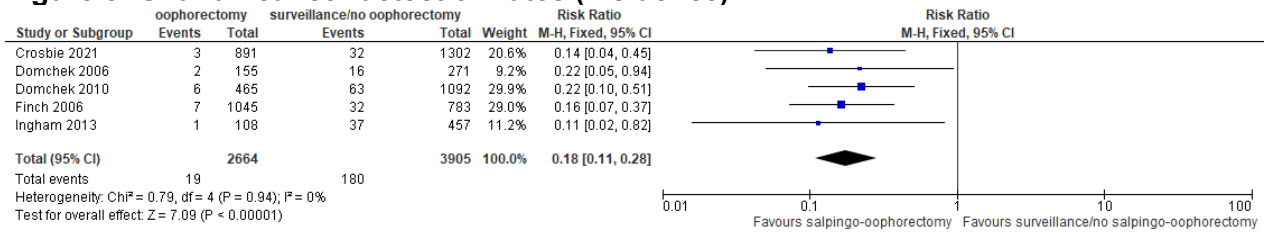
CI: confidence interval

Figure 7: Disease-free survival



CI: confidence interval

Figure 8: Ovarian cancer detection rates (incidence)



CI: confidence interval

1

2

3

Appendix F GRADE tables

GRADE tables for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Table 6: Evidence profile for comparison between bilateral salpingo-oophorectomy vs surveillance

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo oophorectomy	Surveillance	Relative (95% CI)	Absolute		
Health related QOL (SF36): mental health measured cross-sectionally (Better indicated by lower values)												
Fry 2001	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27	28	-	MD 7.8 lower (15.49 to 0.11 lower)	VERY LOW	CRITICAL
Health related QOL (SF36): role-emotional measured cross-sectionally (Better indicated by lower values)												
Fry 2001	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27	28	-	MD 21 lower (38.63 to 3.37 lower)	VERY LOW	CRITICAL
Health related QOL (SF36): social functioning measured cross-sectionally (Better indicated by lower values)												
Fry 2001	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	28	-	MD 16.8 lower (25.65 to 7.95 lower)	LOW	CRITICAL
Health related QOL (SF36): bodily pain measured cross-sectionally (Better indicated by lower values)												
Fry 2001	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	27	28	-	MD 18.3 lower (30.91 to 5.69 lower)	VERY LOW	CRITICAL
Health related QOL (SF36): global health status measured at 12-month follow-up (Better indicated by lower values)												
Madalinska 2007	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	1180	42	-	MD 3.8 lower (9.34 lower to 1.74 higher)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo oophorectomy	Surveillance	Relative (95% CI)	Absolute		
Ovarian cancer related mortality [Mean years follow-up (range) in surgery group 8.17 years (0-27), in no surveillance group 6.8 (1-17) years]												
Evans 2009	observational studies	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/300 (0.33%)	6/506 (1.2%)	RR 0.28 (0.03 to 2.32)	9 fewer per 1000 (from 12 more to 16 more)	VERY LOW	CRITICAL
Overall mortality [Mean years follow-up (range) in surgery group 8.17 years (0-27), in no surveillance group 6.8 (1-17) years]												
Evans 2009	observational studies	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/300 (0%)	4/503 (0.8%)	POR 0.2 (0.03 to 1.53)	6 fewer per 1000 (from 8 fewer to 4 more)	VERY LOW	CRITICAL
Disease-free survival [Mean (range) follow-up: surgery group 40.3 months (6-114.6), no surgery group 37.6 (6.2-119.3)]												
Kauff 2008	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	509	283	HR 0.12 (0.03 to 0.41)[8]	Not calculable	HIGH	CRITICAL
Ovarian cancer detection rates (incidence) [Mean (range) follow-up: surgery group 40.3 months (6-114.6), no surgery group 37.6 (6.2-119.3)]												
2[9]	observational studies	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/809 (0.37%)	27/786 (3.4%)	RR 0.1 (0.03 to 0.34)	31 fewer per 1000 (from 23 fewer to 33 fewer)	MODERATE	CRITICAL

CI: confidence interval; HR: hazard ratio; MD: mean difference; POR: peto odds ratio; RR: risk ratio; QOL: health related quality of life

1 95% CI crosses 1 MID (0.5x control group SD 11.3 = 5.65)

2 95% CI crosses 1 MID (0.5x control group SD 22.3 = 11.15)

3 95% CI crosses 1 MID (0.5x control group SD 17.1 = 8.55)

4 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS I

5 95% CI crosses 1 MID (0.5x control group SD 17.9 = 8.95)

6 Serious risk of bias in the evidence contributing to the outcomes as per ROBIS I

7 95% CI crosses 2 MIDs

8 HR adjusted for age at start of follow-up, parity, personal history of breast cancer, and history of prior use of hormone-replacement therapy

9 Evans 2009, Kauff 2008

Table 7: Evidence profile for comparison between bilateral salpingo-oophorectomy vs no bilateral salpingo-oophorectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo-oophorectomy	No salpingo-oophorectomy	Relative (95% CI)	Absolute		
Health related QOL (SF36): mean difference in physical component summary between surgery vs no surgery												
Wei 2023[1]	observational studies	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	not reported	not reported	-	MD 0.75 lower (2.01 lower to 0.5 higher)	VERY LOW	CRITICAL
Health related QOL (SF36): mean difference in mental component summary between surgery vs no surgery												
Wei 2023[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	not reported	not reported	-	MD 0.14 lower (1.33 lower to 1.04 higher)	LOW	CRITICAL
Health related QOL (SF36): mean difference in physical component summary between surgery vs no surgery >1 year after surgery vs <1 year												
Wei 2023[3]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious [4]	none	not reported	not reported	-	MD 0.64 higher (0.69 lower to 1.98 higher)	VERY LOW	CRITICAL
Health related QOL (SF36): mean difference in mental component summary between surgery vs no surgery >1 year after surgery vs <1 year												
Wei 2023[3]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious [4]	none	not reported	not reported	-	MD 1.19 higher (0.15 lower to 2.52 higher)	VERY LOW	CRITICAL
Health related QOL (SF36) according to menopausal status: mean difference in physical component summary between post-menopausal vs pre-menopausal surgery												
Wei 2023[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious [6]	none	not reported	not reported	-	MD 3.19 lower (7.54 lower to 1.16 higher)	VERY LOW	CRITICAL
Health related QOL (SF36) according to menopausal status: mean difference in mental component summary between post-menopausal vs pre-menopausal surgery												
Wei 2023[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious [6]	none	not reported	not reported	-	MD 0.6 lower (4.95 lower to 3.75 higher)	VERY LOW	CRITICAL
Menopause-related outcomes: menopause symptoms: mean difference in MRS overall score between surgery and no surgery												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo-oophorectomy	No salpingo-oophorectomy	Relative (95% CI)	Absolute		
Wei 2023[7]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious [6]	none	not reported	not reported	-	MD 2.08 higher (0.21 lower to 4.37 higher)	VERY LOW	CRITICAL
Menopause- related outcomes: bone loss/fractures – Osteopenia or osteoporosis (DXA) [The time from menopause to index (DXA) was 7.5 years in women without surgery and 9 years in women with surgery]												
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	158/218 (72.5%)	11/20 (55%)	RR 1.32 (0.88 to 1.98)	176 more per 1000 (from 66 fewer to 539 more)	LOW	CRITICAL
Menopause-related outcomes: bone loss/fractures – Osteoporosis (DXA) [The time from menopause to index (DXA) was 7.5 years in women without surgery and 9 years in women with surgery]												
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	30/218 (13.8%)	1/20 (5%)	RR 2.75 (0.4 to 19.13)	87 more per 1000 (from 30 fewer to 906 more)	VERY LOW	CRITICAL
Menopause-related outcomes: bone loss/fractures – Osteopenia or osteoporosis (self-reported)												
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	53/218 (24.3%)	2/20 (10%)	RR 2.43 (0.64 to 9.24)	143 more per 1000 (from 36 fewer to 824 more)	VERY LOW	CRITICAL
Menopause-related outcomes: bone loss/fractures in women who had pre-menopausal vs post-menopausal surgery – Osteopenia or osteoporosis (DXA) [The time from menopause to index (DXA) was 7.5 years in women without surgery and 9 years in women with surgery]												
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	71/112 (63.4%)	87/106 (82.1%)	RR 0.77 (0.65 to 0.91)	189 fewer per 1000 (from 74 fewer to 287 fewer)	LOW	CRITICAL
Menopause-related outcomes: bone loss/fractures in women who had pre-menopausal vs post-menopausal surgery – Osteoporosis (DXA) [The time from menopause to index (DXA) was 7.5 years in women without surgery and 9 years in women with surgery]												
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	very serious[10]	none	13/112 (11.6%)	17/106 (16%)	RR 0.72 (0.37 to 1.42)	45 fewer per 1000 (from 101 fewer to 67 more)	VERY LOW	CRITICAL
Menopause-related outcomes: bone loss/fractures in women who had pre-menopausal vs post-menopausal surgery – Osteopenia or osteoporosis (self-reported)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo-oophorectomy	No salpingo-oophorectomy	Relative (95% CI)	Absolute		
Powell 2018	observational studies	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/112 (15.2%)	36/106 (34%)	RR 0.45 (0.27 to 0.75)	187 fewer per 1000 (from 85 fewer to 248 fewer)	MODERATE	CRITICAL
Menopause-related outcomes: bone loss – osteopenia [various follow-ups]												
Gaba 2020	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	only women who had surgery, N=832	-	-	Reported as range: 23% to 61% in women who had surgery	LOW	CRITICAL
Menopause-related outcomes: bone loss – osteoporosis [various follow-ups]												
Gaba 2020	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	only women who had surgery, N=1170	-	-	Reported as range: 6% to 20% in women who had surgery	LOW	CRITICAL
Menopause-related outcomes: cardiovascular health: coronary heart disease/myocardial infarction [follow-up not reported]												
Gaba 2020	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	only women who had surgery, N=226	-	-	Reported as range: 1% to 4% in women who had surgery	LOW	CRITICAL
Disease-free survival [various follow-ups]												
2[12]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2526	2632	HR 0.11 (0.06 to 0.19)[13]	Not calculable	HIGH	IMPORTANT
Ovarian cancer detection rates or incidence												
Finkelman 2012	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/1701 (0.71%)	139/2086 (6.7%)	RR 0.11 (0.06 to 0.19)	59 fewer per 1000 (from 27 fewer to 54 fewer)	HIGH	IMPORTANT

CI: confidence interval; DXA: dual-energy x-ray scan; HR: hazard ratio; MD: mean difference; MRS: menopause rating scale; RR: risk ratio; QOL: health related quality of life

1 Wei 2023 systematic review (4 studies (N=1050) contributed to the overall effect estimate but not clear which ones as not reported)

2 Downgraded for inconsistency (I2 86.3%)

3 Wei 2023 systematic review (2 studies (N=351) contributed to the overall effect estimate but not clear which ones as not reported)

4 Optimal information size for imprecision: N<400
5 Wei 2023 systematic review (1 study (N=90) contributed to the effect estimate but not clear which one as not reported)
6 Optimal information size for imprecision: N<200
7 Wei 2023 systematic review (2 studies (N=184) contributed to the overall effect estimate but not clear which ones as not reported)
8 Serious risk of bias in the evidence contributing to the outcomes as per ROBIS I
9 95% CI crosses 1 MID
10 95% CI crosses 2 MIDs
11 Optimal information size for imprecision: N<400
12 Finch 2006, Finkelman 2012
13 HR adjusted for age, gene, country of origin, past history of breast cancer, oral contraceptive use, breast-feeding, parity in Finch 2006 and for age at ascertainment, parity and oral contraceptive use in Finkelman 2012

Table 8: Evidence profile for comparison between bilateral salpingo-oophorectomy vs surveillance/no bilateral salpingo-oophorectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo-oophorectomy	Surveillance/no salpingo-oophorectomy	Relative (95% CI)	Absolute		
Ovarian cancer related mortality [various follow-ups: between 2 and 12 years]												
4[1]	observational studies	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	20/2357 (0.85%)	61/2742 (2.2%)	RR 0.33 (0.11 to 1)	14 fewer per 1000 (from 9 fewer to 18 fewer)	LOW	CRITICAL
Ovarian cancer related mortality [various follow-ups: between 2 and 4 years]												
2[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/1121 (2.2%)	37/1648 (2.2%)	HR 0.12 (0.05 to 0.33)	20 fewer per 1000 (from 15 fewer to 21 fewer)	HIGH	CRITICAL
Overall mortality [various follow-ups]												
4[5]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/2147 (4.8%)	365/2980 (12.2%)	RR 0.36 (0.29 to 0.45)	78 fewer per 1000 (from 67 fewer to 87 fewer)	HIGH	IMPORTANT
Overall mortality [various follow-ups]												
4[6]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1601	2548	HR 0.35 (0.26 to 0.47)	Not calculable	HIGH	IMPORTANT
Disease-free survival [various follow-ups]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingo-oophorectomy	Surveillance/no salpingo-oophorectomy	Relative (95% CI)	Absolute		
2[7]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	673	765	HR 0.04 (0.01 to 0.15)	Not calculable -	HIGH	IMPORTANT
Ovarian cancer detection rates (incidence) [various follow-ups]												
5[8]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/2664 (0.71%)	180/3905 (4.6%)	RR 0.18 (0.11 to 0.28)	38 fewer per 1000 (from 33 fewer to 41 fewer)	HIGH	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: risk ratio
1 Crosbie 2021, Domchek 2006, Domchek 2010, Metcalfe 2015
2 Downgraded for inconsistency I2 64%
3 95% CI crosses 1 MID
4 Domchek 2006, Domchek 2010
5 Crosbie 2021, Domchek 2006, Domchek 2010, Ingham 2013
6 Domchek 2006, Domchek 2010, Ingham 2013, Metcalfe 2015
7 Marcinkute 2022, Rebbeck 2002
8 Crosbie 2021, Domchek 2006, Domchek 2010, Finch 2006, Ingham 2013

Table 9: Evidence profile for comparison between salpingectomy with delayed bilateral salpingo-oophorectomy vs surveillance

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingectomy with delayed oophorectomy	Surveillance	Relative (95% CI)	Absolute		
Health related QOL (RAND36): total score, median difference at 12-month follow-up from baseline												
Nebgen 2018	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19	12	-	median difference in surgery group 2.3, in no surgery group -0.2[3]	VERY LOW	CRITICAL
Patient satisfaction with decision (SWD scale): median difference at 12-month follow-up from baseline												
Nebgen 2018	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious [2]	none	19	12	-	median difference in surgery group 0, in no surgery group -1[3]	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingectomy with delayed oophorectomy	Surveillance	Relative (95% CI)	Absolute		
Menopause-related outcomes: menopause rating scale (MRS): total, median difference at 12-month follow-up from baseline												
Nebgen 2018	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious [2]	none	19	12	-	median difference in surgery group 0, in no surgery group 1[3]	VERY LOW	CRITICAL

CI: confidence interval; MRS: menopause rating scale; QOL: health related quality of life; SWD: satisfaction with decision scale measures satisfaction with health care decisions
1 Serious risk of bias in the evidence contributing to the outcomes as per ROBIS I
2 Optimal information size for imprecision: N<200
3 No CI, standard deviation or standard error reported; reported that there was no statistical difference in the change of score over time between arms

Table 10: Evidence profile for comparison between salpingectomy with delayed bilateral salpingo-oophorectomy vs bilateral salpingo-oophorectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingectomy with delayed oophorectomy	Oophorectomy	Relative (95% CI)	Absolute		
Health related QOL (SF36): physical component, adjusted mean difference at 12-month follow-up from baseline												
Steenbeek 2021	non-randomised RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	296	-	adjusted mean difference 1.9 lower (4.2 lower to 0.5 higher)	MODERATE	CRITICAL
Health related QOL (SF36): mental component, adjusted mean difference at 12-month follow-up from baseline												
Steenbeek 2021	non-randomised RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	296	-	adjusted mean difference 2.4 higher (1.8 lower to 6.6 higher)	MODERATE	CRITICAL
Health related QOL (RAND36): total score, median difference at 12-month follow-up from baseline												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salpingectomy with delayed oophorectomy	Oophorectomy	Relative (95% CI)	Absolute		
Nebgen 2018	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	12	-	median difference in surgery group 2.3, in no surgery group 1.9[4]	VERY LOW	CRITICAL
Patient satisfaction with decision (SWD scale): median difference at 12-month follow-up from baseline												
Nebgen 2018	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	12	-	median difference in surgery group 0, in no surgery group 1.5[4]	VERY LOW	CRITICAL
Menopause-related outcomes: menopause rating scale (MRS): total, median difference at 12-month follow-up from baseline												
Nebgen 2018	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19	12	-	median difference in surgery group 0, in no surgery group 1.5[4]	VERY LOW	CRITICAL
Menopause-related outcomes: Greene Climacteric Scale: total, adjusted mean difference at 12-month follow-up from baseline												
Steenbeek 2021	non-randomised RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40	296	-	adjusted mean difference 6.7 higher (5 to 8.4 higher)[4]	MODERATE	CRITICAL

CI: confidence interval; MRS: menopause rating scale; RCT: randomised controlled trial; SWD: satisfaction with decision scale measures satisfaction with health care decisions: QOL: health related quality of life

1 Optimal information size for imprecision: N<400

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

3 Optimal information size for imprecision: N<200

4 No CI, standard deviation or standard error reported; reported that there was no statistical difference in the change of score over time between arms

Table 11: Evidence profile for comparison between pre-menopausal bilateral salpingo-oophorectomy vs post-menopausal bilateral salpingo-oophorectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-menopausal salpingo-oophorectomy	Post-menopausal salpingo-oophorectomy	Relative (95% CI)	Absolute		
Patient satisfaction/regret with surgery decision: It was the right decision (agree and strongly agree) [follow-up not reported]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-menopausal salpingo-oophorectomy	Post-menopausal salpingo-oophorectomy	Relative (95% CI)	Absolute		
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/161 (88.8%)	80/84 (95.2%)	RR 0.93 (0.87 to 1)	67 fewer per 1000 (from 124 fewer to 0 more)	LOW	CRITICAL
Patient satisfaction/regret with surgery decision: I regret the choice that was made (agree and strongly agree) [follow-up not reported]												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15/160 (9.4%)	1/81 (1.2%)	RR 7.59 (1.02 to 56.48)	81 more per 1000 (from 0 more to 685 more)	VERY LOW	CRITICAL
Patient satisfaction/regret with surgery decision: I would make the same decision if I had to do it over again (agree and strongly agree) [follow-up not reported]												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	141/161 (87.6%)	79/84 (94%)	RR 0.93 (0.86 to 1.01)	66 fewer per 1000 (from 132 fewer to 9 more)	LOW	CRITICAL
Patient satisfaction/regret with surgery decision: The decision did me a lot of harm (agree and strongly agree) [follow-up not reported]												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/160 (11.3%)	4/80 (5%)	RR 2.25 (0.79 to 6.43)	62 more per 1000 (from 10 fewer to 271 more)	VERY LOW	CRITICAL
Patient satisfaction/regret with surgery decision: The decision was a wise one (agree and strongly agree) [follow-up not reported]												
Gaba 2021	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/158 (93%)	77/83 (92.8%)	RR 1 (0.93 to 1.08)	0 fewer per 1000 (from 65 fewer to 74 more)	LOW	CRITICAL

CI: confidence interval; RR: risk ratio
1 95% CI crosses 1 MID
2 95% CI crosses 2 MIDs

Table 12: Evidence profile for comparison between hysterectomy plus bilateral salpingo-oophorectomy vs bilateral salpingo-oophorectomy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hysterectomy + salpingo-oophorectomy	Salpingo-oophorectomy	Relative (95% CI)	Absolute		
Surgery related adverse events: severe (grade III or above) events measured up to 1-month follow-up												
Bogani 2017	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	0/55 (0%)	RD 0 (-0.05 to 0.05)	-	VERY LOW	CRITICAL
Marchetti 2022	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/91 (4.4%)	0/41 (0%)	POR 4.41 (0.52 to 37.6)	-	LOW	CRITICAL

CI: confidence interval; POR: peto odds ratio; RD: risk difference
1 Serious risk of bias in the evidence contributing to the outcomes as per ROBIS I
2 Optimal information size for imprecision: N<400
3 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Table 13: Economic evidence tables for risk-reducing strategies in *BRCA* mutation carriers

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Bommer 2022 Switzerland Cost-utility analysis Source of funding: University of Zurich	Interventions -Risk reducing bilateral mastectomy (RRBM) - Risk reducing bilateral salpingo-oophorectomy (RRBSO) -RRBM plus RRBSO Comparator: -Intensified surveillance, IS (age-related imaging procedures and gynaecological consultations) -Chemoprevention with Tamoxifen (CP)	A cohort of women *BRCA1* or *BRCA2* mutation carriers aged 40 years who had no history of breast or ovarian cancer Modelling study (Markov) Source of baseline data: Various sources, mainly cohort studies Source of effectiveness data: Cohort studies and RCT for chemotherapy Source of cost data: Various published sources supplemented with authors' assumptions	Costs: Surveillance and cancer follow-up (clinical consultations, mammography, magnetic resonance imaging (MRI), computerized tomography (CT) scans, oncologic consultation, blood sampling and analysis, ultrasound, osteodensitometry), RRBM with autologous breast reconstruction or implant-based breast reconstruction, RRBSO, cancer surgery (bilateral mastectomy or bilateral salpingo-oophorectomy), hysterectomy, debulking in abdomen or pelvis, breast reshaping, implant replacement, radiation therapy, palliative care, chemotherapy-associated costs	ICERs: -For both *BRCA1* and *BRCA2* RRBM and RRBSO was dominant Probability of being cost-effective: For both *BRCA1* and *BRCA2* RRBM and RRBSO had a 100% probability of being cost-effective at a willingness-to-pay (WTP) from €0-100,000 per QALY gained Subgroup analysis: NR Sensitivity analysis: Changes in ovarian cancer (OC) incidence after primary breast cancer (BC), RRBSO costs, hazard ratio of RRBSO, RRBM costs with implant reconstruction, costs of	Perspective: Healthcare payer Currency: Euro (€) Cost year: Likely 2019 Time horizon: 60 years (lifetime) Discounting: 3% for costs and QALYs Applicability: Partially Limitations: Minor

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit cost data: National (Swiss diagnosis-related group system, Tarmed national tariff system, Swiss statutory health insurance)	Mean lifetime cost per participant: BRCA1 IS: €141,293 CP: €136,957 RRBM: €115,802 RRBSO: €112,814 RRBM and RRBSO: €76,639 BRCA2 IS: €102,245 CP: €97,091 RRBM: €78,478 RRBSO: €70,562 RRBM and RRBSO: €60,770 The primary measure of outcome: QALYs (with utility weights from various published sources, some were based on EQ-5D) Mean lifetime QALYs per participant: *BRCA1* IS: 14.48 CP: 15.24 RRBM: 17.28	implant replacement, utility values of IS and CP have the most effect on the incremental cost-effectiveness ratios (ICERs). However, the conclusions were unchanged.	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			RRBSO: 16.79 RRBM and RRBSO: 19.24 *BRCA2* IS: 15.52 CP: 16.85 RRBM: 17.58 RRBSO: 19.24 RRBM and RRBSO: 19.85		
Muller 2018 Germany Cost-utility analysis Source of funding: Federal Ministry of Education and Research	Interventions -RRBM, RRBSO, RRBM and RRBSO at 40 years, RRBM and RRBSO at 30 years Comparator - IS (half-yearly palpation and ultrasound, yearly mammography and breast MRI)	A cohort of 30-year-old female *BRCA* mutation carriers aged 30 who had no history of BC or OC Modelling study (Markov) Source of baseline data: Cohort studies Source of effectiveness data: Cohort studies Source of cost data: Various published sources Source of unit cost data: Unclear, some local (prophylactic and	Costs: -Ongoing high-risk screening/monitoring -Risk reducing surgeries, therapeutic breast mastectomy, breast-conserving surgery, therapeutic bilateral salpingo-oophorectomy), BC medication (chemotherapy, endocrine therapy, neutropenic sepsis, pegfilgrastim, antiemetics, bisphosphonates), other BC treatments (adjuvant radiotherapy, local surgeries, psychological treatment in case of cancer diagnosis), lymphatic drainage/physiotherapy, OC medication, palliative care Mean lifetime cost per participant: IS: €45,480	RRBM and RRBSO at age 30: dominant Probability of being cost-effective: At WTP of €0 per QALY gained -RRBM and RRBSO at age 30: 57% -RRBM and RRBSO at age 40: 33% -RRBSO: 10% -RRBM: 0% -IS: 0% At WTP of €50,000 per QALY gained -RRBM and RRBSO at age 30: 86% -RRBM and RRBSO at age 40: 14% -RRBSO: 0%	Perspective: Healthcare payer Currency: Euro (€) Cost year: NR; likely 2016 Time horizon: 75 years (lifetime) Discounting: 3% for costs and QALYs Applicability: Partially Limitations: Minor

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		therapeutic surgical costs from actuarial data from the University Hospital of Cologne)	PBM and PBSO at age 30: €29,434 PBM and PBSO at age 40: €30,810 PBSO: €34,802 PBM: €37,307 The primary measure of outcome: QALYs (utility weights from various published sources) Mean lifetime QALYs per participant: IS: 14.96 PBM and PBSO at age 30: 17.66 PBM and PBSO at age 40: 17.28 PBSO: 16.71 PBM: 16.27	-RRBM: 0% -IS: 0% Subgroup analysis: NR Sensitivity analysis: -The results were robust, including changes in cancer incidence, mortality, utility assumptions, the efficacy of surgical options, the discount rate, differentiating between 'ovarian cancer' (<stage 4) and 'recurrent ovarian cancer' (stage 4) states - Only in case of a lower OC incidence or both OC and BC incidence, does RRBM and RRBSO at age 40 result in lower costs, but RRBS and RRBSO at age 30 remains the cost-effective option -Assuming that the utility after prophylactic surgery increased to that of a healthy woman within a period of 25 years (base-case: 5 years), the ICER of RRBM and RRBSO at 40 years (vs RRBM and RRBSO at age 30): €6,900 per QALY	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Yamauchi 2018 Japan Cost-utility analysis Source of funding: a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare	Intervention - RRBM at 35 years and RRBSO at 45 years - IS from 35 years, RRBSO at 45 years - RRBM at 35 years Comparator IS from age 35 -BC (annual mammogram, MRI, and examination) -OC (biannual blood test, chemistry, transvaginal ultrasound)	A cohort of female *BRCA1* and *BRCA2* mutation carriers aged 35 years who had no cancer diagnosis at baseline Modelling study (Markov) Source of baseline data: A cohort study Source of effectiveness data: Various published studies including case-control and cohort studies Source of resource use data: Receipts, fees and medicine charges in Japan at St. Luke's International Hospital and Keio University Hospital Source of unit cost data: Unclear	Costs: Risk-reducing surgery, breast / ovarian cancer operation, breast / ovarian cancer adjuvant chemotherapy, ovarian and breast cancer screening (mammogram, magnetic resonance imaging, examination, blood test, chemistry, transvaginal ultrasound, computerized tomography scan), adverse event management, progression (chemotherapy, scans, palliative care) Mean cost per participant over 35 years: BRCA1 IS from 35 years: ¥6,119,067 RRBM at age 35, RRBSO at age 45: ¥5,333,801 IS from age 35, RRBSO at age 45: ¥5,803,532 RRBM at age 35: ¥6,185,091 BRCA2 IS from age 35: ¥4,719,326 RRBM at age 35: ¥3,744,163 RRBM at age 35, RRBSO at age 45: ¥4,245,410	For *BRCA1*: RRBM at age 35, RRBSO at age 45 was dominant For *BRCA2*: RRBM at age 35 was dominant Probability of being cost-effective: NR Subgroup analysis: NR Sensitivity analysis: Findings robust to model inputs, including probabilities and costs. However, using lower values for some utilities for preventative surgical procedures resulted in changes in results that favoured IS, but results were not reported.	Perspective: Healthcare payer Currency: Japanese Yen (¥) Cost year: 2016 Time horizon: 35 years Discounting: 2% but unclear if applied to both costs and QALYs Applicability: Partially Limitations: Potentially serious

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			IS from age 35, RRBSO at age 45: ¥5,329,849 The primary measure of outcome: QALYs (utility weights from various published sources) Mean QALYs per participant over 35 years: BRCA1 IS from age 35: 16.57 RRBM at age 35, RRBSO at age 45: 18.06 IS from age 35, RRBSO at age 45: 18.00 RRBM at age 35: 17.61 BRCA2 IS from age 35: 19.29 RRBM at age 35: 21.11 RRBM at age 35, RRBSO at age 45: 20.20 IS from age 35, RRBSO at age 45: 19.94		

Abbreviations: BC: Breast cancer, CP: Chemoprevention, CT: Computerized tomography, EQ-5D: The EuroQol-5 Dimension questionnaire, ICER: Incremental cost-effectiveness ratio, IS: Intensified surveillance, MRI: Magnetic resonance imaging, NR: Not reported, OC: Ovarian cancer, RRBM: Risk reducing bilateral mastectomy, RRBO: Risk reducing bilateral oophorectomy, RRBS: Risk reducing bilateral salpingectomy, RRBSO: Risk reducing bilateral salpingo-oophorectomy, QALY: Quality adjusted life year, RCT: Randomised controlled trial, WTP: Willingness-to-pay

Table 14: Economic evidence tables for risk thresholds for risk-reducing surgeries for ovarian cancer prevention

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Manchanda 2016 UK Cost-utility analysis Source of funding: The National Institute for Health Research University College London Hospitals Biomedical Research Centre	Intervention Risk-reducing salpingo-oophorectomy (RRSO) at different lifetime risks of developing ovarian cancer Comparator No RRSO	Pre-menopausal women >40 years with varying lifetime ovarian cancer risk levels: 2%, 4%, 5%, 6%, 8% and 10%. Modelling study (Decision analysis model) Source of baseline data: Population-based study Source of effectiveness data: Cohort studies Source of resource use data: National guidance and assumptions Source of unit cost data: National sources (NHS reference costs, BNF)	Costs: RSSO, HRT, osteoprotection, diagnosis, treatment and follow-up of ovarian and breast cancers, terminal care, breast cancer screening, coronary heart disease Mean costs per participant: 10% lifetime OC risk No RRSO: £2,904 RRSO: £4,434 Difference: £1,530 8% lifetime OC risk No RRSO: £2,637 RRSO: £4,418 Difference: £3,1781 6% lifetime OC risk No RRSO: £2,369 RRSO: £4,402 Difference: £2,033 5% lifetime OC risk No RRSO: £2,236 RRSO: £4,394 Difference: £2,159	ICERs: £5,031 - 10% lifetime OC risk £7,370 - 8% lifetime OC risk £11,337 - 6% lifetime OC risk £14,573 - 5% lifetime OC risk £19,536 - 4% lifetime OC risk £46,480 - 2% lifetime OC risk Probability of being cost-effective at £20k/QALY threshold: 98% - 10% lifetime OC risk 91% - 8% lifetime OC risk 72% - 6% lifetime OC risk 60% - 5% lifetime OC risk 46% - 4% lifetime OC risk 23% - 2% lifetime OC risk Subgroup analysis: NR Sensitivity analysis: Generally, the influence of various parameters on cost-effectiveness fell with a rise in ovarian cancer risk. Model results were not sensitive to various risk probabilities, costs of surgical prevention or treatment	Perspective: UK's NHS Currency: UK£ Cost year: 2012 Time horizon: Lifetime Discounting: 3.5% for costs and outcomes Applicability: Directly Limitations: Minor Other comments:

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			4% lifetime OC risk No RRSO: £2,102 RRSO: £4,836 Difference: £2,284 2% lifetime OC risk No RRSO: £1,834 RRSO: £4,371 Difference: £2,536 The primary measure of outcome: QALYs (with health-related quality of life scores from various published studies with some valuations using the time-trade-off method) Mean QALYs per participant: 10% lifetime OC risk No RRSO: 21.1 RRSO: 21.36 Difference: 0.30 8% lifetime OC risk No RRSO: 21.1 RRSO: 21.37 Difference: 0.2 6% lifetime OC risk	of ovarian and breast cancer and cardiovascular disease. The results were sensitive to - RRSO utility weight. For example, the RRSO was not cost-effective for the lowermost limit (not reported) of the RRSO utility weight (base case: 0.95) at the 4% OC risk threshold and was only cost-effective at the upper NICE cost-effectiveness threshold of £30k per QALY at the 8.5% risk threshold, with an ICER of £28,532 per QALY. - HRT compliance rate. For example, if this rate was beyond the limits of the analysis (base case: 0.80, 95% CI: [0.76–0.83]), the ovarian cancer risk threshold for cost-effectiveness would need to rise for RRSO to remain cost-effective, that is, if women do not take HRT after RRSO then at ovarian cancer risk of 8.2%, the ICER of RRSO was £29,071 per QALY. In a scenario analysis where the model assumed no reduction in breast cancer risk, RRSO at age ≥40 years was not cost-effective at 4% ovarian cancer risk. RRSO became cost-effective at an upper	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			No RRSO: 21.2 RRSO: 21.37 Difference: 0.2 5% lifetime OC risk No RRSO: 21.22 RRSO: 21.37 Difference: 0.15 4% lifetime OC risk No RRSO: 21.3 RRSO: 21.37 Difference: 0.12 2% lifetime OC risk No RRSO: 21.3 RRSO: 21.38 Difference: 0.06	NICE cost-effectiveness threshold of £30k per QALY at a 6% ovarian cancer risk, with an ICER of £27,212 per QALY gained.	
Manchanda 2015 UK Cost-utility analysis Source of funding: The National Institute for	Intervention Risk-reducing salpingo-oophorectomy (RRSO) at different lifetime risks of developing ovarian cancer Comparator No RRSO	Low/intermediate risk postmenopausal women ≥ 50 years with varying lifetime ovarian cancer risk levels: 2%, 4%, 5%, 6%, 8% and 10%. Modelling study (A decision-analytic model) Source of baseline data: National Statistics	Costs: Risk-reducing surgery, ovarian cancer diagnosis (pelvic examinations, ultrasound scans, CA125 tests, CT scans, percutaneous biopsies and peritoneal cytology) and treatment (complex major procedure, administration of chemotherapy, consultant visits, CT scans, CA125 tests), terminal care costs, coronary heart disease, death	ICERs: £1,864 - 10% lifetime OC risk £4,584 - 8% lifetime OC risk £9,958 - 6% lifetime OC risk £15,247 - 5% lifetime OC risk £25,577 - 4% lifetime OC risk £674,656 - 2% lifetime OC risk Probability of being cost-effective at £20k/QALY threshold: 94% - 10% lifetime OC risk	Perspective: UK's NHS Currency: UK £ Cost year: 2012 prices Time horizon: Lifetime Discounting: 3.5% for costs and outcomes Applicability: Directly

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Health Research University College London Hospitals Biomedical Research Centre		Source of effectiveness data: A cohort study Source of resource use data: National Guidance and assumptions Source of unit cost data: National resources (NHS Reference costs, National Audit office)	Mean cost per participant: 10% lifetime OC risk No RRSO: £1,866 RRSO: £2,277 Difference: £412 8% lifetime OC risk No RRSO: £1,493 RRSO: £2,255 Difference: £762 6% lifetime OC risk No RRSO: £1,119 RRSO: £2,233 Difference: £1,113 5% lifetime OC risk No RRSO: £933 RRSO: £2,221 Difference: £1,288 4% lifetime OC risk No RRSO: £746 RRSO: £2,210 Difference: £1,464 2% lifetime OC risk No RRSO: £373	91% - 8% lifetime OC risk 84% - 6% lifetime OC risk 80% - 5% lifetime OC risk 67% - 4% lifetime OC risk At 2% lifetime OC risk the probability of RRSO being cost-effective was not reported Subgroup analysis: Sensitivity analysis: The results were not very sensitive to treatment costs of RRSO, ovarian cancer or cardiovascular events. Results were sensitive to: - Excess cardiovascular deaths at the 5% threshold but not that sensitive at the 6% and 8% thresholds - Utility scores for RRSO (base-case: 0.95), that is, the model was not cost-effective at the lowermost limit of the utility score for RRSO Generally, the impact of different variables on cost-effectiveness decreased as the ovarian cancer risk threshold increased.	Limitations: Minor Other comments:

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			RRSO: £2,188 Difference: £1,815 The primary measure of outcome: QALYs (with health-related quality of life scores from various published studies with some valuations using the time-trade-off method) Mean QALYs per participant: 10% lifetime OC risk No RRSO: 18.5 RRSO: 18.7 Difference: 0.22 8% lifetime OC risk No RRSO: 18.5 RRSO: 18.7 Difference: 0.17 6% lifetime OC risk No RRSO: 18.58 RRSO: 18.69 Difference: 0.11 5% lifetime OC risk No RRSO: 18.61 RRSO: 18.69 Difference: 0.08		

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			4% lifetime OC risk No RRSO: 18.6 RRSO: 18.7 Difference: 0.057 2% lifetime OC risk No RRSO: 18.7 RRSO: 18.7 Difference: 0.0		

Abbreviations: BNF: British National Formulary, HRT: Hormone replacement therapy, ICER: Incremental cost-effectiveness ratio, k: Thousand, NHS: National Health Service, NR: Not reported, OC: Ovarian cancer, QALY: Quality-adjusted life-year, RRSO: Risk-reducing salpingo-oophorectomy, UK United Kingdom

Appendix I Economic model

Economic model for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Excluded effectiveness studies

Table 15: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Altman, A.M.; Hui, J.Y.C.; Tuttle, T.M. (2018) Quality-of-life implications of risk-reducing cancer surgery. British Journal of Surgery 105(2): e121-e130	- Systematic review used as source of primary studies
Carr, C.E., Chambers, L., Jernigan, A.M. et al. (2021) Short- And long-term outcomes for single-port risk-reducing salpingo-oophorectomy with and without hysterectomy for women at risk for gynecologic cancer. International Journal of Gynecological Cancer 31(2): 215-221	- Comparator in study does not match that specified in this review protocol
Chae, Sumin, Kim, Eun-Kyu, Jang, Ye Rang et al. (2021) Effect of risk-reducing salpingo-oophorectomy on the quality of life in Korean BRCA mutation carriers. Asian journal of surgery 44(8): 1056-1062	- Included in Wei 2023 systematic review
Challberg, J, Ashcroft, L, Lalloo, F et al. (2011) 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 105(1): 22-7	- Included in Gaba systematic 2020 review
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	- Included in Gaba systematic 2020 review
Cheng, Aoshuang, Li, Lei, Wu, Ming et al. (2020) Pathological findings following risk-reducing salpingo-oophorectomy in BRCA mutation carriers: A systematic review and meta-analysis. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 46(1): 139-147	- Comparator in study does not match that specified in this review protocol
Cohen, J V, 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	- Included in Gaba 2020 systematic review
Cortesi, L., De Matteis, E., Toss, A. et al. (2017) Evaluation of Transvaginal Ultrasound plus CA-125 Measurement and Prophylactic Salpingo-Oophorectomy in Women at Different Risk Levels of Ovarian Cancer: The Modena Study Group Cohort Study. Oncology (Switzerland) 93(6): 377-386	- Non-randomised study which does not adjust for differences between groups at baseline

Study	Reason for exclusion
Darelius, A, Lycke, M, Kindblom, J M et al. (2017) Efficacy of salpingectomy at hysterectomy to reduce the risk of epithelial ovarian cancer: a systematic review. BJOG: an international journal of obstetrics and gynaecology 124(6): 880-889	- Systematic review used as source of primary studies
do Valle, H.A., Kaur, P., Kwon, J.S. et al. (2021) Risk of cardiovascular disease among women carrying BRCA mutations after risk-reducing bilateral salpingo-oophorectomy: A population-based study. Gynecologic Oncology 162(3): 707-714	- Comparator in study does not match that specified in this review protocol
Domchek, Susan M and Rebbeck, Timothy R (2010) Preventive surgery is associated with reduced cancer risk and mortality in women with BRCA1 and BRCA2 mutations. LDI issue brief 16(2): 1-4	- Study design not relevant to this review protocol
Eleje, GU, Eke, AC, Ezebialu, IU et al. (2018) Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Escobar, P.F., Starks, D.C., Fader, A.N. et al. (2010) Single-port risk-reducing salpingo-oophorectomy with and without hysterectomy: Surgical outcomes and learning curve analysis. Gynecologic Oncology 119(1): 43-47	- Comparator in study does not match that specified in this review protocol
Fakkert, I.E., Abma, E.M., Westrik, I.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 51(3): 400-408	- Included in Gaba 2020 review
Fakkert, I.E., Van Der Veer, E., Abma, E.M. et al. (2017) Elevated bone turnover markers after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer. PLoS ONE 12(1): e0169673	- Included in Gaba 2020 review
Fang, Carolyn Y, Cherry, Carol, Devarajan, Karthik et al. (2009) A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. Gynecologic oncology 112(3): 594-600	- Included in Wei 2023 review
Finch, Amy, Metcalfe, Kelly A, Chiang, Jaclyn et al. (2013) The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psycho-oncology 22(1): 212-9	- Comparator in study does not match that specified in this review protocol
Finch, Amy, Shaw, Patricia, Rosen, Barry et al. (2006) Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecologic oncology 100(1): 58-64	- Secondary publication of an included study that does not provide any additional relevant information *Partial overlap with Finch et al. 2006*
Garcia, C., Lyon, L., Conell, C. et al. (2015) Osteoporosis risk and management in BRCA1 and BRCA2 carriers who undergo risk-reducing	- Included in Gaba 2020 review

Study	Reason for exclusion
salpingo-oophorectomy. Gynecologic Oncology 138(3): 723-726	
Gronwald, J., Lubinski, J., Huzarski, T. et al. (2019) A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy. Gynecologic Oncology 155(2): 270-274	- Non-randomised study which does not adjust for differences between groups at baseline
Harmsen, Marline G, IntHout, Joanna, Arts-de Jong, Marieke et al. (2016) Salpingectomy With Delayed Oophorectomy in BRCA1/2 Mutation Carriers: Estimating Ovarian Cancer Risk. Obstetrics and gynecology 127(6): 1054-1063	- Study design not relevant to this review protocol
Heemskerk-Gerritsen, B.A.M., Seynaeve, C., Van Asperen, C.J. et al. (2015) Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: Revisiting the evidence for risk reduction. Journal of the National Cancer Institute 107(5)	- Outcomes in study do not match those specified in this review protocol
Huo, Xiaqin, Yao, Liang, Han, Xue et al. (2019) Hysterectomy and risk of ovarian cancer: a systematic review and meta-analysis. Archives of gynecology and obstetrics 299(3): 599-607	- Population not relevant to this review protocol
Islam, R.M., Davis, S.R., Bell, R.J. et al. (2021) A prospective controlled study of sexual function and sexually related personal distress up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. Menopause 28(7):748-755	- Comparator in study does not match that specified in this review protocol
Jeffers, L., Reid, J., Fitzsimons, D. et al. (2019) Interventions to improve psychosocial well-being in female BRCA-mutation carriers following risk-reducing surgery. Cochrane Database of Systematic Reviews: cd012894	- Intervention in study does not match that specified in this review protocol
Jiang, H., Robinson, D.L., Lee, P.V.S et al. (2021) Loss of bone density and bone strength following premenopausal risk-reducing bilateral salpingo-oophorectomy: a prospective controlled study (WHAM Study). Jan;32(1):101-112	- Comparator in study does not match that specified in this review protocol
Kauff, N.D., Satagopan, J.M., Robson, M.E. et al. (2002) Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. New England Journal of Medicine 346(21): 1609-1615	- Secondary publication of an included study that does not provide any additional relevant information *Population overlap with Kauff 2008*
Kotsopoulos, J., Gronwald, J., Lubinski, J. et al. (2020) Does preventive oophorectomy increase the risk of depression in BRCA mutation carriers? Menopause 27(2): 156-161	- Outcomes in study do not match those specified in this review protocol
Kotsopoulos, J., Lubinski, J., Gronwald, J. et al. (2022) Bilateral Oophorectomy and the Risk of Breast Cancer in BRCA1 Mutation Carriers: A Reappraisal. Cancer Epidemiology Biomarkers and Prevention 31(7): 1351-1358	- Outcomes in study do not match those specified in this review protocol
Kramer, J.L., Velazquez, I.A., Chen, B.E. et al. (2005) Prophylactic oophorectomy reduces	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. Journal of Clinical Oncology 23(34): 8629-8635	
Kwon, J.S., Tinker, A., Pansegrau, G. et al. (2013) Prophylactic Salpingectomy and Delayed Oophorectomy as an Alternative for BRCA Mutation Carriers. Obstetrics and Gynecology 121(1): 14-24	- Study design not relevant to this review protocol
Le, A.-L., Xie, R., Liao, Y. et al. (2022) Outcomes of Concurrent Prophylactic Mastectomy and Oophorectomy, Compared to Mastectomy and Hysterectomy, in Hereditary Breast and Gynecologic Cancer: A National Surgical Quality Improvement Program Database Analysis. Journal of Gynecologic Surgery 38(2): 148-152	- Comparator in study does not match that specified in this review protocol
Mavaddat, N.; Peock, S.; Frost, D. et al. (2012) Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. Journal of the National Cancer Institute; 2013; vol. 105 (no. 11); 812-822	- Outcomes in study do not match those specified in this review protocol
Li, X., You, R., Wang, X. et al. (2016) Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: A meta-analysis and systematic review. Clinical Cancer Research 22(15): 3971-3981	- Systematic review used as source of primary studies
Lim, H., Kim, S.I., Hyun, S. et al. (2021) Uptake rate of risk-reducing salpingo-oophorectomy and surgical outcomes of female germline brca1/2 mutation carriers: A retrospective cohort study. Yonsei Medical Journal 62(12): 1090-1097	- Outcomes in study do not match those specified in this review protocol
Loizzi, V., Cicinelli, E., Vecchio, V.D. et al. (2022) A prospective multicentric study of risk-reducing salpingo-oophorectomy in BRCA mutation patients. Acta Biomedica 93(4): e2022051	- Outcomes in study do not match those specified in this review protocol
Ludwig, K.K., Neuner, J., Butler, A. et al. (2016) Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. American Journal of Surgery 212(4): 660-669	- Systematic review used as source of primary studies
Madalinska, J.E., Hollenstein, J., Bleiker, E. et al. (2005) Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. Journal of Clinical Oncology 23(28): 6890-6898	- Included in Wei 2023 systematic review
Mai PL, Huang HQ, Wenzel LB et al. (2020) Prospective follow-up of quality of life for participants undergoing risk-reducing salpingo-oophorectomy or ovarian cancer screening in GOG-0199: An NRG Oncology/GOG study. Gynecologic oncology 156(1): 131-139	- Included in Wei 2023 systematic review
Mai, P.L., Miller, A., Gail, M.H. et al. (2020) Risk-reducing salpingo-oophorectomy and breast	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
cancer risk reduction in the gynecologic oncology group protocol-0199 (GOG-0199). JNCI Cancer Spectrum 4(1): pkz075	
Manchanda, R., Abdelraheim, A., Johnson, M. et al. (2011) Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG: An International Journal of Obstetrics and Gynaecology 118(7): 814-824	- Comparator in study does not match that specified in this review protocol
Manchanda, R., Burnell, M., Abdelraheim, A. et al. (2012) Factors influencing uptake and timing of risk reducing salpingo- oophorectomy in women at risk of familial ovarian cancer: A competing risk time to event analysis. BJOG: An International Journal of Obstetrics and Gynaecology 119(5): 527-536	- Outcomes in study do not match those specified in this review protocol
Marchetti, C., De Felice, F., Palaia, I. et al. (2014) Risk-reducing salpingo-oophorectomy: A meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Women's Health 14(1): 150	- Systematic review used as source of primary studies
Meeuwissen, P.A.M., Seynaeve, C., Brekelmans, C.T.M. et al. (2005) Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. Gynecologic Oncology 97(2): 476-482	- Outcomes in study do not match those specified in this review protocol
Michelsen, T.M.; Dorum, A.; Dahl, A.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): 128-133	- Included in Gaba 2020 systematic review
Michelsen, T.M., Pripp, A.H., Tonstad, S. et al. (2009) Metabolic syndrome after risk-reducing salpingo-oophorectomy in women at high risk for hereditary breast ovarian cancer: A controlled observational study. European Journal of Cancer 45(1): 82-89	- Included in Gaba 2020 systematic review
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	- Included in Gaba 2020 systematic review
Nelson, H.D., Pappas, M., Zakher, B. et al. (2014) Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: A systematic review to update the U.S. preventive services task force recommendation. Annals of Internal Medicine 160(4): 255-266	- Systematic review used as source of primary studies
Obermair, A., Youlden, D.R., Baade, P.D. et al. (2014) The impact of risk-reducing hysterectomy and bilateral salpingo- oophorectomy on survival in patients with a history of breast cancer - A	- Population not relevant to this review protocol

Study	Reason for exclusion
population-based data linkage study. International Journal of Cancer 134(9): 2211-2222	
Ofshteyn, A., Jiang, B., Bingmer, K. et al. (2020) Prophylactic Gynecologic Surgery at Time of Colectomy Benefits Women with Lynch Syndrome and Colon Cancer: A Markov Cost-Effectiveness Analysis. Diseases of the Colon and Rectum 63(10): 1393-1402	- Outcomes in study do not match those specified in this review protocol
Olivier, R.I., Van Beurden, M., Lubsen, M.A.C. et al. (2004) Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. British Journal of Cancer 90(8): 1492-1497	- Comparator in study does not match that specified in this review protocol
Olopade, Olufunmilayo I and Artioli, Grazia (2004) Efficacy of risk-reducing salpingo-oophorectomy in women with BRCA-1 and BRCA-2 mutations. The breast journal 10suppl1: 5-9	- Duplicate publication
Piver (1996) Prophylactic Oophorectomy: Reducing the U.S. Death Rate from Epithelial Ovarian Cancer. A Continuing Debate. The oncologist 1(5): 326-330	- Outcomes in study do not match those specified in this review protocol
Powell, C.B., Alabaster, A., Le, A. et al. (2020) Sexual function, menopausal symptoms, depression and cancer worry in women with BRCA mutations. Psycho-Oncology 29(2): 331-338	- Included in Wei 2023 systematic review
Powell, CB, Chen, LM, McLennan, J et al. (2011) Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. International journal of gynecological cancer 21(5): 846-851	- Outcomes in study do not match those specified in this review protocol
Razzaboni, E., Tazzioli, G., Andreotti, A. et al. (2012) Prophylactic surgery to reduce the risk of developing breast cancer: Issues and clinical implications. Current Women's Health Reviews 8(1): 94-103	- Systematic review used as source of primary studies
Rebbeck, T.R.; Kauff, N.D.; Domchek, S.M. (2009) Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. Journal of the National Cancer Institute 101(2): 80-87	- Systematic review used as source of primary studies
Rebbeck, Timothy R, Friebel, Tara, Lynch, Henry T et al. (2004) Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 22(6): 1055-62	- Outcomes in study do not match those specified in this review protocol
Rebbeck, TR, Levin, AM, Eisen, A et al. (1999) Breast cancer risk after bilateral prophylactic	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
oophorectomy in BRCA1 mutation carriers. Journal of the National Cancer Institute 91(17): 1475-1479	
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	- Outcomes in study do not match those specified in this review protocol
Rutter, J.L., Wacholder, S., Chetrit, A. et al. (2003) Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: An Israeli population-based case-control study. Journal of the National Cancer Institute 95(14): 1072-1078	- Population not relevant to this review protocol
Salhab, M.; Bismohun, S.; Mokbel, K. (2010) Risk-reducing strategies for women carrying brca1/2 mutations with a focus on prophylactic surgery. BMC Women's Health 10: 28	- Study design not relevant to this review protocol
Schmeler, Kathleen M, Lynch, Henry T, Chen, Lee-may et al. (2006) Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. The New England journal of medicine 354(3): 261-9	- Comparator in study does not match that specified in this review protocol
Schmeler, KM, Sun, CC, Bodurka, DC et al. (2006) Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. Obstetrics and gynecology 108(3pt1): 515-520	- Outcomes in study do not match those specified in this review protocol
Schrag, D, Kuntz, K M, Garber, J E et al. (1997) Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. The New England journal of medicine 336(20): 1465-71	- Outcomes in study do not match those specified in this review protocol
Steenbeek, Miranda P, van Bommel, Majke H D, Bulten, Johan et al. (2022) Risk of Peritoneal Carcinomatosis After Risk-Reducing Salpingo-Oophorectomy: A Systematic Review and Individual Patient Data Meta-Analysis. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 40(17): 1879-1891	- Comparator in study does not match that specified in this review protocol
Struewing JP, Watson P, Easton DF et al. (1995) Prophylactic oophorectomy in inherited breast/ovarian cancer families. Journal of the National Cancer Institute. Monographs: 33-35	- Outcomes in study do not match those specified in this review protocol
Stuursma, A., van Driel, C.M.G., Wessels, N.J. et al. (2018) Severity and duration of menopausal symptoms after risk-reducing salpingo-oophorectomy. Maturitas 111: 69-76	- Comparator in study does not match that specified in this review protocol
Tiller, K., Meiser, B., Butow, P. et al. (2002) Psychological impact of prophylactic oophorectomy in women at increased risk of developing ovarian cancer: A prospective study. Gynecologic Oncology 86(2): 212-219	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
Tschernichovsky, R. and Goodman, A. (2017) Risk-reducing strategies for ovarian cancer in BRCA mutation carriers: A balancing act. Oncologist 22(4): 450-459	- Systematic review used as source of primary studies
Tucker, P.E. and Cohen, P.A. (2017) Sexuality and risk-reducing salpingo-oophorectomy. International Journal of Gynecological Cancer 27(4): 847-852	- Systematic review used as source of primary studies
Tzortzatos, G., Andersson, E., Soller, M. et al. (2015) The gynecological surveillance of women with Lynch syndrome in Sweden. Gynecologic Oncology 138(3): 717-722	- Outcomes in study do not match those specified in this review protocol
van Bommel, M.H.D., de Jong, M.A., Steenbeek, M.P. et al. (2021) No signs of subclinical atherosclerosis after risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers. Journal of Cardiology 77(6): 570-575	- Comparator in study does not match that specified in this review protocol
van Lieshout, LAM, Steenbeek, MP, De Hullu, JA et al. (2019) Hysterectomy with opportunistic salpingectomy versus hysterectomy alone. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol

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2 **Excluded economic studies**

3 See Supplement 2 for the list of excluded studies across all reviews.

Appendix K Research recommendations – full details

Research recommendations for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

No research recommendations were made for this review question.

Appendix L Testimony from expert witness

Testimony from expert witness for review question: How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

Section A: Developer to complete	
Name:	Xia Wei
Role:	Academic
Institution/Organisation (where applicable):	Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine Centre for Prevention, Detection & Diagnosis, Wolfson Institute of Population Health, CRUK Barts Cancer Centre, Queen Mary University of London
Guideline title:	**Ovarian cancer: identifying and managing familial and genetic risk**
Guideline Committee:	Guideline committee meeting 11 (May 2023)
Subject of expert testimony:	Ovarian cancer risk-reducing surgery cost-effectiveness
Evidence gaps or uncertainties:	How effective is risk-reducing surgery for women at increased risk of familial ovarian cancer (also considering risk threshold, age and extent and types of surgery)?

One of the key areas of interest identified during the scoping phase for this guideline was the effectiveness of risk-reducing surgery for women at increased risk of familial ovarian cancer. Not all women opt for risk-reducing surgery as they may wish to preserve their fertility, choose to avoid surgery or are not well enough to undergo surgery. The proposed benefit of risk-reducing surgery for ovarian cancer in those with familial cancer risk is to reduce the risk of developing ovarian cancer and improve survival outcomes.

The review question addressing risk-reducing surgery found limited non-UK economic evidence, which generally indicated that risk-reducing surgery was cost-effective in people with BRCA pathogenic variants. However, these studies evaluated various risk-reducing surgery strategies and initiation ages, making it difficult for the committee to draw firm conclusions from this non-UK evidence.

Furthermore, all economic studies assessed the cost-effectiveness of risk-reducing surgery in women with *BRCA* pathogenic variants. The committee noted that ovarian cancer incidence varies by pathogenic variant and they wanted to understand how this might impact the cost-effectiveness of risk-reducing surgery in women with an

increased ovarian cancer risk due to pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D* and *BRIP1* cancer susceptibility genes. Additionally, given that ovarian cancer incidence varies by age, the committee was also interested in finding out the optimal age for initiating risk-reducing surgery in women carrying these susceptibility genes.

The committee identified this area as one of key priorities for economic modelling. However, the committee identified an ongoing economic evaluation that modelled the cost-effectiveness of risk-reducing surgery in women with increased ovarian cancer risk due to pathogenic variants in *BRCA1/BRCA2/PALB2/RAD51C/RAD51D/BRIP1* cancer susceptibility genes.

The technical team for this guideline, in collaboration with the committee, worked closely with the authors of this economic analysis to ensure that model inputs, such as the effectiveness of risk-reducing surgery, aligned with the findings of the effectiveness review undertaken by the guideline's technical team. The committee also provided input on the model structure and other inputs to ensure their representation of current practice.

The expert testimony is in relation to this economic study.

Section B: Expert to complete

Summary testimony:

Women with pathogenic variants (PVs) in *BRCA1/BRCA2* cancer susceptibility genes (CSGs) have a high risk of ovarian cancer (OC) of around 44% in *BRCA1* and 17% in *BRCA2* till the age of 80 years. They are also associated with a 69-72% risk of breast cancer (BC). *RAD51C*, *RAD51D* and *BRIP1* CSGs are validated moderate OC CSGs, with OC risks of 11%, 13%, and 5.8% respectively. More recent data (unpublished, personal communication) suggest *BRIP1* may have an OC risk of around 9%. *RAD51C* and *RAD51D* are also associated with a moderate risk of BC of around 21% and 20% respectively. Additionally, *PALB2* has a moderate OC risk of ~5% but is also a high risk BC gene with BC risk of ~53%.

Risk-reducing salpingo-oophorectomy (RRSO) is the most clinically effective strategy for reducing OC risk and is now offered to *BRCA1*/*BRCA2*/*PALB2*/*RAD51C*/*RAD51D*/*BRIP1* PV carriers in clinical practice. Risk-reducing mastectomy (RRM) is the most effective option for reducing BC risk and is available for *BRCA1*, *BRCA2*, and *PALB2* PV carriers. Women at moderate/high BC risk may also opt for medical prevention with tamoxifen if premenopausal or anastrozole if post-menopausal. Additionally intensive breast cancer screening is available to high risk women (*BRCA1*/*BRCA2*/*PALB2*) and moderate risk screening to women with PVs in *RAD51C* or *RAD51D* CSGs.

Cost-effectiveness of risk-reducing surgery in individual OC CSGs (*BRCA1*/*BRCA2*/*PALB2*/*RAD51C*/*RAD51D*/*BRIP1*) has not previously been undertaken or reported in the UK population.

We have undertaken Markov modelling to evaluate cost-effectiveness of RRSO and where relevant RRM (for high risk CSGs) compared to the base case of no surgery (but inclusive of guideline recommended screening for BC and medical prevention for BC in the above CSGs which may also be high or moderate risk of BC). We have also undertaken comprehensive sensitivity analysis including one-way sensitivity

analysis and probabilistic sensitivity analysis to evaluate the robustness of the outcomes.

The base case results are tabulated in appendix L-1.

For *BRCA1*, *BRCA2* and *PALB2*, compared with enhanced BC screening and medical prevention alone, RRM and RRSO is cost-effective (cost-saving in *BRCA1*), providing the maximum life years gained (LYG) and quality-adjusted life years (QALYs) as well as the largest net monetary benefit (NMB). While RRSO alone (with enhanced BC screening and medical prevention but no RRM) is also cost-effective (cost-saving in *BRCA1*/*BRCA2*), but the LYG, QALY and NMB is slightly lower compared to undergoing both RRSO and RRM.

For *BRCA1*/*BRCA2*, combined RRM (30 years) and RRSO (35 years) appears to be the optimal strategy and can prevent an additional 536/387 BC/OC cases and 56/246 BC/OC deaths per 1,000 *BRCA1* PV-carriers; or an additional 565/163 BC/OC cases and 69/103 BC/OC deaths per 1,000 *BRCA2* PV-carriers. For *PALB2*, combined RRM (40 years) and RRSO (45 years) is the optimal strategy and can prevent an additional 422/42 BC/OC cases and 102/28 BC/OC deaths per 1,000 *PALB2* PV-carriers.

For *RAD51C* and *RAD51D*, RRSO is cost-effective compared to moderate risk BC screening and medical prevention alone. For *BRIP1*, RRSO is cost-effective compared to no intervention. RRSO (45 years) is the optimal strategy for *RAD51C*, *RAD51D*, and *BRIP1*, which can prevent an additional 6 BC deaths and 102/64 OC cases/deaths per 1,000 *RAD51C* PV-carriers; an additional 5 BC deaths and 118/76 OC cases/deaths per 1,000 *RAD51D* PV-carriers; an additional 55/37 OC cases/deaths per 1,000 *BRIP1* PV-carriers. More recent data indicate potentially higher penetrance of around 9% lifetime OC risk for *BRIP1* than the estimates in our base case of 5.8%. This will further increase cost-effectiveness and number of cancers prevented for *BRIP1*.

The one-way sensitivity analysis indicated that model parameters including BC/OC incidence, costs of surgical preventions, BC/OC treatment costs, utility scores, and transition probabilities had little influence on the cost-effectiveness of RRM, RRSO, or combined RRM and RRSO for *BRCA1*/*BRCA2*/*PALB2* and the cost-effectiveness of RRSO for *RAD51C*/*RAD51D*/*BRIP1*. Despite varying parameters at extremes of their confidence intervals/ranges, the ICERs of risk-reducing surgeries were lower than the willingness-to-pay (WTP) threshold of £20,000/QALY.

Probabilistic sensitivity analysis showed that at £20,000/QALY WTP threshold, RRSO and RRM combined is the most cost-effective strategy in 95.9% simulations for *BRCA1*, 88.5% simulations for *BRCA2*, 84.7% simulations for *PALB2*. RRSO at age 45 years was the optimal cost-effective strategy for *RAD51C*/*RAD51D*/*BRIP1* in 100% simulations.

Taken together, combined RRM at age 30 years and RRSO at age 35 years was the most cost-effective prevention strategy for *BRCA1*/*BRCA2*/*PALB2*, which prevented the highest number of BC/OC cases and deaths. RRSO at age 45 years was cost-effective for *RAD51C*/*RAD51D*/*BRIP1*. These results were robust in one-way and probabilistic sensitivity analyses. Surgery at later ages was still cost-effective for these CSGs, but this would reduce the life years and QALYs gained.

References:

Wei X, Oxley S, Sideris M, Kalra A, Sun L, Yang L, Legood R, Manchanda R. Cost-Effectiveness of Risk-Reducing Surgery for Breast and Ovarian Cancer Prevention: A Systematic Review. Cancers. 2022; 14(24):6117. https://doi.org/10.3390/cancers14246117

Disclosure:

None

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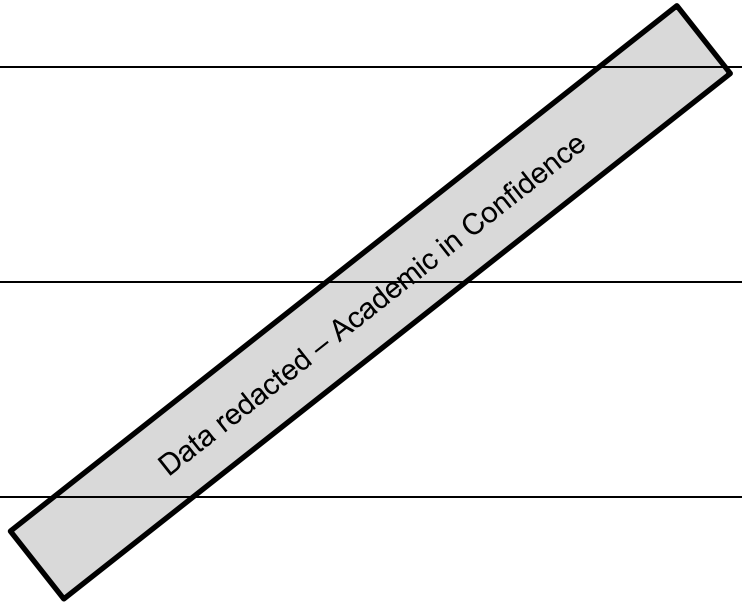
L.1 Lifetime health-effects, costs, ICER and NMB of risk-reducing surgery by cancer susceptibility gene type

Strategy	BC incidence	BC death	OC incidence	OC death	Life years	QALYs	Costs (£)	ICER (£/QALY)	NMB# (£)	INMB (£)
BRCA1										
High-risk BC screening and tamoxifen from age 30*										
RRM at age 30										
RRSO at age 35 with high-risk BC screening and tamoxifen from age 30										
RRM at age 30 with RRSO at age 35										
BRCA2										
High-risk BC screening and tamoxifen from age 30*										
RRSO at age 35 with high-risk BC screening and tamoxifen from age 30										
RRM at age 30										
RRM at age 30 with RRSO at age 35										
PALB2										
High-risk BC screening and tamoxifen from age 30*										
RRM at age 40										
RRSO at age 45 with high-risk BC screening and tamoxifen from age 30										
RRM at age 40 with RRSO at age 45										
RAD51C										
Moderate-risk BC screening and tamoxifen from age 40*										
RRSO at age 45 with moderate-risk BC screening and tamoxifen from age 40										
RAD51D										
Moderate-risk BC screening and tamoxifen from age 40*										
RRSO at age 45 with moderate-risk BC screening and tamoxifen from age 40										
BRIP1										
No surgery*										



RRSO at age 45	/	/	0.71%	0.31%	25.12	21.06	3,571	2,326	417,542	15,583

*Reference case. #The willingness to pay threshold used for NMB calculation was £20,000. BC, breast cancer; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; NMB, net monetary benefit; OC, ovarian cancer; QALY, quality-adjusted life-year; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.