Quality of life after risk-reducing surgery for breast and ovarian cancer prevention: a systematic review and meta-analysis

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OBJECTIVE: This study aimed to assess the impact of risk-reducing surgery for breast cancer and ovarian cancer prevention on quality of life. We considered risk-reducing mastectomy, risk-reducing salpingo-oophorectomy, and risk-reducing early salpingectomy and delayed oophorectomy.

DATA SOURCES: We followed a prospective protocol (International Prospective Register of Systematic Reviews: CRD42022319782) and searched MEDLINE, Embase, PubMed, and Cochrane Library from inception to February 2023.

STUDY ELIGIBILITY CRITERIA: We followed a PICOS (population, intervention, comparison, outcome, and study design) framework. The population included women at increased risk of breast cancer or ovarian cancer. We focused on studies reporting quality of life outcomes (health-related quality of life, sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety, or depression) after risk-reducing surgery, including risk-reducing mastectomy for breast cancer and risk-reducing salpingo-oophorectomy or risk-reducing early salpingectomy and delayed oophorectomy for ovarian cancer.

METHODS: We used the Methodological Index for Non-Randomized Studies (MINORS) for study appraisal. Qualitative synthesis and fixed-effects meta-analysis were performed.

RESULTS: A total of 34 studies were included (risk-reducing mastectomy: 16 studies; risk-reducing salpingo-oophorectomy: 19 studies; risk-reducing early salpingectomy and delayed oophorectomy: 2 studies). Health-related quality of life was unchanged or improved in 13 of 15 studies after risk-reducing mastectomy (N=986) and 10 of 16 studies after risk-reducing salpingo-oophorectomy (N=1617), despite short-term deficits (N=96 after risk-reducing mastectomy and N=459 after risk-reducing salpingo-oophorectomy). Sexual function (using the Sexual Activity Questionnaire) was affected in 13 of 16 studies (N=1400) after risk-reducing salpingo-oophorectomy in terms of decreased sexual pleasure (−1.21 [−1.53 to −0.89]; N=3070) and increased sexual discomfort (1.12 [0.93−1.31]; N=1400). Hormone replacement therapy after premenopausal risk-reducing salpingo-oophorectomy was associated with an increase (1.16 [0.17−2.15]; N=291) in sexual pleasure and a decrease (−1.20 [−1.75 to −0.65]; N=157) in sexual discomfort. Sexual function was affected in 4 of 13 studies (N=147) after risk-reducing mastectomy, but stable in 9 of 13 studies (N=799). Body image was unaffected in 7 of 13 studies (N=605) after risk-reducing mastectomy, whereas 6 of 13 studies (N=391) reported worsening. Increased menopause symptoms were reported in 12 of 13 studies (N=1759) after risk-reducing salpingo-oophorectomy with a reduction (−1.96 [−2.81 to −1.10]; N=1745) in the Functional Assessment of Cancer Therapy - Endocrine Symptoms. Cancer-related distress was unchanged or decreased in 5 of 5 studies after risk-reducing mastectomy (N=365) and 8 of 10 studies after risk-reducing salpingo-oophorectomy (N=1223). Risk-reducing early salpingectomy and delayed oophorectomy (2 studies, N=413) led to better sexual function and menopause-specific quality of life.

CONCLUSION: Risk-reducing surgery may be associated with quality of life outcomes. Risk-reducing mastectomy and risk-reducing salpingo-oophorectomy reduce cancer-related distress, and do not affect health-related quality of life. Women and clinicians should be aware of body image problems after risk-reducing mastectomy, and of sexual dysfunction and menopause symptoms after risk-reducing salpingo-oophorectomy. Risk-reducing early salpingectomy and delayed oophorectomy may be a promising alternative to mitigate quality of life−related risks of risk-reducing salpingo-oophorectomy.

Key words: breast cancer, meta-analysis, ovarian cancer, quality of life, risk-reducing surgery

Introduction

Approximately 4% of breast cancer (BC)[1,2] and 15% to 20% of ovarian cancer (OC)[3,4] are caused by known pathogenic variants (PVs) in a variety of cancer susceptibility genes (CSGs). Common BC/OC CSGs include *BRCA1* and *BRCA2*, associated with approximately 69% to 72% (59%−79%) and 67% to 69% (51%−80%) of lifetime BC-risk, and 44% to 48% (36%−65%) and 17% to 30% (11%−46%) of lifetime OC-risk, respectively,[5,6] as opposed to the population lifetime risk of 12.9% to 15% for BC and 1.3% to 2% for OC.[7,8] Increasing awareness and acceptability of genetic testing, falling costs, changes in clinical practice including increasing genetic testing at cancer diagnosis,[3,9] and recent calls for population testing[10−13] are leading to ever increasing identification of unaffected women at increased BC/OC risk. In addition, complex risk algorithms incorporating genetic (CSGs and polygenic risk score) along with

AJOG at a Glance

Why was this study conducted?

Evidence synthesis on quality-of-life (QoL) outcomes following risk-reducing mastectomy (RRM), risk-reducing salpingo-oophorectomy (RRSO), and risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) is needed for breast and ovarian cancer prevention decision-making.

Key findings

RRM/RRSO reduced cancer-related distress, with health-related QoL unaffected. Body image problems were reported after RRM, and sexual dysfunction and menopause symptoms after RRSO. Preliminary results showed that early salpingectomy leads to better sexual function and fewer menopause symptoms.

What does this add to what is known?

We demonstrate that RRM and RRSO are well-tolerated and reduce cancer distress. Women and clinicians should be aware of the negative impact of RRM on body image and of RRSO on sexual dysfunction and menopause-related symptoms. RRESDO may be a promising alternative to mitigate QoL-related risks of RRSO, but long-term outcomes are awaited.

nongenetic (family history [FH]/epidemiologic/reproductive/hormonal profile/mammographic density) variables are now available and provide personalized risk prediction for BC and OC.[14–16]

Effective strategies that reduce cancer incidence or improve survival are available for women at increased BC/OC risk and recommended by clinical guidelines. This includes enhanced screening (BC), medical prevention (selective estrogen receptor modulators/aromatase inhibitors for BC, contraceptive pill for OC), risk-reducing mastectomy (RRM), and risk-reducing salpingo-oophorectomy (RRSO).[17–20] OC screening does not reduce mortality,[21,22] and surveillance programs are unavailable for high-risk women. Among these strategies, risk-reducing surgery (RRS) remains the most clinically effective preventive option whose uptake has increased enormously over the years.[23]

RRM is offered to women with a lifetime BC-risk over 30% to 40%,[17,24] providing 89% to 95% cancer risk reduction.[25–27] The timing of reconstruction including synthetic implants/autologous tissue (TRAM/DIEP) flaps[28] can vary, with most preferring immediate reconstruction. RRSO is the gold-standard OC preventive strategy, reducing OC-risk by 80% to 97%.[29–31] RRSO has been undertaken for *BRCA1/BRCA2* carriers, or women with a strong FH of OC. Broadening access has led to RRSO now being offered to women at more than 4% to 5% lifetime OC-risk, including newer moderate-penetrance OC CSGs and women with a first-degree relative with high-grade serous OC.[19,32,33]

Premenopausal oophorectomy leads to premature surgical menopause, affecting quality-of-life (QoL) outcomes such as sexual function and vasomotor/menopausal symptoms.[34,35] It is associated with long-term detrimental sequelae such as coronary heart disease, osteoporosis, and cognitive decline,

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This study was presented at the annual scientific meeting of the British Gynaecological Cancer Society, London, United Kingdom, July 7–8, 2022.

The data sets used or analyzed during this study are publicly available. Data generated from the analysis are presented. Any additional data needed can be made available on reasonable request to the corresponding author.

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although these may be ameliorated by hormone replacement therapy (HRT).[36] In addition, a higher decision regret rate for premenopausal (compared with postmenopausal) RRSO has been reported.[37] The widespread acceptance of the fallopian tube as the site of origin of most serous epithelial OCs, along with the detrimental health sequelae of early menopause, has supported the introduction of a novel 2-step strategy of risk-reducing early salpingectomy (RRES) and delayed oophorectomy (DO) (RRESDO).[38–40] This allows premenopausal women wishing to decline/delay RRSO a degree of OC risk reduction while avoiding premature menopause. Given the limited outcome data, RRESDO is not considered standard of care[41] and is currently offered in clinical trials within the United States and Europe.[42–44]

For women with increased BC/OC risk, the decision of whether and when to undergo RRS is complex and changes over time. Several factors may influence this, such as carrying a PV, cancer risk perception, FH/personal history of cancer, menopause status, fertility wishes, and relationship status.[45] Although surgery substantially reduces BC or OC risk and improves cancer-related worry,[27] it involves surgical risks, particularly with complex breast reconstruction. RRM may adversely affect the psychological/physical well-being of patients following consequent morbidities and body image issues.[46] Although HRT may ameliorate outcomes of premature menopause, it remains contraindicated for many women with BC. RRES is of unproven benefit, and unlike RRSO does not improve BC mortality in women with BC.[47]

It is crucial for women and their clinicians to have robust data on relevant QoL outcomes to guide informed decision-making and minimize decision regret. To our knowledge, no systematic review has attempted to collectively summarize the impact of RRM/RRSO/RRESDO on QoL outcomes, including health-related QoL (HRQoL), sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety, or depression. Therefore, robust evidence synthesis on generic and condition-specific QoL after RRM, RRSO, and RRESDO is required.

Objectives

The primary aim of this review is to assess the impact of RRS for BC and OC prevention on QoL outcomes. We considered RRM, RRSO, and RRESDO. Secondary aims are to compare long-term with short-term QoL outcomes after RRS; assess the impact of menopausal status and/or use of HRT following RRSO; and determine whether confirmed diagnosis of PV in BC or OC CSGs vs FH-based diagnosis affects postoperative QoL outcomes.

Methods

We conducted the systematic review and meta-analysis using a prospectively registered protocol (PROSPERO: CRD4202 2319782) and reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[48]

Literature search

We searched MEDLINE, Embase, PubMed, and Cochrane Library from inception to February 2023 for publications in English and human studies, using a predefined search strategy (Appendix 1, developed by X.W., S.O., and M.S.). The search strategy was validated[48] by evaluating whether it could identify a set of 4 clearly eligible studies identified on preliminary searches.[49–52] In addition, reference lists from relevant studies/reviews were searched manually.

Inclusion criteria

We followed a population, intervention, comparison, outcome, and study design (PICOS) framework[53] to specify our inclusion criteria (Figure 1). Population was defined as women at increased BC or OC risk, including diagnosis of PV in BC or OC CSGs or documented FH of BC or OC, amounting to a more than 30% to 40% or >5% lifetime risk of BC or OC, respectively.[19] For the intervention, we focused on RRM for BC prevention, and RRSO or RRESDO for OC prevention. Comparison of QoL outcomes was done between women undergoing RRS and those who did not. We then compared QoL outcomes across different subgroups: (1) long-term vs short-term follow-up: for RRSO or RRESDO ≥1-year, and for RRM ≥2-year period was defined as long-term follow-up; (2) women with PVs in BC/OC CSGs (eg, *BRCA1/BRCA2*) vs those with FH-based risk; (3) postmenopausal vs premenopausal RRSO; and (4) premenopausal RRSO in HRT users vs nonusers. For outcome, we included studies reporting QoL outcomes such as HRQoL, sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety, or depression using validated questionnaires/tools. Any study design (prospective/retrospective cohort studies, randomized/nonrandomized trials, or case-series) that follows our PICOS framework was included.

Exclusion criteria

Excluded studies included case reports, review articles, and studies involving women who: (1) underwent RRM with a personal history of BC; (2) underwent RRSO/RRESDO with a personal history of OC; and (3) are at population risk (not increased risk) of BC or OC.

Selection process

Retrieved titles were transferred into EndNote (version: 20.2; Clarivate, London, United Kingdom), and duplicates were removed. Two reviewers (X.W./S.O.) independently screened titles and abstracts. Full texts of the shortlisted abstracts were subsequently retrieved independently by X.W./S.O. to assess eligibility for inclusion. Disagreements were resolved by a third reviewer (M.S.) or senior author (R.M.).

Quality assessment

Two reviewers (X.W./S.O.) independently assessed the methodological quality of included studies using the Methodological Index for Non-Randomized Studies (MINORS), with any discrepancies resolved by M.S. A 3-point scale graded the quality of each item, ranging from 0 (not reported), 1 (reported but inadequate), to 2 (reported and adequate). The maximum global score is 16 for noncomparative (8

items) and 24 for comparative studies (12 items). Scores ≤12 for non-comparative and ≤20 for comparative studies were considered to indicate high risk of bias.[54] We also assessed the external validity of the included studies (representativeness of findings) on the basis of whether the included population was definitely high-risk for BC or OC (PV in BC/OC CSGs or confirmed FH). Studies not specifying the high-risk criteria for BC or OC were deemed at high-risk of bias for external validity.

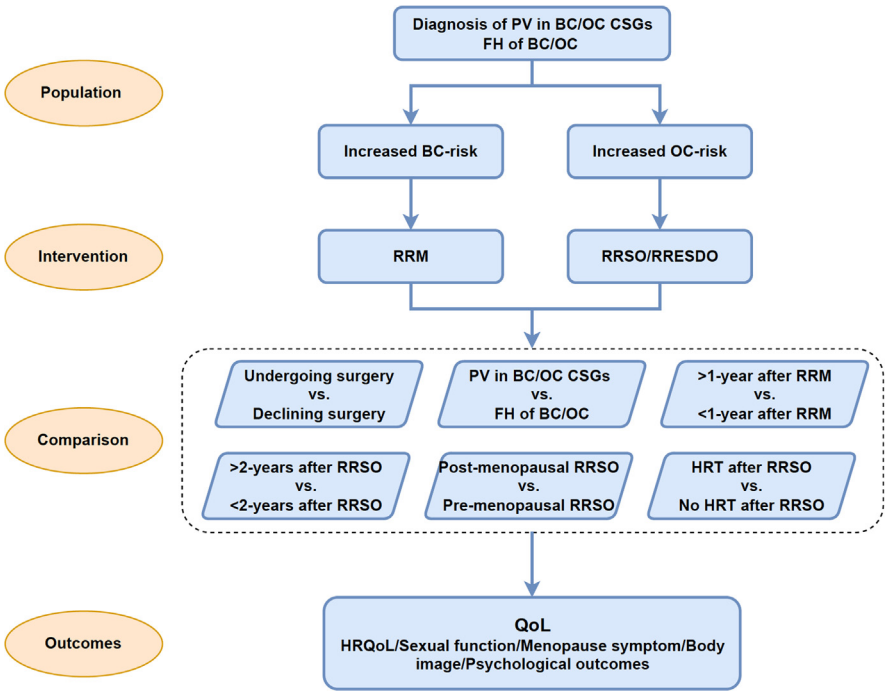
Data extraction

X.W. extracted data using predesigned tables, and S.O. cross-checked this, with any disagreements resolved by M.S./R.M. We extracted data on study design, population, and interventions, and reported QoL outcomes (HRQoL, sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety, or depression). For qualitative synthesis, we summarized the main findings about QoL after RRM, RRSO, or RRESDO and the comparison among predesigned subgroups.

Statistical analysis

For quantitative synthesis, fixed-effects meta-analysis was used to calculate summary estimates of QoL with 95% confidence intervals (CIs) after RRS vs no surgery where data allowed. We chose fixed-effects meta-analysis models because the outcome measures comprised the same validated questionnaires considered consistent across studies. However, we also undertook sensitivity analysis using random-effects meta-analysis. We undertook further predesigned subgroup analyses to assess any difference in QoL outcomes for: (1) the first 2 years after RRM vs after this period; (2) the first year after RRSO/RRESDO vs after this period; (3) women with PVs in BC/OC CSGs vs FH-based diagnosis; (4) postmenopausal vs premenopausal RRSO; and (5) women after premenopausal RRSO with vs without HRT. Heterogeneity was assessed using the I^2 statistic, with values <50% indicating minimal, 50% to 75% moderate, and >75% high heterogeneity. Analyses were performed using Stata, version 15.0 (StataCorp, College Station, TX).

FIGURE 1
Structure of the systematic review and meta-analysis



BC, breast cancer; *CSG*, cancer susceptibility gene; *FH*, family history; *HRQoL*, health-related quality of life; *HRT*, hormone replacement therapy; *OC*, ovarian cancer; *PV*, pathogenic variant; *QoL*, quality of life; *RRESDO*, risk-reducing early salpingectomy and delayed oophorectomy; *RRM*, risk-reducing mastectomy; *RRSO*, risk-reducing salpingo-oophorectomy.

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Results

Study characteristics

Figure 2 summarizes the study selection process. From 11,731 citations, we included 34 studies (N=3762 with RRS vs N=3002 without RRS) in our qualitative synthesis, which consisted of 16 (N=1102) RRM, 19 (N=2247) RRSO, and 2 (N=413) RRESDO studies. The postsurgery follow-up ranged from 1 to 23 years for RRM, 1 to 6 years for RRSO, and 1 year for RRESDO. RRM was offered to high-risk women following CSG diagnosis in 3 studies (N=202), or on the basis of mixed (CSG/FH-based) or unspecified criteria in 13 studies (N=900). RRSO was offered following CSG diagnosis in 8 studies (N=621), or on the basis of mixed/unspecified criteria in 11 studies (N=1626). RRESDO was offered following CSG diagnosis (2 studies). Table 1 summarizes the characteristics of included studies.

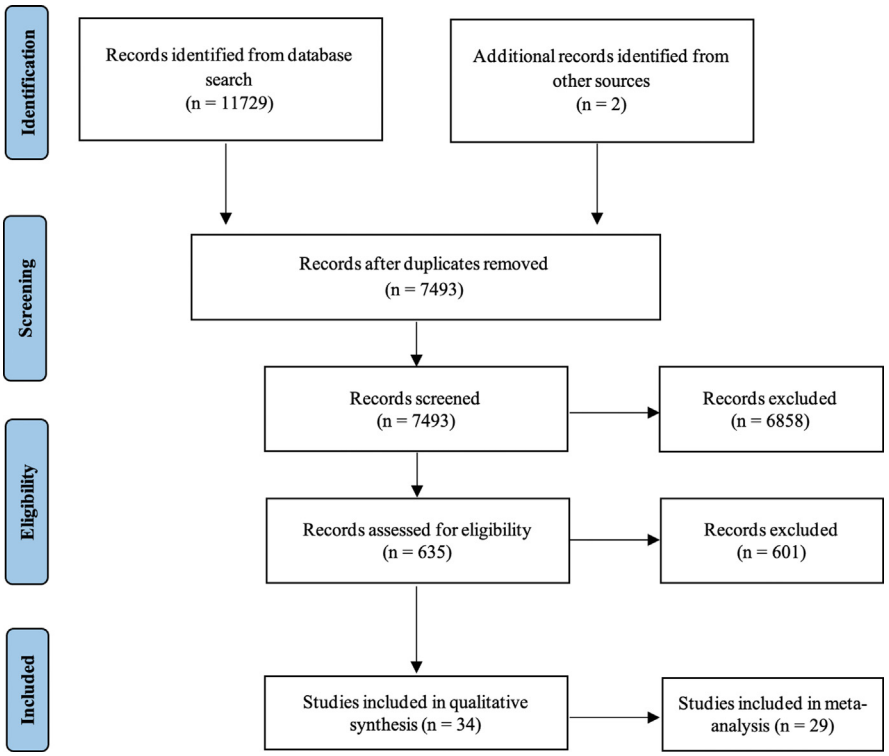
Outcomes reported

The outcomes reported and relevant questionnaires are summarized in Appendix 2. Fifteen studies (N=1082) reported HRQoL after RRM, 16 studies (N=1983) after RRSO, and 2 studies (N=413) after RRESDO. The most commonly used questionnaires were the 36-Item Short-Form Health Survey (SF-36, 8 studies) and BREAST-Q (7 studies); 6 other validated questionnaires were used by 7 studies.

Thirteen studies (N=946) reported sexual function after RRM, 16 studies (N=1611) after RRSO, and 2 studies (N=413) after RRESDO. Most studies (N=13) adopted the Sexual Activity Questionnaire (SAQ); 6 other validated/study-specific questionnaires were used by 14 studies.

Thirteen studies (N=1789) reported menopause symptoms after RRSO and 2 studies (N=413) after RRESDO. The most frequently used questionnaires were the Menopause-Specific Quality of

FIGURE 2
PRISMA flowsheet



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Life (MENQOL, 3 studies), Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES, 3 studies), and Menopause Rating Scale (MRS, 3 studies). Four studies used 4 other questionnaires.

Thirteen studies (N=996) reported body image after RRM, 5 studies (N=416) after RRSO, and 1 study (N=19) after RRESDO. The most commonly used questionnaire was the Body Image Scale (BIS, 7 studies); 6 other validated/study-specific questionnaires were used by 12 studies.

Psychological outcomes including cancer-related distress or worry, anxiety, or depression were reported by 9 studies (N=696) after RRM, 14 studies (N=1797) after RRSO, and 2 studies (N=413) after RRESDO. The most common questionnaires were the Impact of Event Scale (IES, 10 studies), Hospital Anxiety and Depression Scale (HADS, 5 studies), State-Trait Anxiety Inventory (STAI, 5 studies), Cancer Worry Scale (CWS, 3 studies), and 6 other questionnaires by 8 studies.

Quality assessment

MINORS scores are shown in Figure 3 and Appendix 3. The median MINORS score was 20 (interquartile range [IQR], 19−21) for 11 comparative and 12 (IQR, 12−13) for 23 noncomparative studies. Short (<1 year after RRSO or <2 years after RRM) or no reported duration of follow-up, >5% of participants lost to follow-up, and no sample size calculation were the main potential biases. Thirteen studies (N=2801) were deemed at low risk of bias for methodological quality, whereas 21 studies (N=4046) were at high risk of bias. Regarding external validity, 9 studies (N=2255) were deemed at high risk of bias, and 25 studies (N=4509) were at low risk of bias.

Data synthesis

Table 2 demonstrates the qualitative synthesis of QoL outcomes following RRS in 34 studies. Among them, 29 studies provided data for meta-analysis. On the basis of the number of studies using each questionnaire (Appendix 2), we undertook quantitative synthesis from studies where means and standard deviation (SD) of questionnaire results were extractable. For HRQoL, SF-36 data were meta-analyzed. To maximize available data, we used SD estimates of SF-36 summary score from the country-specific general population[83] when studies lacked this information. For sexual function, we meta-analyzed SAQ results. BIS results for body image were not meta-analyzed because of data insufficiency. Results of FACT-ES and MRS were meta-analyzed for menopause symptoms, whereas MENQOL results were not because only 1 study provided SD. HADS results were meta-analyzed for anxiety and depression, whereas IES and STAI (cancer-related distress) lacked SD. Where data allowed, prespecified subgroup analyses were undertaken. The fixed-effects meta-analysis results are summarized in Table 3 (RRM) and Table 4 (RRSO). A table comparing random-effects meta-analysis outcomes with the fixed-effects outcomes is included in Appendix 4 and 5, which demonstrates similar results from both models.

Quality of life outcomes after risk-reducing mastectomy

Health-related quality of life

The HRQoL including physical and mental components was unaffected in 12 studies[49,55−59,61,62,64−66,68] and improved in 1 study[67] following RRM. Geiger et al[59] found similar long-term HRQoL in both high-risk women undergoing RRM and controls. Spindler et al[68] demonstrated similar HRQoL after RRM with simultaneous reconstruction compared with general population reference values. Bai et al[55] found that long-term HRQoL remained unchanged after RRM. Miseré et al[67] found improved physical well-being for autologous reconstruction vs implant-based reconstruction after RRM. However, Gopie et al[60] reported that generic mental health improved but generic physical health declined 6 months after RRM, returning to baseline level at 21

TABLE 1
Study characteristics

Studies	Country	Study design	Population	Type of RRS	Sample size	Time since RRS	Main findings
Bai et al,[55] 2019	Sweden	Prospective cohort	*BRCA1/2* or FH of BC	RRM	99	11.5 y	HRQoL and anxiety unchanged in long-term follow-up Increased depression in long-term follow-up Body image concerns persisted in long-term follow-up
Brandberg et al,[56] 2008	Sweden	Prospective cohort	*BRCA1/2* or FH of BC	RRM	90	1 y	No negative impact on HRQoL and depression Decrease in general anxiety Negative impact on sexual function and body image
Gahm et al,[57] 2010	Sweden	Prospective cohort	*BRCA1/2* or FH of BC	RRM	59	29 mo	No negative impact on HRQoL Reduced sexual function (85% sensation, 75% pleasure)
Gandhi et al,[58] 2022	United Kingdom	Prospective cohort	FH of BC	RRM	241	NR	No negative impact on HRQoL, sexual function, and body image Higher preoperative anxiety levels negatively affecting postoperative psychosocial well-being
Geiger et al,[59] 2007	United States	Cross-sectional	Increased BC-risk	RRM/ Controls	106/62	2–23 y	No impact on long-term HRQoL and depression
Gopie et al,[60] 2013	The Netherlands	Prospective cohort	*BRCA1/2* or FH of BC	RRM	48	21.7 mo	No negative impact on HRQoL in long-term follow-up Negative impact on body image No negative impact on sexual function Decrease in cancer-related distress
Herold et al,[61] 2022	Germany	Prospective cohort	*BRCA1/2*	RRM	43	43.3 mo	No negative impact on HRQoL, sexual function, and body image
Isern et al,[62] 2008	Sweden	Retrospective cohort	PV in BC/OC CSGs or FH of BC	RRM	30	42 mo	No impact on general anxiety and depression No impact on HRQoL Satisfactory body image
Mansour et al,[63] 2023	Australia	Prospective cohort	>25% lifetime BC-risk	RRM	48	59 mo	Negative impact on physical and sexual well-being No negative impact on body image with reconstruction
McCarthy et al,[49] 2017	United States/ Canada	Prospective cohort	Increased BC-risk	RRM	204	5 y	No negative impact on HRQoL and sexual function High satisfaction with body image Decrease in general anxiety No impact on depression
Metcalfe et al,[64] 2004	Canada	Cross-sectional	Increased BC-risk	RRM	60	52.2 mo	No negative impact on HRQoL No negative impact on cancer-related distress, sexual activity, and body image

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TABLE 1
Study characteristics *(continued)*

Studies	Country	Study design	Population	Type of RRS	Sample size	Time since RRS	Main findings
Metcalfe et al,[65] 2005	Canada	Cross-sectional	Increased BC-risk	RRM	60	52.2 mo	No negative impact on HRQoL
Metcalfe et al,[66] 2015	United States/ Canada	Cross-sectional	*BRCA1/2*	RRM	137	50.0 mo	Improved body image and sexual function after nipple and areola-sparing RRM vs skin-sparing RRM Comparable levels of HRQoL and cancer-related distress Comparable levels of anxiety and depression
Miseré et al,[67] 2022	The Netherlands	Cross-sectional	PV in BC CSGs or FH of BC	RRM	47	39—39.5 mo	Improved physical well-being and body image, and comparable sexual well-being after immediate autologous reconstruction vs implant-based reconstruction
Spindler et al,[68] 2021	Germany	Prospective cohort	PV in BC/OC CSGs	RRM	22	2.15 y	No negative impact on HRQoL and sexual function No negative impact on body image with reconstruction
Chae et al,[69] 2021	Korea	Cross-sectional	*BRCA1/2*	RRSO/ Controls	30/22	NR	No difference in mental component of HRQoL, sexual function, menopause symptoms, cancer-related distress, and depression Negative impact on physical component of HRQoL
Elit et al,[34] 2001	Canada	Retrospective cohort	PV in BC/OC CSGs or FH of OC	RRSO	40	5 y	No negative impact on HRQoL Considerable decrease in cancer-related distress Development of menopausal symptoms Negative impact on sexual function
Fang et al,[70] 2009	United States	Prospective cohort	PV in BC/OC CSGs or FH of BC/OC	RRSO/ Controls	38/37	1 y	Short-term deficits in physical component of HRQoL, which recovered by 6 and 12 mo Potential impact on short-term sexual function No negative impact on body image and depression
Finch et al,[71] 2013	Canada	Prospective cohort	*BRCA1/2*	RRSO	96	13.7 mo	No negative impact on HRQoL Persistent moderate to severe cancer-related distress in a subgroup of women
Finch et al,[72] 2011	Canada	Prospective cohort	*BRCA1/2*	RRSO	114	13.6 mo	Increase in vasomotor symptoms Decrease in sexual function in premenopause women Menopause symptoms and sexual dysfunction mitigated by HRT, but not to presurgical levels

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TABLE 1
Study characteristics *(continued)*

Studies	Country	Study design	Population	Type of RRS	Sample size	Time since RRS	Main findings
Hall et al,[73] 2019	Canada	Prospective cohort	*BRCA1/2*	RRSO	140	3.5 y	Premenopausal: no impact on HRQoL, development of menopause symptoms, decline in sexual function; menopause symptoms and sexual dysfunction mitigated by HRT, but not to presurgical levels Postmenopausal: negative impact on HRQoL (physical components), decline in sexual function
Johansen et al,[50] 2016	Norway	Retrospective cohort	Increased BC/OC risk	RRSO/ Controls	294/1228	5 y	Improved HRQoL Negative impact on sexual function Sexual discomfort reduced by use of HRT
Madalinska et al,[74] 2005	The Netherlands	Cross-sectional	FH of BC/OC	RRSO/ Controls	369/477	2.8 y	No negative impact on HRQoL Decrease in cancer-related distress Negative impact on menopause symptoms and sexual function
Mai et al,[75] 2020	United States/ Australia	Prospective cohort	Increased OC-risk	RRSO/ Controls	562/1010	5 y	Decrease in cancer-related distress/depression Improved HRQoL after RRSO vs screening Negative impact on menopause symptoms and sexual function
Michelsen et al,[76] 2009	Norway	Prospective cohort	*BRCA1/2* or FH of BC/OC	RRSO/ Controls	301/903	5.3 y	No negative impact on HRQoL
Philp et al,[77] 2022	United States	Prospective cohort	PV in BC/OC CSGs or FH of OC	RRSO	72	NR	Decrease in cancer-related worry Negative impact on body image Negative impact on sexual function and short-term HRQoL
Powell et al,[78] 2020	United States	Cross-sectional	*BRCA1/2*	RRSO/ Controls	223/21	5 y	Decrease in cancer-related worry No impact on sexual function Negative impact on menopause symptoms Negative impact on depression in premenopausal women
Robson et al,[35] 2003	United States	Cross-sectional	Increased OC-risk	RRSO	54	23.8 mo	No impact on HRQoL and depression Negative impact on sexual function Persistent cancer-related distress in a subgroup of women

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TABLE 1
Study characteristics *(continued)*

Studies	Country	Study design	Population	Type of RRS	Sample size	Time since RRS	Main findings
Stanisz et al,[79] 2019	Poland	Prospective cohort	*BRCA1/2*	RRSO	62	353 d	Negative impact on HRQoL Negative impact on depression and menopause symptoms Decrease in cancer-related distress
Touboul et al,[80] 2011	France	Retrospective cohort	Increased BC/OC risk	RRSO	112	6.0 y	No impact on HRQoL Decreased cancer-related distress Negative impact on menopause symptoms Decrease in sexual function
Tucker et al,[81] 2021	Australia	Cross-sectional	BC survivors	RRSO	76	26 mo	No impact on HRQoL Baseline sexual function reduced before RRSO (on diagnosis of BC) RRSO does not affect sexual function further
Heiniger et al,[82] 2015	Australia/ New Zealand	Prospective cohort	FH of BC/OC	RRM/ Controls RRSO/ Controls	17/39 38/94	3 y	No negative impact on general anxiety and depression after RRM/RRSO Decrease in cancer-related distress after RRM No negative impact on body image and sexual function after RRM No negative impact on body image and cancer-related distress after RRSO Negative impact on sexual function and menopause symptoms after RRSO
Nebgen et al,[51] 2018	United States	Prospective nonrandomized study	*BRCA1/2*	RRESDO/ RRSO/ Controls	19/12/12	1 y	No impact on HRQoL and body image Decrease in cancer-related worry and distress Trend of stable sexual function after salpingectomy, decrease in sexual function (discomfort) after RRSO Trend of no menopause symptoms after salpingectomy, mild menopause symptoms after RRSO
Steenbeek et al,[52] 2021	The Netherlands	Nonrandomized controlled preference trial	*BRCA1/2*	RRESDO/ RRSO	394/154	1 y	Decreased cancer-related worry No impact on HRQoL after salpingectomy, and short-term decline in physical component after RRSO Improved sexual function and menopause symptoms after salpingectomy vs RRSO, regardless of HRT

BC, breast cancer; *CSG*, cancer susceptibility gene; *FH*, family history; *HRQoL*, health-related quality-of-life; *HRT*, hormone replacement therapy; *OC*, ovarian cancer; *PV*, pathogenic variant; *QoL*, quality-of-life; *RRESDO*, risk-reducing early salpingectomy and delayed oophorectomy; *RRM*, risk-reducing mastectomy; *RRS*, risk-reducing surgery; *RRSO*, risk-reducing salpingo-oophorectomy.

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TABLE 2
Qualitative synthesis of quality of life outcomes following risk-reducing surgery

Studies	Type of RRS	HRQoL	Sexual function	Menopause symptoms	Body image	Cancer distress	Cancer worry	Anxiety	Depression
Bai et al,[55] 2019	RRM	Not affected	Decline (habit)	Not applicable	Affected	Not investigated	Not investigated	Not affected	Increased
Brandberg et al,[56] 2008	RRM	Not affected	Decline (pleasure)	Not applicable	Affected	Not investigated	Not investigated	Decreased	Not affected
Gahm et al,[57] 2010	RRM	Not affected	Decline (sensation, pleasure)	Not applicable	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Gandhi et al,[58] 2022	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Not reported	Not reported
Geiger et al,[59] 2007	RRM	Not affected	Not investigated	Not applicable	Not investigated	Not affected	Not investigated	Not investigated	Not affected
Gopie et al,[60] 2013	RRM	Generic mental health improved and generic physical health declined Reversed by 21 months	Not affected	Not applicable	Affected	Decreased	Not investigated	Not investigated	Not investigated
Heiniger et al,[82] 2015	RRM	Not investigated	Not affected	Not applicable	Not affected	Decreased	Not investigated	Not affected	Not affected
Herold et al,[61] 2022	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Not investigated	Not investigated
Isern et al,[62] 2008	RRM	Not affected	Not investigated	Not applicable	Not affected	Not investigated	Not investigated	Not affected	Not affected
Mansour et al,[63] 2023	RRM	Generic physical health declined	Affected sexual well-being	Not applicable	Not affected (with reconstruction)	Not investigated	Not investigated	Not investigated	Not investigated
McCarthy et al,[49] 2017	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Decreased	Not affected
Metcalfe et al,[64] 2004	RRM	Not affected	Not affected	Not applicable	Improved (with reconstruction)	Not affected	Not investigated	Not investigated	Not investigated
Metcalfe et al,[65] 2005	RRM	Not affected	Not investigated	Not applicable	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Metcalfe et al,[66] 2015	Nipple and areola-sparing RRM vs skin-sparing RRM	Comparable	Improved sexual well-being	Not applicable	Improved	Comparable	Not investigated	Comparable	Comparable
Miseré et al,[67] 2022	RRM with immediate autologous vs implant-based reconstruction	Improved physical well-being	Comparable	Not applicable	Improved	Not investigated	Not investigated	Not investigated	Not investigated

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(continued)

TABLE 2
Qualitative synthesis of quality of life outcomes following risk-reducing surgery *(continued)*

Studies	Type of RRS	HRQoL	Sexual function	Menopause symptoms	Body image	Cancer distress	Cancer worry	Anxiety	Depression
Spindler et al,[68] 2021	RRM	Not affected	Not affected	Not applicable	Not affected (with reconstruction)	Not investigated	Not investigated	Not investigated	Not investigated
Chae et al,[69] 2021	RRSO	Decline (physical component)	Not affected	Not affected	Not investigated	Not affected	Not investigated	Not investigated	Not affected
Elit et al,[34] 2001	RRSO	Not affected	Decline (desire, vaginal dryness)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Not investigated
Fang et al,[70] 2009	RRSO	Short-term decline (physical component) Recovered by 6 mo	Short-term decline (activity, pleasure, discomfort)	Not investigated	Not affected	Not investigated	Not investigated	Not investigated	Not affected
Finch et al,[71] 2013	RRSO	Not affected	Not investigated	Not investigated	Not investigated	Persistent cancer-related distress in a subgroup	Not investigated	Not investigated	Not investigated
Finch et al,[72] 2011	RRSO	Not investigated	Decline in premenopausal women (desire, pleasure, habit, discomfort) Mitigated by HRT, but not to presurgical levels	Increased Mitigated by HRT, but not to presurgical levels	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Hall et al,[73] 2019	RRSO	Decline in postmenopausal women (physical component)	Decline (pleasure, discomfort) Mitigated by HRT, but not to presurgical levels	Increased in premenopausal women Mitigated by HRT, but not to presurgical levels	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Heiniger et al,[82] 2015	RRSO	Not investigated	Decline (discomfort)	Increased	Not affected	Not affected	Not investigated	Not affected	Not affected

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(continued)

TABLE 2
Qualitative synthesis of quality of life outcomes following risk-reducing surgery *(continued)*

Studies	Type of RRS	HRQoL	Sexual function	Menopause symptoms	Body image	Cancer distress	Cancer worry	Anxiety	Depression
Johansen et al,[50] 2016	RRSO	Improved	Decline in premenopausal women (pleasure, discomfort) Mitigated by HRT, but not to presurgical levels	Not investigated	Not affected	Not investigated	Not investigated	Not investigated	Not investigated
Madalinska et al,[74] 2005	RRSO	Not affected	Decline (pleasure, discomfort)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Not investigated
Mai et al,[75] 2020	RRSO	Improved	Decline (pleasure, discomfort)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Decreased
Michelsen et al,[76] 2009	RRSO	Not affected	Not investigated	Not investigated	Not reported	Not investigated	Not investigated	Not reported	Not reported
Nebgen et al,[51] 2018	RRSO	Not affected	Trend of decline (discomfort)	Trend of increase	Not affected	Decreased	Decreased	Not investigated	Not investigated
Philp et al,[77] 2022	RRSO	Short-term decline (memory, social activities)	Decline (habit, interest)	Not investigated	Affected	Not investigated	Decreased	Not investigated	Not investigated
Powell et al,[78] 2020	RRSO	Not investigated	Not affected	Increased in premenopause women	Not investigated	Not investigated	Decreased	Not investigated	Increased
Robson et al,[35] 2003	RRSO	Not affected	Decline (discomfort)	Increased	Not investigated	Persistent cancer-related distress in a subgroup	Not investigated	Not investigated	Not affected
Stanisz et al,[79] 2019	RRSO	Decline (sleep problems)	Not investigated	Increased	Not investigated	Decreased	Not investigated	Not investigated	Increased
Steenbeek et al,[52] 2021	RRSO	Short-term decline (physical component)	Decline (function, distress) Mitigated by HRT, but not to presurgical levels	Increased Mitigated by HRT, but not to presurgical levels	Not investigated	Not investigated	Decreased	Not investigated	Not investigated
Touboul et al,[80] 2011	RRSO	Not affected	Decline (discomfort)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Not investigated
Tucker et al,[81] 2021	RRSO	Not affected	Not affected	Not reported	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated

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(continued)

TABLE 2
Qualitative synthesis of quality of life outcomes following risk-reducing surgery *(continued)*

Studies	Type of RRS	HRQoL	Sexual function	Menopause symptoms	Body image	Cancer distress	Cancer worry	Anxiety	Depression
Nebgen et al,[51] 2018	RRESDO	Not affected	Trend of unaffected	Trend of unaffected	Not affected	Decreased	Decreased	Not investigated	Not investigated
Steenbeek et al,[52] 2021	RRESDO	Not affected	Not affected	Not affected	Not investigated	Not investigated	Decreased	Not investigated	Not investigated

HRQoL, health-related quality-of-life; *HRT*, hormone replacement therapy; *RRESDO*, risk-reducing early salpingectomy and delayed oophorectomy; *RRM*, risk-reducing mastectomy; *RRS*, risk-reducing surgery; *RRSO*, risk-reducing salpingo-oophorectomy.
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months after surgery. Mansour et al[63] also reported poor physical well-being after RRM.

Table 3 summarizes pooled estimates of QoL outcomes after RRM, with 4 of 8 studies providing SF-36 data for meta-analysis. There was no difference in SF-36 scores across different follow-up time frames (>2 years vs <2 years; N=92) (Table 3).

Sexual function

Four studies[55–57,63] concluded that RRM negatively affected sexual function, including reduced sexual frequency, sensation, and pleasure. Metcalfe et al[66] found better sexual well-being after nipple and areola-sparing RRM vs skin-sparing RRM. However, another 8 studies[49,58,60,61,64,67,68,82] reported unchanged sexual function (pleasure/discomfort/habit) after RRM with reconstruction.

Three of 4 studies provided SAQ data for meta-analysis. Comparing RRM with no surgery found little difference in any SAQ component from the pooled estimates of 1 study[82] (Table 3). When comparing different follow-up time frames (>2 years vs <2 years), despite little difference in the pleasure component, an increase of 0.20 (95% CI, 0.06−0.34; I^2=0%; N=92) in the habit component (more frequent intercourse) and 0.50 (95% CI, 0.03−0.97; I^2=0%; N=92) in the discomfort component (more discomfort) of SAQ was observed in women at >2-year follow-up (Table 3). However, these results were based on a single study.[55]

Body image

Women reported satisfactory aesthetic outcomes following RRM with reconstruction.[49,58,61–63,68,82] Women undergoing reconstruction following RRM reported higher satisfaction with general body shape and appearance than those without reconstruction.[64] In addition, women reported better body image with nipple and areola-sparing RRM than with skin-sparing RRM,[66] and higher satisfaction with breasts following autologous reconstruction than implant-based reconstruction.[67] Another 3 studies[55,56,60] reported body image problems after RRM despite reconstruction, with problems persisting long-term (11.5-year follow-up).[55] Four studies using BIS lacked SD for meta-analysis.

Cancer-related distress

Two studies[60,82] reported decreased cancer-related distress after RRM, whereas 2[59,64] found little appreciable difference following RRM vs no surgery. A comparable level of cancer-related distress was reported after nipple and areola-sparing RRM vs skin-sparing RRM.[66] Metcalfe et al[64] reported higher cancer-related distress in women with strong FH of BC or *BRCA1/2* PV than in those with limited FH after RRM. Four studies evaluated cancer-related distress using IES but lacked SD for meta-analysis.

Anxiety or depression

Two studies[49,56] reported decreased general anxiety, whereas other studies found little impact on general anxiety[62,66,82] and depression[49,56,59,62,66,82] after RRM. Bai et al[55] reported unchanged general anxiety but higher levels of depression with long-term follow-up.

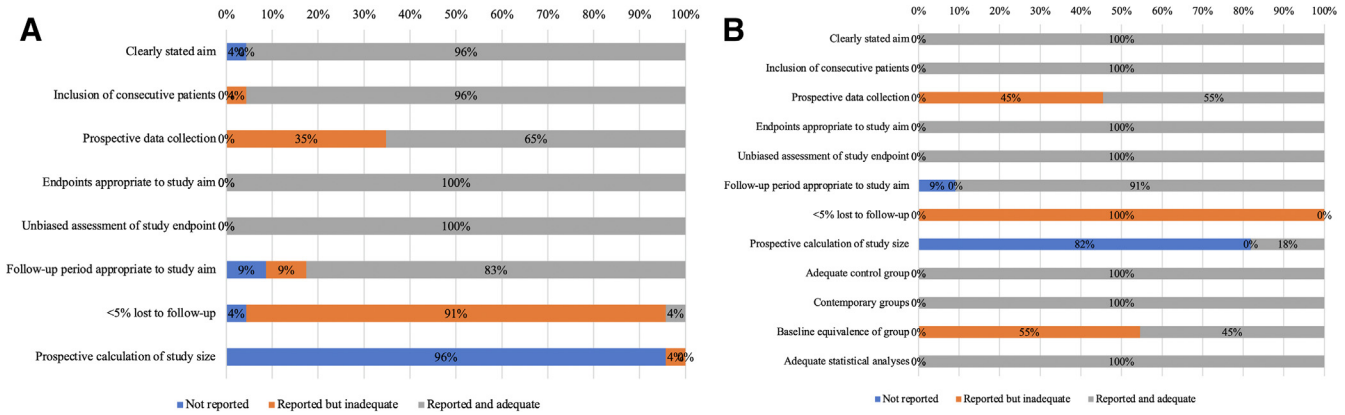
Three of 5 studies using HADS provided data for meta-analysis. There was no significant difference when comparing women who underwent RRM vs no surgery (N=56) or across different follow-up time frames (N=92) (Table 3).

Quality of life outcomes after risk-reducing salpingo-oophorectomy

Health-related quality of life

Eight studies[34,35,51,71,74,76,80,81] reported that HRQoL including physical and mental components was unaffected after RRSO. Mai et al[75] and Johansen et al[50] reported improved HRQoL after RRSO, and stable HRQoL with screening for women with increased OC-risk. Five studies[52,69,70,77,79] reported short-term deficits (poorer physical/social functioning, more physical role limitations, greater pain/discomfort, less vitality) following RRSO; Fang et al[70] reported that despite short-term deficits in most components (1 month, SF-36), most women recovered to baseline functioning at 6- and 12-month follow-up. Hall et al[73] concluded that premenopausal RRSO did not affect HRQoL, whereas the physical component declined among postmenopausal women.

FIGURE 3
Methodological quality of studies



Methodological quality of **A**, noncomparative and **B**, comparative studies.

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Table 4 summarizes pooled QoL estimates following RRSO. Six of 10 studies using SF-36 provided data for HRQoL meta-analysis. No difference in SF-36 score was found in different subgroups (RRSO vs no surgery, N=1050; >1-year follow-up vs <1-year, N=351) (Table 4).

Sexual function

Decreased sexual pleasure, more sexual discomfort, and less frequent sex were reported after RRSO in 13 studies.[34,35,50–52,70,72–75,77,80,82] This included both pre- and postmenopausal women. Four studies[50,52,72,73] showed that HRT may mitigate these risks for premenopausal women but not to presurgical levels. Fang et al[70] reported that sexual discomfort improved after 1-year follow-up compared with 6 months, whereas Mai et al[75] concluded that sexual function declined during 5-year follow-up. In contrast, 3 studies[69,78,81] found little difference in sexual function after RRSO vs no surgery, and in sexual function between pre- and postmenopausal RRSO.[78]

Nine of 10 studies using SAQ provided data for meta-analysis. However, 4 studies[72–75] used reversed scores for the discomfort component of SAQ, and hence could not be meta-analyzed with the remaining studies. Our meta-analysis (Table 4) demonstrated a significant decrease in the pleasure domain (−1.21 [95% CI, −1.53 to −0.89]; I^2=0%; N=3070) and an increase in the discomfort domain (1.12 [95% CI, 0.93−1.31]; I^2=0%; N=1400) in women undergoing RRSO vs no surgery. There was a reduction in sexual pleasure (−0.70 [95% CI, −1.33 to −0.07]; I^2=0%; N=313) across different time frames after RRSO (>1 year vs <1 year). In premenopausal RRSO, HRT (vs no HRT) was associated with an increase in sexual pleasure (1.16 [95% CI, 0.17−2.15]; I^2=0%; N=291) and a decrease in sexual discomfort (−1.20 [95% CI, −1.75 to −0.65]; I^2=0%; N=157). Little difference was reported across all other comparisons.

Menopause symptoms

Twelve studies[34,35,51,52,72–75,78–80,82] reported increased menopause symptoms, including hot flashes, night sweats, and sleep disturbances following RRSO vs no surgery, whereas Chae et al[69] reported little difference in menopause symptoms between RRSO and no surgery. Three studies[52,72,73] concluded that menopause symptoms could be mitigated by HRT, but not to presurgical levels.

Two of 3 studies using FACT-ES, and 2 of 3 studies using MRS provided data for meta-analysis. Our meta-analysis showed increased menopause symptoms with RRSO vs no surgery, with a reduction in FACT-ES score (−1.96 [95% CI, −2.81 to −1.10]; I^2=92%; N=1745) and a trend difference of 2.08 (95% CI, −0.21 to 4.37; I^2=0%; N=184) for MRS score (Table 4).

Body image

Four studies[50,51,70,82] reported unaffected body image after RRSO, whereas women reported feeling less physically attractive in 1 study.[77] Three studies using BIS did not provide SD for meta-analysis.

Cancer-related distress or worry

Six studies[34,51,74,75,79,80] reported decreased cancer-related distress after RRSO, whereas another 2 studies[69,82] found little difference. Two studies[35,71] found that a proportion of women continued to report moderate to severe cancer-related distress after RRSO, and these women were at risk for psychological distress. In addition, 4 studies[51,52,77,78] reported decreased cancer worry after RRSO.

Six studies using IES and 4 studies using STAI looked at cancer distress but lacked SD for meta-analysis. Three studies looked at cancer worry using CWS and also lacked SD for meta-analysis.

Anxiety or depression

Four studies found that RRSO had no negative impact on general anxiety[82] and depression.[35,69,70,82] Although Mai et al[75] reported decreased depression after RRSO, Powell et al[78] and Stanisz

TABLE 3
Quality of life outcomes following risk-reducing mastectomy

	RRM				No surgery				RRM vs no surgery			
(1) Intervention	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SAQ												
Pleasure	3	149	80.50%	11.07 (10.36–11.79)	1	39	0.00%	12.10 (10.75–13.45)	1	56	0.00%	1.00 (−1.37 to 3.37)
Discomfort	3	149	36.10%	1.53 (1.23–1.82)	1	39	0.00%	1.10 (0.57–1.63)	1	56	0.00%	0.00 (−0.89 to 0.89)
Habit	3	149	74.60%	0.95 (0.87–1.03)	1	39	0.00%	0.70 (0.54–0.86)	1	56	0.00%	0.20 (−0.05 to 0.45)
HADS												
Anxiety	3	246	62.70%	5.49 (4.97–6.01)	1	39	0.00%	5.50 (4.31–6.69)	1	56	0.00%	0.10 (−1.76 to 1.96)
Depression	3	246	34.30%	2.21 (1.89–2.53)	1	39	0.00%	3.10 (2.19–4.01)	1	56	0.00%	−0.90 (−2.29 to 0.49)
	<2-y follow-up				>2-y follow-up				>2-y follow-up vs <2-y follow-up			
(2) Follow-up	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SF-36												
PCS	2	140	0.00%	53.12 (51.87–54.37)	3	161	35.3%	51.42 (50.14–52.71)	1	92	0.00%	−1.20 (−3.74 to 1.34)
MCS	2	140	67.50%	51.93 (50.32–53.53)	3	161	0.00%	50.47 (49.01–51.94)	1	92	0.00%	−2.20 (−5.06 to 0.66)
SAQ												
Pleasure	1	92	0.00%	11.30 (10.15–12.10)	3	149	80.50%	11.07 (10.36–11.79)	1	92	0.00%	−1.10 (−2.30 to 0.10)
Discomfort	1	92	0.00%	1.00 (0.71–1.29)	3	149	36.10%	1.53 (1.23–1.82)	1	92	0.00%	0.50 (0.03–0.97)[a]
Habit	1	92	0.00%	0.70 (0.60–0.80)	3	149	74.60%	0.95 (0.87–1.03)	1	92	0.00%	0.20 (0.06–0.34)[a]
HADS												
Anxiety	1	92	0.00%	4.20 (3.44–4.96)	3	246	62.70%	5.49 (4.97–6.01)	1	92	0.00%	0.30 (−0.86 to 1.46)
Depression	1	92	0.00%	1.90 (1.35–2.45)	3	246	34.30%	2.21 (1.89–2.53)	1	92	0.00%	0.70 (−0.12 to 1.52)

The following meta-analyses were conducted for quality of life (QoL) outcomes after RRM: (1) intervention: QoL outcomes in women who underwent RRM vs those who did not; data were available for SAQ and HADS; (2) follow-up: long-term vs short-term QoL outcomes following RRM; a period of ≥2 years was defined as long-term follow-up for RRM, and data were available for SF-36, SAQ, and HADS. For each comparison, the effect size of each single arm and the difference between the 2 arms were calculated.

CI, confidence interval; *HADS*, Hospital Anxiety and Depression Scale; *MCS*, Mental Component Summary; *PCS*, Physical Component Summary; *RRM*, risk-reducing mastectomy; *SAQ*, Sexual Activity Questionnaire; *SF-36*, 36-Item Short Form Health Survey.

[a] A *P* value of <.05 was considered as statistically significant.

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TABLE 4
Quality of life outcomes following risk-reducing salpingo-oophorectomy

	RRSO				No surgery				RRSO vs no surgery			
(1) Intervention	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SF-36												
PCS	7	539	91.10%	51.71 (50.86–52.56)	4	657	96.40%	53.08 (52.34–53.82)	4	1050	86.30%	−0.75 (−2.01 to 0.50)
MCS	7	539	91.20%	49.00 (48.20–49.80)	4	657	94.40%	50.04 (49.32–50.77)	4	1050	0.00%	−0.14 (−1.33 to 1.04)
SAQ												
Pleasure	11	1406	77.30%	10.43 (10.22–10.64)	6	1914	89.10%	11.48 (11.30–11.66)	6	3070	0.00%	−1.21 (−1.53 to −0.89)[a]
Discomfort	6	571	96.20%	2.47 (2.41–2.54)	5	888	95.20%	0.94 (0.85–1.03)	5	1400	0.00%	1.12 (0.93–1.31)[a]
Habit	10	1205	90.70%	0.83 (0.78–0.88)	5	1190	94.90%	0.88 (0.85–0.92)	5	2145	5.50%	−0.02 (−0.08 to 0.03)
MRS												
Overall score	2	68	0.00%	11.67 (9.85–13.49)	2	116	65.90%	8.85 (7.21–9.89)	2	184	0.00%	2.08 (−0.21 to 4.37)
FACT-ES												
Overall score	2	682	97.20%	58.16 (57.49–58.83)	2	1063	69.20%	60.33 (59.80–60.85)	2	1745	92.00%	−1.96 (−2.81 to −1.10)[a]
	<1-y follow-up				>1-y follow-up				>1-y follow-up vs <1-y follow-up			
(2) Follow-up	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SF-36												
PCS	2	566	0.00%	50.35 (49.52–51.17)	7	539	91.10%	51.71 (50.86–52.56)	2	351	0.00%	0.64 (−0.69 to 1.98)
MCS	2	566	41.72%	49.95 (49.12–50.77)	7	539	91.20%	49.00 (48.20–49.80)	2	351	0.00%	1.19 (−0.15 to 2.52)
SAQ												
Pleasure	1	528	0.00%	11.30 (10.92–11.68)	11	1406	77.30%	10.43 (10.22–10.64)	1	313	0.00%	−0.70 (−1.33 to −0.07)[a]
Discomfort	0	0	NA	NA	6	571	95.90%	2.44 (2.38–2.50)	0	0	NA	NA
Habit	1	528	0.00%	0.70 (0.64–0.76)	10	1205	90.70%	0.83 (0.78–0.88)	1	313	0.00%	0.05 (−0.05 to 0.15)
MRS												
Overall score	0	0	NA	NA	2	68	0.00%	11.67 (9.85–13.49)	0	0	NA	NA
FACT-ES												
Overall score	1	528	0.00%	58.00 (57.29–58.71)	2	682	97.20%	58.16 (57.49–58.83)	1	313	0.00%	2.10 (0.94–3.26)

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(continued)

TABLE 4
Quality of life outcomes following risk-reducing salpingo-oophorectomy *(continued)*

(3) High-risk definition	Diagnosis of PV in BC/OC CSGs				Mixed or unknown basis				Diagnosis of PV in BC/OC CSGs vs mixed or unknown basis			
	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SF-36												
PCS	4	135	94.90%	53.94 (52.18–55.69)	3	404	0.00%	51.02 (50.05–52.00)	0	0	NA	NA
MCS	4	135	83.80%	44.89 (43.48–46.29)	3	404	0.00%	50.97 (50.00–51.95)	0	0	NA	NA

(4) Menopause status	Premenopausal RRSO				Postmenopausal RRSO				Postmenopausal RRSO vs premenopausal RSSO			
	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SF-36												
PCS	2	75	97.91%	55.39 (53.13–57.65)	1	30	0.00%	48.71 (45.13–52.29)	1	90	0.00%	−3.19 (−7.54 to 1.16)
MCS	2	75	0.00%	47.95 (45.69–50.22)	1	30	0.00%	47.0 (43.42–50.58)	1	90	0.00%	−0.60 (−4.95 to 3.75)
SAQ												
Pleasure	4	266	0.00%	11.34 (10.85–11.84)	3	160	76.50%	11.29 (10.59–11.99)	3	414	65.03%	−0.13 (−1.00 to 0.74)
Discomfort	2	126	91.20%	3.41 (3.02–3.79)	1	109	0.00%	3.67 (3.25–4.09)	1	223	0.00%	0 (−0.59 to 0.59)
Habit	4	266	98.30%	1.24 (1.14–1.33)	3	160	99.10%	1.04 (0.96–1.12)	3	414	0.00%	−0.04 (−0.17 to 0.10)

(5) HRT use following premenopausal RRSO	HRT				No HRT				HRT vs no HRT			
	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Score (95% CI)	Studies	N	I^2	Difference (95% CI)
SAQ												
Pleasure	3	126	0.00%	11.59 (10.87–12.30)	4	224	0.00%	10.44 (9.86–11.02)	3	291	0.00%	1.16 (0.17–2.15)[a]
Discomfort	1	66	0.00%	1.20 (0.86–1.54)	2	150	0.00%	2.14 (1.80–2.48)	1	157	0.00%	−1.20 (−1.75 to −0.65)[a]
Habit	2	60	0.00%	0.80 (0.61–0.99)	3	133	71.90%	0.80 (0.70–0.91)	2	134	0.00%	0.16 (−0.09 to 0.42)

The following meta-analyses were conducted for quality of life (QoL) outcomes after RRSO: (1) intervention: QoL outcomes in women who underwent RRSO vs those who did not; data were available for SF-36, SAQ, MRS, and FACT-ES; (2) follow-up: long-term vs short-term QoL outcomes following RRSO; a period of ≥1 year was defined as long-term follow-up for RRSO, and data were available for SF-36, SAQ, MRS, and FACT-ES; (3) high-risk definition: QoL outcomes in high-risk women with PVs in BC/OC CGSs (eg, *BRCA1/BRCA2*) vs high-risk women according to mixed (CSG or family history) or unspecified criteria; data were available for SF-36; (4) menopause status: QoL outcomes following postmenopausal RRSO vs premenopausal RRSO; data were available for SF-36 and SAQ; and (5) HRT use: QoL outcomes in women undergoing premenopausal RRSO who took HRT vs those who did not; data were available for SAQ. For each comparison, the effect size of each single arm and the difference between the 2 arms were calculated.

BC, breast cancer; *CI*, confidence interval; *CSG*, cancer susceptibility gene; *FACT-ES*, Functional Assessment of Cancer Therapy - Endocrine Symptoms; *HRT*, hormone replacement therapy; *MCS*, Mental Component Summary; *MRS*, Menopause Rating Scale; *NA*, not applicable; *OC*, ovarian cancer; *PCS*, Physical Component Summary; *PV*, pathogenic variant; *RRSO*, risk-reducing salpingo-oophorectomy; *SAQ*, Sexual Activity Questionnaire; *SF-36*, 36-Item Short Form Health Survey.

[a] A *P* value of <.05 was considered as statistically significant.

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et al[79] found increased depressive symptoms after RRSO. Only 1 study used HADS, and thus no meta-analysis was conducted.

Quality of life outcomes after risk-reducing early salpingectomy and delayed oophorectomy

Nebgen et al,[51] in a pilot study of 43 premenopausal *BRCA1/2* carriers (early salpingectomy: 19; RRSO: 12; screening: 12), reported that women undergoing early salpingectomy postoperatively experienced decreased cancer-related worry and distress, with unaffected HRQoL and body image. They described a trend of unaffected sexual function and no menopausal symptoms after early salpingectomy.

The TUBA study[52] recruited 577 premenopausal *BRCA1/2* carriers and reported initial 1-year follow-up outcomes for 548 patients (394 for early salpingectomy vs 154 for RRSO). They found that early salpingectomy reduced cancer-related worry, with unaffected HRQoL. Importantly, they found increased menopausal symptoms (Greene Climacteric Scale) from baseline 1 year after RRSO in women without HRT (effect size: 6.7; 95% CI, 5.0−8.4) and with HRT (effect size: 3.6; 95% CI, 2.3−4.8) compared with women undergoing early salpingectomy. In addition, they reported more frequently impaired sexual function following RRSO over 1 year (baseline: 35.8%; 1 year: 55.6%), but not with early salpingectomy (baseline: 31.2%; 1 year: 28.2%). Compared with RRSO, early salpingectomy has better menopause-specific QoL and sexual function.

Comment

Findings

Our systematic review summarizes published evidence and provides a meta-analysis of various QoL outcomes following RRS in women with increased BC/OC risk. Overall, HRQoL was unlikely to be negatively affected after RRM or RRSO, although short-term physical deficits were reported in a small number of studies for RRM and RRSO. For RRSO, this was supported by a meta-analysis including 1050 women (Table 4). Sexual function seemed negatively affected (reduced sexual frequency, sensation, and pleasure) in 4 of 13 studies after RRM, although this could not be supported by a meta-analysis. However, our meta-analysis including 3070 women confirmed that RRSO negatively affected sexual function, particularly with respect to sexual pleasure and sexual discomfort, which were worse in premenopausal women not on HRT (Table 4). The evidence on body image after RRM was conflicting, with some studies reporting long-term body image problems despite reconstruction. Body image is not a problem reported after RRSO because it involves no disfigurement. However, significant menopause symptoms occur, especially in premenopausal women, after RRSO. This was reconfirmed in our meta-analysis of RSSO vs no RRSO involving 1745 women and FACT-ES scores (Table 4). Although studies indicate that HRT can mitigate these symptoms, data could not be meta-analyzed by menopause status or HRT use. Preliminary data suggested that early salpingectomy did not detrimentally affect sexual function, and involved fewer menopause symptoms than RRSO. Most studies reported decreased cancer-related distress after RRM or RRSO, despite 2 studies[35,71] reporting moderate to severe cancer-related distress in a small proportion after RRSO. RRM and RRSO did not negatively affect general anxiety or depression in most studies, although 3 studies reported increased depressive symptoms after RRM[55] and RRSO.[78,79] For RRM, this was supported by the pooled estimation of 56 women (Table 3).

Interpretation

This systematic review can act as a guide or tool (Appendix 6) for clinicians counseling women about RRS. Where evidence allows, we delineate the actual burden of the impact of RRS on HRQoL, sexual function, body image, menopause, and psychological well-being. Whether to undergo RRS can be a complex and dynamic decision, which changes with time, and this will be influenced by other risk factors including presence of a PV in CSGs or a personal history or FH of cancer.[45] Although effective in reducing cancer risk, women need to be made aware that these operations may detrimentally affect other long-term health outcomes. The summarized QoL impact of RRS can facilitate improved informed decision-making for women at increased BC/OC risk to choose between surgical prevention and other available options (BC screening or BC/OC medical prevention).

Although RRM is a well-established prevention strategy in women at high risk of BC, apart from surgical risks,[84,85] a consensus regarding its impact on QoL outcomes is lacking. Despite unaffected HRQoL after RRM, along with reconstructive surgery, RRM has a substantial complication rate and an equivocal impact on body image, with several studies reporting no impact[49,58,61−63,68,82] and potential deficits with reconstruction.[55,56,60,64,66,67] This is reflected in the disutility of 0.88 that has been reported for RRM.[86] Although a number of studies reported reduced cancer-related distress after RRM, 1 study indicated that perceived distress and body image might be worse in *BRCA1/2* carriers and women with a strong FH.[64] There is some evidence of a negative impact of RRM with less frequent sex within 2 years after surgery, as opposed to after 2 years, although less sexual discomfort was also reported. The potential effects of RRM on sexual function and/or body image should be discussed with women during decision-making. Patient pathways in many centers include mandatory appointments with a psychologist as part of the decision-making process. Nevertheless, RRM is cost-effective and has high satisfaction of ∼97% and minimal decision regret,[64] which along with our systematic review findings strongly supports RRM as an acceptable approach for BC prevention.

Current guidelines from the National Comprehensive Cancer Network, Royal College of Obstetricians and Gynaecologists (RCOG), and UK Cancer Genetics Group recommend RRSO as the standard of care for OC-risk reduction for women at increased risk of OC.[19,41,87] RRSO is the most clinically effective strategy for reducing OC-risk. It reduces OC mortality and is cost-effective for

BRCA1/2 carriers[88] and women with more than 4% to 5% lifetime OC-risk,[32,33] saving a mean 7 to 10 life years at this risk threshold. RRSO is normally performed via minimal-access surgery and has a 3% to 5% complication rate.[89] In premenopausal women, RRSO increases the long-term health risks of osteoporosis/osteopenia, heart disease, and neurocognitive decline.[36] Our review and meta-analysis demonstrate that RRSO is unlikely to affect generic HRQoL, and any short-term deficits usually seem to resolve in the long term. Nevertheless, RRSO has a negative impact on sexual function in pre- and postmenopausal women. Although sexual function seemed worse in terms of effect size in postmenopausal compared with premenopausal women, there was a lack of baseline data before RRSO, which precludes the ability to determine the difference in effect of RRSO between the 2 groups. In addition, most studies (12/13) found that both pre- and postmenopausal women reported de novo or aggravated menopause symptoms after RRSO. Several studies[50,52,72,73] demonstrated that HRT may mitigate menopause symptoms and improve sexual function, and the latter was confirmed in our meta-analysis (Table 4). However, HRT cannot fully resolve menopause symptoms or sexual dysfunction, which remains worse compared with women not undergoing surgery. Short-term HRT in these women seems safe and (if not contraindicated) is recommended until the age of natural menopause.[19,36] HRT management following premature surgical menopause is thus critically important for symptom control, sexual function, and ameliorating long-term detrimental health consequences. HRT compliance and satisfaction seem higher in women managed in specialist centers or high-risk familial cancer clinics.[36,90] RRSO also alleviates cancer-related distress and worry, and has high acceptability and satisfaction rates (>85%),[74] although the decision regret rate is much higher in premenopausal (∼9%) than in postmenopausal (∼1%) women.[36,37] Women undergoing RRSO should receive nondirective counseling and information on the pros and cons of surgery to facilitate informed decision-making. Emerging data suggest that women would like to be offered psychological support and prefer to be managed in specialist clinics.[90] There is an emerging demand for joint RRSO and RRM procedures undertaken concurrently,[37] but relevant QoL outcome data in this context are lacking.

The detrimental long-term health sequelae, menopause symptoms, and sexual dysfunction observed after RRSO and highlighted in our meta-analysis indicate the importance of and need for using HRT, making further efforts to improve symptom management, and studying novel approaches such as RRESDO. RRESDO has high acceptability among women concerned about menopause/sexual dysfunction,[37] but only 2 studies report preliminary results.[51,52] Preliminary data from the TUBA study demonstrated improved sexual function and menopause symptoms compared with RRSO with and without HRT.[52] However, the effect size of OC risk reduction from early salpingectomy and risk of interval cancers remains unknown. In addition, the long-term impact on menopause or endocrine function is not established. These issues need addressing before recommending change in clinical practice guidelines and widespread implementation.[87,91] RRESDO is not considered standard of care,[41] and is currently offered in the context of clinical trials within the United States and Europe.[42–44] The UK Cancer Genetics Group and RCOG recommend RRSO as the primary method of surgical prevention and that early salpingectomy is best offered in a research setting.[19,87] RRESDO requires comprehensive counseling, ideally in specialist centers, along with thorough pathology evaluation incorporating the SEE-FIM (Sectioning and Extensively Examining the Fimbriated End Protocol) protocol[92] and pelvic peritoneal washings, with any serous tubal intraepithelial carcinoma lesions urgently referred for completion surgery and reviewed by a gynecologic oncology multidisciplinary team.

Our review summarizes the QoL outcomes reported (HRQoL, sexual function, body image, menopause symptoms, psychological well-being) and highlights the various commonly used tools/questionnaires for each of them (Appendix 2). There is a clear need to establish a unified approach and develop core outcome sets for reporting QoL outcomes after RRS to optimize potential evidence synthesis. In addition, the questionnaires/methodologies used preclude the ability to obtain utility scores of RRS from these studies, although the SF-36 used by some could be converted to utility scores using algorithms.[93] Utility scores are necessary for cost-effectiveness analysis to support health policy decision-making. Currently, only Grann et al[86,94] investigated the utility scores for RRM and RRSO using time trade-off survey, where participants did not undergo the relevant surgery. High-quality prospective studies are needed in women undergoing RRS using an appropriate reporting tool.

Strengths and limitations

This was a comprehensive systematic review of all available QoL outcomes after RRS in women at increased BC/OC risk. We followed high-standard prospective methodology per PRISMA guidelines, and provided quantitative QoL outcome data using meta-analysis to support our qualitative results. Sensitivity analysis with random-effects models showed similar results to those of fixed-effects models. Our results can guide future prospective studies to address knowledge gaps and missing or conflicting evidence where applicable. We clearly highlight the outcomes and reporting tools used in measuring QoL after RRS, which can serve as a guide for future trials or evidence synthesis studies.

We recognize a series of limitations. QoL is a heterogeneous topic with several outcomes and many reporting tools/questionnaires. This did not allow a good proportion of the data to be used for meta-analysis for more robust results. An agreed-upon standardized core outcome set for RRS outcomes needs to be developed. We noted substantial heterogeneity (I^2 >75%) for only 2 comparisons (Appendix 4 and 5), indicating that differences between study populations or procedures might affect

results. On several occasions, aggregate data were not fully available for inclusion in the meta-analysis, despite contacting the authors. Most studies (21/34) were deemed at high risk of bias for methodological quality, including short or unspecified duration of follow-up, >5% of participants lost to follow-up, and missing sample size calculation. This was considered during qualitative synthesis of data to draw conclusions. Most of our conclusions were compared and found to be in line with the high-quality studies. Similarly, studies that were deemed at high risk for external validity bias (9/34) lacked clarity on the criteria for high risk of BC/OC. However, we were unable to undertake sensitivity analysis for high-quality studies alone given the lack of adequate data.

Conclusions and implications

RRS may be associated with QoL outcomes. RRM and RRSO are well-tolerated procedures, do not seem to affect generic HRQoL, and reduce cancer-related distress and worry. There is strong evidence that RRSO detrimentally affects sexual function and leads to increased menopause symptoms, and HRT may mitigate those risks. Limited data suggest that RRM may affect sexual function, and studies stress the importance of discussing body image issues despite reconstruction. Effects of RRM and RRSO on QoL should be part of the counseling process, and women and clinicians should be aware of the potential effects. RRESDO may be a promising alternative to mitigate QoL-related risks compared with RRSO, but ongoing/future trials need to address evidence gaps such as cancer incidence to properly inform clinical practice. ■

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Appendix 1 Search strategy

1. Ovid MEDLINE

1 (utilit* or disutilit* or quality of life or QoL or health related quality of life or HRQoL).mp.
2 exp "Quality of Life"/
3 1 or 2
4 exp Prophylactic Surgical Procedures/
5 exp Mastectomy/
6 exp Ovariectomy/ or exp Salpingo-oophorectomy/
7 exp Salpingectomy/
8 ((prophylac* or prophylaxis or prevent* or risk-reduc* or risk reduc*) adj5 (surg* or procedur* or interven* or mastectom* or RRM or salping* or oophorectomy* or ovar* or RRSO or RRESDO)).mp.
9 4 or 5 or 6 or 7 or 8
10 exp Breast Neoplasms/
11 exp Ovarian Neoplasms/
12 exp Fallopian Tube Neoplasms/
13 exp Peritoneal Neoplasms/
14 ((ovar* or fallopian* or peritone* or breast or mammary) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).mp.
15 10 or 11 or 12 or 13 or 14
16 3 and 9 and 15
17 limit 16 to (english language and humans)

2. Embase Classic + Embase

1 exp prophylactic surgical procedure/
2 exp prophylactic mastectomy/ or exp mastectomy/
3 exp salpingooophorectomy/
4 exp ovariectomy/
5 exp salpingectomy/
6 ((prophylac* or prophylaxis or prevent* or risk-reduc* or risk reduc*) adj5 (surg* or procedur* or interven* or mastectom* or RRM or salping* or oophorectomy* or ovar* or RRSO or RRESDO)).mp.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp "quality of life"/
9 exp utility value/
10 (utilit* or disutilit* or quality of life or QoL or health related quality of life or HRQoL).mp.
11 8 or 9 or 10
12 exp breast tumor/
13 exp ovary tumor/
14 exp uterine tube tumor/
15 exp peritoneum tumor/
16 ((ovar* or fallopian* or peritone* or breast or mammary) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).mp.
17 12 or 13 or 14 or 15 or 16
18 7 and 11 and 17
19 limit 18 to (human and english language)

3. Cochrane Library

ID Search
#1 MeSH descriptor: [Mastectomy] explode all trees
#2 MeSH descriptor: [Salpingo-oophorectomy] explode all trees
#3 MeSH descriptor: [Ovariectomy] explode all trees
#4 MeSH descriptor: [Salpingectomy] explode all trees
#5 MeSH descriptor: [Prophylactic Surgical Procedures] explode all trees
#6 ((prophylac* or prophylaxis or prevent* or risk-reduc* or risk reduc*) near/5 (surg* or procedur* or interven* or mastectom* or RRM or salping* or oophorectomy* or ovar* or RRSO or RRESDO)):ti,ab,kw (Word variations have been searched)
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Breast Neoplasms] explode all trees
#9 MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees
#10 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#11 MeSH descriptor: [Peritoneal Neoplasms] explode all trees
#12 ((ovar* or fallopian* or peritone* or breast or mammary) near/5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)):ti,ab,kw (Word variations have been searched)
#13 #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Quality of Life] explode all trees
#15 (utilit* or disutilit* or quality of life or QoL or health related quality of life or HRQoL):ti,ab,kw (Word variations have been searched)
#16 #14 or #15
#17 #7 and #13 and #16

4. PubMed

1 prophylactic surgical procedure [MeSH Terms]
2 mastectomy[MeSH Terms]
3 salpingo-oophorectomy[MeSH Terms]
4 ovariectomy[MeSH Terms]
5 salpingectomy[MeSH Terms]
6 ((prophylac* or prophylaxis or prevent* or risk-reduc* or risk reduc*) near (surg* or procedur* or interven* or mastectom* or RRM or salping* or oophorectomy* or ovar* or RRSO or RRESDO))
7 breast neoplasm[MeSH Terms]
8 ovary neoplasm[MeSH Terms]
9 fallopian tube neoplasm[MeSH Terms]
10 peritoneal neoplasm[MeSH Terms]
11 (ovar* or fallopian* or peritone* or breast or mammary) near (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)
12 #1 or #2 or #3 or #4 or #5 or #6
13 #7 or #8 or #9 or #10 or #11
14 quality of life[MeSH Terms]
15 utilit* or disutilit* or quality of life or QoL or health related quality of life or HRQoL
16 #14 or #15
17 #12 and #13 and #16

APPENDIX 4

Results comparison between fixed-effects and random-effects models for risk-reducing mastectomy

Comparison	Fixed-effects model				Random-effects model			
	Studies	N	I^2	Difference (95% CI)	Studies	N	I^2	Difference (95% CI)
RRM vs no surgery								
SAQ								
Pleasure	1	56	0.00%	1.00 (−1.37 to 3.37)	1	56	0.00%	1.00 (−1.37 to 3.37)
Discomfort	1	56	0.00%	0.00 (−0.89 to 0.89)	1	56	0.00%	0.00 (−0.89 to 0.89)
Habit	1	56	0.00%	0.20 (−0.05 to 0.45)	1	56	0.00%	0.20 (−0.05 to 0.45)
HADS								
Anxiety	1	56	0.00%	0.10 (−1.76 to 1.96)	1	56	0.00%	0.10 (−1.76 to 1.96)
Depression	1	56	0.00%	−0.90 (−2.29 to 0.49)	1	56	0.00%	−0.90 (−2.29 to 0.49)
>2-y follow-up vs <2-y follow-up after RRM								
SF-36								
PCS	1	92	0.00%	−1.20 (−3.74 to 1.34)	1	92	0.00%	−1.20 (−3.74 to 1.34)
MCS	1	92	0.00%	−2.20 (−5.06 to 0.66)	1	92	0.00%	−2.20 (−5.06 to 0.66)
SAQ								
Pleasure	1	92	0.00%	−1.10 (−2.30 to 0.10)	1	92	0.00%	−1.10 (−2.30 to 0.10)
Discomfort	1	92	0.00%	0.50 (0.03−0.97)[a]	1	92	0.00%	0.50 (0.03−0.97)[a]
Habit	1	92	0.00%	0.20 (0.06−0.34)[a]	1	92	0.00%	0.20 (0.06−0.34)[a]
HADS								
Anxiety	1	92	0.00%	0.30 (−0.86 to 1.46)	1	92	0.00%	0.30 (−0.86 to 1.46)
Depression	1	92	0.00%	0.70 (−0.12 to 1.52)	1	92	0.00%	0.70 (−0.12 to 1.52)

CI, confidence interval; *HADS*, Hospital Anxiety and Depression Scale; *MCS*, Mental Component Summary; *PCS*, Physical Component Summary; *RRM*, risk-reducing mastectomy; *SAQ*, Sexual Activity Questionnaire; *SF-36*, 36-Item Short Form Health Survey.

[a] A *P* value of <.05 was considered as statistically significant.

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APPENDIX 5
Results comparison between fixed-effects and random-effects models for risk-reducing salpingo-oophorectomy

	Fixed-effects model				Random-effects model			
Comparison	**Studies**	**N**	I^2	**Difference (95% CI)**	**Studies**	**N**	I^2	**Difference (95% CI)**
RRSO vs no surgery								
SF-36								
PCS	4	1050	86.30%	−0.75 (−2.01 to 0.50)	4	1050	94.70%	1.24 (−7.63 to 10.12)
MCS	4	1050	0.00%	−0.14 (−1.33 to 1.04)	4	1050	0.00%	−0.14 (−1.33 to 1.04)
SAQ								
Pleasure	6	3070	0.00%	−1.21 (−1.53 to −0.89)[a]	6	3070	0.00%	−1.21 (−1.53 to −0.89)[a]
Discomfort	5	1400	0.00%	1.12 (0.93–1.31)[a]	5	1400	0.00%	1.12 (0.93–1.31)[a]
Habit	5	2145	5.50%	−0.02 (−0.08 to 0.03)	5	2145	5.50%	−0.02 (−0.08 to 0.03)
MRS								
Overall score	2	184	0.00%	2.08 (−0.21 to 4.37)	2	184	0.00%	2.08 (−0.21 to 4.37)
FACT-ES								
Overall score	2	1745	92.00%	−1.96 (−2.81 to −1.10)[a]	2	1745	91.97%	−2.13 (−5.17 to 0.90)
>1-y follow-up vs <1-y follow-up after RRSO								
SF-36								
PCS	2	351	0.00%	0.64 (−0.69 to 1.98)	2	351	0.00%	0.64 (−0.69 to 1.98)
MCS	2	351	0.00%	1.19 (−0.15 to 2.52)	2	351	0.00%	1.19 (−0.15 to 2.52)
SAQ								
Pleasure	1	313	0.00%	−0.70 (−1.33 to −0.07)[a]	1	313	0.00%	−0.70 (−1.33 to −0.07)[a]
Discomfort	0	0	NA	NA	0	0	NA	NA
Habit	1	313	0.00%	0.05 (−0.05 to 0.15)	1	313	0.00%	0.05 (−0.05 to 0.15)
MRS								
Overall score	0	0	NA	NA	0	0	NA	NA
FACT-ES								
Overall score	1	313	0.00%	2.10 (0.94–3.26)	1	313	0.00%	2.10 (0.94–3.26)
Diagnosis of PV in BC/OC CSGs vs mixed or unknown basis (for high-risk definition)								
SF-36								
PCS	0	0	NA	NA	0	0	NA	NA

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(continued)

APPENDIX 5

Results comparison between fixed-effects and random-effects models for risk-reducing salpingo-oophorectomy *(continued)*

	Fixed-effects model				Random-effects model			
Comparison	**Studies**	**N**	I^2	**Difference (95% CI)**	**Studies**	**N**	I^2	**Difference (95% CI)**
MCS	0	0	NA	NA	0	0	NA	NA
Postmenopausal RRSO vs premenopausal RSSO								
SF-36								
PCS	1	90	0.00%	−3.19 (−7.54 to 1.16)	1	90	0.00%	−3.19 (−7.54 to 1.16)
MCS	1	90	0.00%	−0.60 (−4.95 to 3.75)	1	90	0.00%	−0.60 (−4.95 to 3.75)
SAQ								
Pleasure	3	414	65.03%	−0.13 (−1.00 to 0.74)	3	414	62.74%	−0.59 (−2.19 to 1.02)
Discomfort	1	223	0.00%	0 (−0.59 to 0.59)	1	223	0.00%	0 (−0.59 to 0.59)
Habit	3	414	0.00%	−0.04 (−0.17 to 0.10)	3	414	0.00%	−0.04 (−0.17 to 0.10)
HRT vs no HRT following premenopausal RRSO								
SAQ								
Pleasure	3	291	0.00%	1.16 (0.17−2.15)[a]	3	291	0.00%	1.16 (0.17−2.15)[a]
Discomfort	1	157	0.00%	−1.20 (−1.75 to −0.65)[a]	1	157	0.00%	−1.20 (−1.75 to −0.65)[a]
Habit	2	134	0.00%	0.16 (−0.09 to 0.42)	2	134	0.00%	0.16 (−0.09 to 0.42)

BC, breast cancer; *CI*, confidence interval; *CSG*, cancer susceptibility gene; *FACT-ES*, Functional Assessment of Cancer Therapy - Endocrine Symptoms; *HRT*, hormone replacement therapy; *MCS*, Mental Component Summary; *MRS*, Menopause Rating Scale; *NA*, not applicable; *OC*, ovarian cancer; *PCS*, Physical Component Summary; *PV*, pathogenic variant; *RRSO*, risk-reducing salpingo-oophorectomy; *SAQ*, Sexual Activity Questionnaire; *SF-36*, 36-Item Short Form Health Survey.

[a] A *P* value of $<.05$ was considered as statistically significant.

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