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

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**Condensation:** Risk-reducing surgery is associated with body image problems post-mastectomy and sexual dysfunction and menopause symptoms post-salpingo-oophorectomy, while, early-salpingectomy has better sexual function and fewer menopause symptoms.

**Short title:** Breast/ovarian cancer prevention surgery quality-of-life

**AJOG at a Glance**

**A. Why was this study conducted?**

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

**B. What are the key findings?**

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

**C. What does this study add to what is already known?**

We demonstrate RRM/RRSO are well-tolerated, and reduce cancer distress. Women and clinicians should be aware of the negative impact of RRM on body image, and 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.

**Abstract**

**Objective**: To assess the impact of risk-reducing surgery (RRS) for breast cancer (BC) and ovarian cancer (OC) prevention on quality-of-life (QoL). We consider risk-reducing mastectomy (RRM), risk-reducing salpingo-oophorectomy (RRSO), and risk-reducing early-salpingectomy and delayed-oophorectomy (RRESDO).

**Data sources:** We followed a prospective protocol (PROSPERO: CRD42022319782) and searched MEDLINE, EMBASE, PubMed, and Cochrane Library from inception to February 2023.

**Study eligibility criteria:** We followed a PICOS framework. The population included women at increased risk of BC or OC. We focused on studies reporting QoL outcomes (health-related QoL (HRQoL), sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety or depression) after RRS, including RRM for BC and RRSO or RRESDO for OC.

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

**Results:** Thirty-four studies were included (RRM:16 studies, RRSO: 19 studies, RRESDO: 2 studies). HRQoL was unchanged or improved in 13/15 studies post-RRM (N=986) and 10/16 studies post-RRSO (N=1617), despite short-term deficits (N=96 post-RRM and N=459 post-RRSO). Sexual function (using Sexual Activity Questionnaire) was affected in 13/16 studies (N=1400) post-RRSO, in terms of decreased sexual pleasure (-1.21[-1.53,-0.89]; N=3070) and increased sexual discomfort (1.12[0.93,1.31]; N=1400). Hormone replacement therapy after pre-menopausal RRSO was associated with an increase (1.16[0.17,2.15]; N=291) in sexual

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pleasure and a decrease (-1.20[-1.75,-0.65]; N=157) in sexual discomfort. Sexual function was affected in 4/13 studies (N=147) post-RRM, but stable in 9/13 studies (N=799). Body image was unaffected in 7/13 studies (N=605) post-RRM, whereas 6/13 studies (N=391) reported worsening. Increased menopause symptoms were reported in 12/13 studies (N=1759) post-RRSO with a reduction (-1.96[-2.81,-1.10]; N=1745) in Functional Assessment of Cancer Therapy-Endocrine Subscale. Cancer-related distress was unchanged or decreased in 5/5 studies post-RRM (N=365) and 8/10 studies post-RRSO (N=1223). RRESDO (2 studies, N=413) had better sexual function and menopause-specific QoL.

**Conclusion:** RRS may be associated with QoL outcomes. RRM and RRSO reduce cancer-related distress, and do not affect HRQoL. Women and clinicians should be aware of body image problems post-RRM, together-with sexual dysfunction and menopause symptoms post-RRSO. RRESDO may be a promising alternative to mitigate QoL-related risks of RRSO.

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

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## INTRODUCTION

Around 4% of breast cancer (BC)[1,2] and 15–20% 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 around 69–72% (59–79%) and 67–69% (51–80%) lifetime BC-risk, and 44–48% (36–65%) and 17–30% (11–46%) lifetime OC-risk, respectively.[5,6] This compares to the population lifetime risk of 12.9–15% for BC and 1.3–2% for OC.[7,8] Increasing awareness and acceptability of genetic testing, falling costs, coupled with 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. Additionally, complex risk algorithms incorporating genetic (CSGs and polygenic risk score (PRS)) along-with non-genetic (family history (FH)/epidemiologic/reproductive/hormonal profile/mammographic density) variables are now available and provide personalised risk prediction for BC and OC.[14-16]

Effective strategies which 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 oestrogen 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 programmes are unavailable for high-risk women. Among these strategies, risk-reducing surgery (RRS) remains the most clinically effective preventive option whose uptake has hugely increased over the years.[23]

RRM is offered to women with a lifetime BC-risk over 30–40%,[17,24] providing 89–95% cancer risk-reduction.[25-27] The timing of reconstruction including synthetic implants/autologous tissue

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(TRAM/DIEP) flaps,[28] can vary, with most preferring immediate reconstruction. RRSO is the gold-standard OC preventive strategy, reducing OC-risk by 80–97%.[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 >4–5% lifetime OC-risk, including newer moderate-penetrance OC CSGs and women with a first-degree-relative with high-grade serous OC.[19,32,33]

Pre-menopausal oophorectomy leads to premature surgical menopause, impacting quality-of-life (QoL) outcomes like sexual function and vasomotor/menopausal symptoms.[34,35] It is associated with long-term detrimental sequelae like coronary heart disease, osteoporosis, and cognitive decline, although these may be ameliorated by hormone replacement therapy (HRT).[36] Besides, a higher decision regret rate for pre-menopausal (compared to post-menopausal) RRSO has been reported.[37] The widespread acceptance of the fallopian tube as the site of origin of most serous epithelial OC along-with the detrimental health sequelae of early menopause has supported introduction of a novel two-step strategy of risk-reducing early-salpingectomy (RRES) and delayed-oophorectomy (DO) (RRESDO).[38-40] This allows pre-menopausal women wishing to decline/delay RRSO, a degree of OC risk-reduction, whilst avoiding premature menopause. Given limited outcome data, it is not considered standard of care[41] and currently offered in clinical trials within USA/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. A number of factors may influence this such as, carrying a PV, cancer risk perception, FH/personal history of cancer, menopause status, fertility wishes, relationship status.[45] Whilst surgery significantly reduces BC or OC risk and improves cancer-related worry,[27] it encompasses surgical risks, particularly with complex breast reconstruction.

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RRM may adversely impact the psychological/physical well-being of patients following consequent morbidities and body image issues.[46] While HRT may ameliorate outcomes of premature menopause, it remains contraindicated for many women with BC. RRES is of unproven benefit, and unlike RRSO will 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 minimise decision regret. To our knowledge, no systematic review has attempted to collectively summarise 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 consider RRM, RRSO, and RRESDO. Secondary aims are to compare long-term vs short-term QoL outcomes after RRS; the impact of menopausal status and/or use of HRT following RRSO; and whether confirmed diagnosis of PV in BC or OC CSGs vs. FH-based diagnosis affects post-operative QoL outcomes.

## METHODS

We conducted the systematic review and meta-analysis using a prospectively registered protocol (PROSPERO: CRD42022319782) and reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[48]

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*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 XW/SO/MS). The search strategy was validated[48] by evaluating whether it could identify a set of four clearly eligible studies identified on preliminary searches.[49-52] Additionally, 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: 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 >30–40% or >5% lifetime risk of BC or OC respectively.[19] Intervention: We focused on RRM for BC prevention, and RRSO or RRESDO for OC prevention. Comparison: We compared QoL outcomes in women undergoing RRS vs 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-years period was defined as long-term follow-up; (2) women with PVs in BC/OC CSGs (e.g., *BRCA1/BRCA2*) vs. those with FH-based risk; (3) post-menopausal vs. pre-menopausal RRSO; (4) pre-menopausal RRSO in HRT users vs. non-users. Outcome: We included studies reporting QoL outcomes on HRQoL, sexual function, menopause symptoms, body image, cancer-related distress or worry, anxiety or depression using validated questionnaires/tools. Study design: We included any study design (prospective/retrospective cohort studies, randomised/non-randomised trials, or case-series), that follows our PICOS framework.

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*Exclusion criteria*

Excluded studies included women who (1) underwent RRM with a personal history of BC; (2) underwent RRSO/RRESDO with a personal history of OC; (3) are at population risk (not increased risk) of BC or OC; (4) case reports; (5) review articles.

*Selection process*

Retrieved titles were transferred into EndNote (version: 20.2, Clarivate Analytics) and duplicates removed. Two reviewers (XW/SO) independently screened titles and abstracts. Full texts of the shortlisted abstracts were subsequently retrieved independently by XW/SO to assess eligibility for inclusion. Disagreements were resolved by a third reviewer (MS) or senior author (RM).

*Quality assessment*

Two reviewers (XW/SO) independently assessed the methodological quality of included studies using the Methodological index for non-randomized studies (MINORS), with any discrepancies resolved by MS. A three-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 non-comparative (8 items) and 24 for comparative studies (12 items). A score $\leq$12 for non-comparative and $\leq$20 for comparative studies was considered high-risk of bias.[54] We also assessed the external validity of included studies (representativeness of findings) based on 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 as high-risk of bias for external validity.

*Data extraction*

XW extracted Data using predesigned tables, and SO cross-checked this, with any disagreements resolved by MS/RM. We extracted data on study design, population, 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 pre-designed subgroups.

*Statistical analysis*

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

## RESULTS

*Study characteristics*

Figure-2 summarises the study selection process. From 11731 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 post-surgery

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follow-up ranged 1-23 years for RRM, 1-6 years for RRSO and 1-year for RRESDO. RRM was offered to high-risk women following CSG diagnosis in 3 studies (N=202), or mixed (CSG/FH-based) or unspecified criteria in 13 studies (N=900). RRSO was offered following CSG diagnosis in 8 studies (N=621), or mixed/unspecified criteria in 11 studies (N=1626). RRESDO was offered following CSG diagnosis (2 studies). Table-1 summarises 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 questionnaire was 36-Item Short-Form Health Survey (SF-36, 8 studies) and BREAST-Q (7 studies). Six 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). Six other validated/study specific questionnaires were used by 14 studies.

Thirteen studies (N=1789) after RRSO and 2 studies (N=413) after RRESDO reported menopause symptoms. The most frequently used questionnaires were Menopause-Specific Quality-of-Life (MENQOL, 3 studies), Functional-Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES, 3 studies) and Menopause Rating-Scale (MRS, 3 studies). Four studies used 4 other questionnaires.

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

Psychological outcomes including cancer-related distress or worry, anxiety or depression was reported by 9 studies (N=696) after RRM, 14 studies (N=1797) after RRSO and 2 studies (N=413) after RRESDO. The commonest questionnaires were Impact of Event Scale (IES, 10 studies), Hospital Anxiety-&-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*

For MINORS score see Figure-3 and Appendix-3. The median MINORS score was 20(IQR:19–21) for 11 comparative and 12(IQR:12–13) for 23 non-comparative studies. Short (<1-year post-RRSO or <2-years post-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 low-risk of bias for methodological quality, whereas 21 studies (N=4046) were high-risk of bias. Regarding external validity, 9 studies (N=2255) were deemed high-risk of bias and 25 studies (N=4509) were low-risk of bias.

*Data synthesis*

Table-2 demonstrates the qualitative synthesis of QoL outcomes following RRS in 34 studies. Amongst them, 29 studies provided data for meta-analysis. Based on the number of studies using each questionnaire (Appendix-2), we undertook quantitative synthesis from studies where means and standard deviation (SD) of questionnaire results was extractable. For HRQoL,

SF-36 data was meta-analysed. To maximize available data, we used SD estimates of SF-36 summary score from the country-specific general population[55] when studies lacked this information. For sexual function, we meta-analysed SAQ results. BIS results for body image were not meta-analysed due to data insufficiency. Results of FACT-ES and MRS were meta-analysed for menopause symptoms, while MENQOL results were not as only one study provided SD. HADS results were meta-analysed for anxiety and depression, while IES and STAI (cancer-related distress) lacked SD. Where data allowed, pre-specified subgroup analyses were undertaken. The fixed-effects meta-analysis results are summarised in Table-3 (RRM) and Table-4 (RRSO). A table comparing random-effects meta-analysis outcomes to the fixed-effects outcomes is given in Appendix-4, which demonstrates similar results from both models.

*QoL outcomes after RRM*

-HRQoL

The HRQoL including physical and mental components was unaffected in twelve studies[49,56-66] and improved in one study[67] following RRM. Geiger[59] found similar long-term HRQoL in both high-risk women undergoing RRM and controls. Spindler[62] demonstrated similar HRQoL after RRM with simultaneous reconstruction compared to general population reference values. Bai[56] found long-term HRQoL remained unchanged after RRM. Miseré[67] found improved physical well-being for autologous reconstruction vs. implant-based reconstruction after RRM. However, Gopie[68] reported generic mental health improved but generic physical health declined 6-months after RRM, returning to baseline level 21-months after surgery. Mansour[69] also reported poor physical well-being post-RRM.

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

-Sexual function

Four studies[56-58,69] concluded that RRM negatively impacted sexual function, including reduced sexual frequency, sensation and pleasure. Metcalfe[64] found better sexual well-being after nipple and areola-sparing RRM vs. skin-sparing RRM. However, another eight studies[49,62,63,65-68,70] reported unchanged sexual function (pleasure/discomfort/habit) after RRM with reconstruction.

Three of four studies provided SAQ data for meta-analysis. Comparing RRM vs. no surgery found little difference in any SAQ component from the pooled estimates of one study[70] (Table-3). When comparing different follow-up timeframes (>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 seen in women >2-years follow-up (Table-3). However, these results were based on a single study.[56]

-Body image

Women reported satisfactory aesthetic outcomes following RRM with reconstruction.[49,60,62,63,66,69,70] Women undergoing reconstruction following RRM reported higher satisfaction with general body shape and appearance than those without reconstruction.[65] Additionally, women reported better body image with nipple and areola-sparing RRM than skin-sparing RRM;[64] and higher satisfaction with breasts following

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348 autologous reconstruction than implant-based reconstruction.[67] Another three studies[56,57,68]
349 reported body image problems post-RRM despite reconstruction, with problems persisting
350 long-term (11.5-years follow-up)[56]. Four studies using BIS lacked SD for meta-analysis.
351
352 -Cancer-related distress
353 Two studies[68,70] reported decreased cancer-related distress after RRM, while two[59,65] found
354 little appreciable difference following RRM vs. no surgery. Comparable level of cancer-related
355 distress was reported after nipple and areola-sparing RRM vs. skin-sparing RRM.[64] Metcalfe[65]
356 reported higher cancer-related distress in women with strong FH of BC or *BRCA1/2* PV than
357 those with limited FH after RRM. Four studies evaluated cancer-related distress using IES but
358 lacked SD for meta-analysis.
359
360 -Anxiety or depression
361 Two studies[49,57] reported decreased general anxiety, while other studies found little impact on
362 general anxiety[60,64,70] and depression[49,57,59,60,64,70] post-RRM. Bai[56] reported unchanged general
363 anxiety but higher levels of depression with long-term follow-up.
364
365 Three of five studies using HADS provided data for meta-analysis. There was no significant
366 difference when comparing women who underwent RRM vs. no surgery (N=56) or across
367 different follow-up timeframes (N=92) (Table-3).
368
369 *QoL outcomes after RRSO*
370 -HRQoL
371 Eight studies[34,35,51,71-75] reported HRQoL including physical and mental components was
372 unaffected after RRSO. Mai[76] and Johansen[50] reported improved HRQoL post-RRSO, and

stable HRQoL with screening for women with increased OC-risk. Five studies[52,77-80] reported short-term deficits (poorer physical/social functioning, more physical role limitations, greater pain/discomfort, less vitality) following RRSO; Fang[77] reported that despite short-term deficits in most components (1-month, SF-36), most women recovered to baseline functioning at 6 and 12-months follow-up. Hall[81] concluded that pre-menopausal RRSO did not affect HRQoL, while the physical component declined amongst post-menopausal women.

Table-4 summarises pooled QoL estimates following RRSO. Six of ten 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.[34,35,50-52,70,72,74,76-78,81,82] This included both pre-menopausal and post-menopausal women. Four studies[50,52,81,82] showed that HRT may mitigate these risks for pre-menopausal women but not to pre-surgical levels. Fang[77] reported sexual discomfort improved after 1-year follow-up compared to 6-months, while Mai[76] concluded sexual function declined during 5-years follow-up. In contrast, three studies[75,80,83] found little difference in sexual function post-RRSO vs. no surgery; and also reported little difference in sexual function between pre- vs. post-menopausal RRSO.[83]

Nine of ten studies using SAQ provided data for meta-analysis. However, four studies[72,76,81,82] used reversed score for the discomfort component of SAQ, and hence, could not be meta-analysed with the remaining studies. Our meta-analysis (Table-4) demonstrated a significant decrease in the pleasure domain (-1.21(95%CI:-1.53,-0.89); $I^2$=0%; N=3070), and an increase

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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,-0.07); $I^2$=0%; N=313) across different timeframes after RRSO (>1-year vs. <1-year). In pre-menopausal 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,-0.65); $I^2$=0%; N=157). Little difference was reported across any other comparison.

-Menopause symptoms

Twelve studies[34,35,51,52,70,72,74,76,79,81-83] reported increased menopause symptoms including hot flashes, night sweats, and sleep disturbances following RRSO vs. no surgery, while Chae[80] reported little difference in menopause symptoms between RRSO and no surgery. Three studies[52,81,82] concluded that menopause symptoms could be mitigated by HRT, but not to pre-surgical levels.

Two of three studies using FACT-ES, and two of three 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,-1.10); $I^2$=92%; N=1745) and a trend difference of 2.08 ((95%CI:-0.21,4.37); $I^2$=0%; N=184) for MRS score (Table-4).

-Body image

Four studies[50,51,70,77] reported unaffected body image after RRSO, while women reported being less physically attractive in one study.[78] Three studies using BIS did not provide SD for meta-analysis.

-Cancer-related distress or worry

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Six studies[34,51,72,74,76,79] reported decreased cancer-related distress after RRSO, while another two studies[70,80] found little difference. Two studies[35,71] found a proportion of women continued to report moderate to severe cancer-related distress after RRSO, and these women were at risk for psychological distress. Additionally, four studies[51,52,78,83] reported decreased cancer worry after RRSO.

Six studies using IES and four 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 RRSO had no negative impact on general anxiety[70] and depression[35,70,77,80]. Although Mai[76] reported decreased depression after RRSO, Powell[83] and Stanisz[79] found increased depressive symptoms post-RRSO. Only one study used HADS, so no meta-analysis was conducted.

*QoL outcomes after RRESDO*

Nebgen[51], in a pilot study of 43 pre-menopausal *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 pre-menopausal *BRCA1/2* carriers and reported initial 1-year follow-up outcomes for 548 patients (394 for early-salpingectomy vs. 154 for RRSO). They

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448 found early-salpingectomy reduced cancer-related worry, with unaffected HRQoL.
449 Importantly, they found increased menopausal symptoms (Greene Climacteric Scale) from
450 baseline, 1-year after RRSO in women without HRT (effect-size: 6.7(95%CI:5.0,8.4)) and with
451 HRT (effect-size: 3.6(95%CI:2.3,4.8)) compared to women undergoing early-salpingectomy.
452 Additionally, they reported higher impaired sexual function following RRSO over 1-year
453 (baseline:35.8%, 1-year:55.6%) but not with early-salpingectomy (baseline:31.2%, 1-
454 year:28.2%). Compared with RRSO, early-salpingectomy has better menopausal-specific QoL
455 and sexual function.
456
457 **COMMENT**
458 *Findings*
459 Our systematic review summarizes published evidence and provides the first meta-analysis of
460 various QoL outcomes following RRS in women with increased BC/OC risk. Overall, HRQoL
461 was unlikely to be negatively affected after RRM or RRSO, although short-term physical
462 deficits were reported in a small number of studies for RRM and RRSO. For RRSO this was
463 supported by a meta-analysis including 1050 women (Table-4). Sexual function appeared
464 negatively affected (reduced sexual frequency, sensation and pleasure) in 4/13 studies post-
465 RRM, although this could not be supported by a meta-analysis. However, our meta-analysis in
466 3070 women confirmed RRSO negatively impacted sexual function, particularly with respect
467 to sexual pleasure and sexual discomfort, which were worse in pre-menopausal women not on
468 HRT (Table-4). The evidence on body image after RRM was conflicting, with some studies
469 reporting long-term body image problems despite reconstruction. Body image is not a problem
470 reported post-RRSO, as there is no disfigurement. However, significant menopause symptoms
471 occur, especially in pre-menopausal women after RRSO. This was re-confirmed in our meta-
472 analysis of RSSO vs no RRSO in 1745 women for FACT-ES score (Table-4). While studies

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indicate HRT can mitigate these symptoms, data could not be meta-analyzed by menopause status or HRT use. Preliminary data suggested early-salpingectomy did not detrimentally affect sexual function and had 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 or RRSO did not negatively impact general anxiety or depression in most studies, although 3 studies reported increased depressive symptoms after RRM[56] or RRSO[79,83]. For RRM this was supported by the pooled estimation of 56 women (Table-3).

*Interpretation*

This systematic review can act as a guide/tool (Appendix-5) for clinicians counselling 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. To undergo RRS or not 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] While effective in reducing cancer risk, women need to be made aware that these operations may detrimentally impact other long-term health outcomes. The summarised 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).

While 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 post-RRM, it along-with reconstructive surgery has a significant complication rate and an equivocal impact on body image with several studies reporting no

498 impact[49,60,62,63,66,69,70] and potential deficits with reconstruction[56,57,64,65,67,68]. This is reflected in
499 the disutility of 0.88 which has been reported for RRM.[86] While a number of studies reported
500 reduced cancer-related distress after RRM, one study indicated perceived distress and body
501 image might be worse in *BRCA1/2* carriers and women with a strong FH.[65] There is some
502 evidence of a negative impact of RRM with less frequent sex within 2-years post-surgery,
503 compared to after 2-years, although less sexual discomfort was also reported. The potential
504 effects of RRM on sexual function and/or body image should be discussed with women during
505 decision-making. Patient pathways in many/most centers include mandatory appointments with
506 a psychologist as part of the decision-making process. Nevertheless, RRM is cost-effective,
507 has high satisfaction of ~97% and minimal decision regret,[65] which along-with our systematic
508 review findings strongly supports RRM as an acceptable approach for BC prevention.
509
510 Current guidelines including NCCN, RCOG and UK Cancer Genetics Group recommend
511 RRSO as the standard of care for OC-risk reduction for women at increased risk of OC.[19,41,87]
512 RRSO is the most clinically effective strategy for reducing OC-risk, it reduces OC mortality
513 and is cost-effective for *BRCA1/2* carriers[88] and women >4–5% lifetime OC-risk[32,33], saving a
514 mean 7–10 life years at this risk threshold. RRSO is normally performed via minimal-access
515 surgery and has a 3–5% complication rate.[89] In pre-menopausal women, RRSO increases the
516 long-term health risks of osteoporosis/osteopenia, heart disease and neurocognitive decline.[36]
517 Our review and meta-analysis demonstrate that RRSO is unlikely to affect generic HRQoL,
518 and any short-term deficits usually seem to resolve in the long-term. Nevertheless, RRSO has
519 a negative impact on sexual function in pre- and post-menopausal women. Although sexual
520 function appeared worse in terms of effect size in post-menopausal compared to pre-
521 menopausal women, there was a lack of baseline data prior to RRSO which precludes the ability
522 to determine the difference in effect of RRSO between the two groups. Additionally, most

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studies (12/13) found that post-RRSO women reported de-novo or aggravation of menopause symptoms both in pre- and post-menopausal women. Several studies[50,52,81,82] demonstrated 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 to women not undergoing surgery. Short-term HRT in these women appears safe and (if not contraindicated) is recommended till 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 appear higher in women managed in specialist centres or high-risk familial cancer clinics.[36,90] RRSO also alleviates cancer-related distress, worry and has high acceptability and satisfaction rates (>85%),[72] although the decision regret rate is much higher in pre-menopausal (~9%) than post-menopausal (~1%) women.[36,37] Women undergoing RRSO should receive non-directive counselling and support highlighting the pros and cons of surgery to facilitate informed decision-making. Emerging data suggests 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 is lacking.

The detrimental long-term health sequelae, menopause symptoms and sexual dysfunction seen post-RRSO and highlighted in our meta-analysis establishes the importance/need for using HRT, extra efforts to improve symptom management, and study novel approaches like RRESDO. RRESDO has high acceptability among women concerned about menopause/sexual dysfunction,[37] but only two studies report preliminary results.[51,52] Preliminary data from the TUBA study demonstrated improved sexual function and menopause symptoms compared to

RRSO with/without HRT.[52] However, the effect size of OC risk-reduction from early-salpingectomy and risk of interval cancers remains unknown. Additionally, 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 USA/Europe.[42-44] 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 counselling, ideally in specialist centres, along with thorough pathology evaluation incorporating the SEE-FIM protocol[92] and pelvic peritoneal washings, with any serous tubal intraepithelial carcinoma (STIC) lesions urgently referred for completion surgery and reviewed by a gynaecological oncology MDT.

Our review summarises 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 optimise potential evidence synthesis. In addition, the questionnaires/methodologies used precludes 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[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.

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*Strengths and weaknesses*

To the best of our knowledge, this is the first comprehensive systematic review of all available QoL outcomes after RRS in women at increased BC/OC risk. We followed high standard prospective methodology as 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 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 post-RRS, which can serve as a guide for future trials or evidence synthesis studies.

We recognise a series of limitations. QoL is a heterogenous 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 standardised core outcome set for RRS outcomes needs developing. We noted substantial heterogeneity ($I^2$ >75%) for only two comparisons (Appendix-4), indicating that differences between study populations or procedures might affect results. On several occasions aggregate data was not fully available to include in the meta-analysis, despite contacting the authors. The majority of studies (21/34 studies) were assessed high-risk of bias for methodological quality, including short or unspecified duration of follow-up, >5% 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 high-risk for external validity bias (9/34 studies) 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 lack of adequate data.

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## CONCLUSIONS AND IMPLICATIONS

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

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622 **Data Availability Statement:** The datasets used or analyzed during the current study are
623 publicly available. Data generated from the analysis are presented. Any additional data needed
624 can be made available on reasonable request from the corresponding author.

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933 Table-1 Study characteristics

| Studies | Country | Study design | Population | Type of RRS | Sample size | Time since RRS | Main findings |
|---|---|---|---|---|---|---|---|
| Bai, 2019[56] | Sweden | Prospective cohort | *BRCA1/2* or FH of BC | RRM | 99 | 11.5 years | HRQoL and anxiety unchanged in long-term follow-up<br>Increased depression in long-term follow-up<br>Body image concerns persisted in long-term follow-up |
| Brandberg, 2008[57] | Sweden | Prospective cohort | *BRCA1/2* or FH of BC | RRM | 90 | 1 year | No negative impact on HRQoL and depression<br>Decrease in general anxiety<br>Negative impact on sexual function and body image |
| Gahm, 2010[58] | Sweden | Prospective cohort | *BRCA1/2* or FH of BC | RRM | 59 | 29 months | No negative impact on HRQoL<br>Reduced sexual function (85% sensation, 75% pleasure) |
| Gandhi, 2021[63] | UK | Prospective cohort | FH of BC | RRM | 241 | NR | No negative impact on HRQoL, sexual function and body image<br>Higher preoperative anxiety levels negatively affecting postoperative psychosocial well-being |
| Geiger, 2007[59] | USA | Cross-sectional | Increased BC-risk | RRM/Controls | 106/62 | 2-23 years | No impact on long-term HRQoL and depression |
| Gopie, 2013[68] | Netherlands | Prospective cohort | *BRCA1/2* or FH of BC | RRM | 48 | 21.7 months | No negative impact on HRQoL in long-term follow-up<br>Negative impact on body image<br>No negative impact on sexual function<br>Decrease in cancer-related distress |

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|---|---|---|---|---|---|---|---|
| Herold, 2022[66] | Germany | Prospective cohort | *BRCA1/2* | RRM | 43 | 43.3 months | No negative impact on HRQoL, sexual function and body image |
| Isern, 2008[60] | Sweden | Retrospective cohort | PV in BC/OC CSGs or FH of BC | RRM | 30 | 42 months | No impact on general anxiety and depression<br>No impact on HRQoL<br>Satisfactory body image |
| Mansour, 2023[69] | Australia | Prospective cohort | >25% lifetime BC-risk | RRM | 48 | 59 months | Negative impact on physical and sexual well-being<br>No negative impact on body image with reconstruction |
| McCarthy, 2017[49] | USA/Canada | Prospective cohort | Increased BC-risk | RRM | 204 | 5 years | No negative impact on HRQoL and sexual function<br>High satisfaction with body image<br>Decrease in general anxiety<br>No impact on depression |
| Metcalfe, 2004[65] | Canada | Cross-sectional | Increased BC-risk | RRM | 60 | 52.2 months | No negative impact on HRQoL<br>No negative impact on cancer-related distress, sexual activity, and body image |
| Metcalfe, 2005[61] | Canada | Cross-sectional | Increased BC-risk | RRM | 60 | 52.2 months | No negative impact on HRQoL |
| Metcalfe, 2015[64] | USA/Canada | Cross-sectional | *BRCA1/2* | RRM | 137 | 50.0 months | Improved body image and sexual function after nipple and areola-sparing RRM vs. skin-sparing RRM<br>Comparable levels of HRQoL and cancer-related distress<br>Comparable levels of anxiety or depression |

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|---|---|---|---|---|---|---|---|
| Miseré, 2022[67] | Netherlands | Cross-sectional | PV in BC CSGs or FH of BC | RRM | 47 | 39-39.5 months | Improved physical well-being and body image, together-with comparable sexual well-being after immediate autologous reconstruction vs. implant-based reconstruction |
| Spindler, 2021[62] | Germany | Prospective cohort | PV in BC/OC CSGs | RRM | 22 | 2.15 years | No negative impact on HRQoL and sexual function<br>No negative impact on body image with reconstruction |
| Chae, 2021[80] | 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<br>Negative impact on physical component of HRQoL |
| Elit, 2001[34] | Canada | Retrospective cohort | PV in BC/OC CSGs or FH of OC | RRSO | 40 | 5 years | No negative impact on HRQoL<br>Significant decrease in cancer-related distress<br>Development of menopausal symptoms<br>Negative impact on sexual function |
| Fang, 2009[77] | USA | Prospective cohort | PV in BC/OC CSGs or FH of BC/OC | RRSO/Controls | 38/37 | 1 year | Short-term deficits in physical component of HRQoL which recovered by 6- and 12-month<br>Potential impact on short-term sexual function<br>No negative impact on body image and depression |
| Finch,2013[71] | Canada | Prospective cohort | *BRCA1/2* | RRSO | 96 | 13.7 months | No negative impact on HRQoL<br>Persistent moderate to severe cancer-related distress in a subgroup of women |

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|---|---|---|---|---|---|---|---|
| Finch,2011[82] | Canada | Prospective cohort | *BRCA1/2* | RRSO | 114 | 13.6 months | Increase in vasomotor symptoms<br>Decrease in sexual function in pre-menopause women<br>Menopause symptoms and sexual dysfunction mitigated by HRT, but not to pre-surgical levels |
| Hall, 2019[81] | Canada | Prospective cohort | *BRCA1/2* | RRSO | 140 | 3.5 years | Pre-menopausal: no impact on HRQoL, development of menopause symptoms, decline in sexual function; menopause symptoms and sexual dysfunction mitigated by HRT, but not to pre-surgical levels<br>Post-menopausal: negative impact on HRQoL (physical components), decline in sexual function |
| Johansen, 2016[50] | Norway | Retrospective cohort | Increased BC/OC risk | RRSO/Controls | 294/1228 | 5 years | Improved HRQoL<br>Negative impact on sexual function<br>Sexual discomfort reduced by use of HRT |
| Madalinska, 2005[72] | Netherlands | Cross-sectional | FH of BC/OC | RRSO/Controls | 369/477 | 2.8 years | No negative impact on HRQoL<br>Decrease in cancer-related distress<br>Negative impact on menopause symptoms and sexual function |
| Mai, 2020[76] | USA/Australia | Prospective cohort | Increased OC-risk | RRSO/Controls | 562/1010 | 5 years | Decrease in cancer-related distress/depression<br>Improved HRQoL after RRSO vs. screening<br>Negative impact on menopause symptoms and sexual function |

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|---|---|---|---|---|---|---|---|
| Michelsen, 2009[73] | Norway | Prospective cohort | *BRCA1/2* or FH of BC/OC | RRSO/Controls | 301/903 | 5.3 years | No negative impact on HRQoL |
| Philp, 2021[78] | USA | Prospective cohort | PV in BC/OC CSGs or FH of OC | RRSO | 72 | NR | Decrease in cancer-related worry<br>Negative impact on body image<br>Negative impact on sexual function and short-term HRQoL |
| Powell, 2020[83] | USA | Cross-sectional | *BRCA1/2* | RRSO/Controls | 223/21 | 5 years | Decrease in cancer-related worry<br>No impact on sexual function<br>Negative impact on menopause symptoms<br>Negative impact on depression in pre-menopausal women |
| Robson, 2003[35] | USA | Cross-sectional | Increased OC-risk | RRSO | 54 | 23.8 months | No impact on HRQoL and depression<br>Negative impact on sexual function<br>Persistent cancer-related distress in a subgroup of women |
| Stanisz, 2019[79] | Poland | Prospective cohort | *BRCA1/2* | RRSO | 62 | 353 days | Negative impact on HRQoL<br>Negative impact on depression and menopause symptoms<br>Decrease in cancer-related distress |
| Touboul, 2011[74] | France | Retrospective cohort | Increased BC/OC risk | RRSO | 112 | 6.0 years | No impact on HRQoL<br>Decreased cancer-related distress<br>Negative impact on menopause symptoms<br>Decrease in sexual function |
| Tucker, 2020[75] | Australia | Cross-sectional | BC survivors | RRSO | 76 | 26 months | No impact on HRQoL |

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| | | | | | | | Baseline sexual function reduced prior RRSO (on diagnosis of BC)<br>RRSO does not impact sexual function further |
| Heiniger, 2015[70] | Australia/New Zealand | Prospective cohort | FH of BC/OC | RRM/Controls<br>RRSO/Controls | 17/39<br>38/94 | 3 years | No negative impact on general anxiety and depression after RRM/RRSO<br>Decrease in cancer-related distress after RRM<br>No negative impact on body image and sexual function after RRM<br>No negative impact on body image and cancer-related distress after RRSO<br>Negative impact on sexual function and menopause symptoms after RRSO |
| Nebgen, 2018[51] | USA | Prospective non-randomized study | *BRCA1/2* | RRESDO/RRSO /Controls | 19/12/12 | 1 year | No impact on HRQoL and body image<br>Decrease in cancer-related worry and distress<br>Trend of stable sexual function after salpingectomy, decrease in sexual function (discomfort) after RRSO<br>Trend of no menopause symptoms after salpingectomy, mild menopause symptoms after RRSO |
| Steenbeek, 2021[52] | Netherlands | Non-randomized controlled preference trial | *BRCA1/2* | RRESDO/RRSO | 394/154 | 1 year | Decreased cancer-related worry<br>No impact on HRQoL after salpingectomy, and short-term decline in physical component after RRSO |

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|---|---|
| | 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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937 Table-2 Qualitative synthesis of QoL outcomes following RRS

| Studies | Type of RRS | HRQoL | Sexual function | Menopause symptoms | Body image | Cancer distress | Cancer worry | Anxiety | Depression |
|---|---|---|---|---|---|---|---|---|---|
| Bai, 2019[56] | RRM | Not affected | Decline (habit) | Not applicable | Affected | Not investigated | Not investigated | Not affected | Increased |
| Brandberg, 2008[57] | RRM | Not affected | Decline (pleasure) | Not applicable | Affected | Not investigated | Not investigated | Decreased | Not affected |
| Gahm, 2010[58] | RRM | Not affected | Decline (sensation, pleasure) | Not applicable | Not investigated | Not investigated | Not investigated | Not investigated | Not investigated |
| Gandhi, 2021[63] | RRM | Not affected | Not affected | Not applicable | Not affected | Not investigated | Not investigated | Not reported | Not reported |
| Geiger, 2007[59] | RRM | Not affected | Not investigated | Not applicable | Not investigated | Not affected | Not investigated | Not investigated | Not affected |
| Gopie, 2013[68] | 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, 2015[70] | RRM | Not investigated | Not affected | Not applicable | Not affected | Decreased | Not investigated | Not affected | Not affected |
| Herold, 2022[66] | RRM | Not affected | Not affected | Not applicable | Not affected | Not investigated | Not investigated | Not investigated | Not investigated |
| Isern, 2008[60] | RRM | Not affected | Not investigated | Not applicable | Not affected | Not investigated | Not investigated | Not affected | Not affected |

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|---|---|---|---|---|---|---|---|---|---|
| Mansour, 2023[69] | RRM | Generic physical health declined | Affected sexual well-being | Not applicable | Not affected (with reconstruction) | Not investigated | Not investigated | Not investigated | Not investigated |
| McCarthy, 2017[49] | RRM | Not affected | Not affected | Not applicable | Not affected | Not investigated | Not investigated | Decreased | Not affected |
| Metcalfe, 2004[65] | RRM | Not affected | Not affected | Not applicable | Improved (with reconstruction) | Not affected | Not investigated | Not investigated | Not investigated |
| Metcalfe, 2005[61] | RRM | Not affected | Not investigated | Not applicable | Not investigated | Not investigated | Not investigated | Not investigated | Not investigated |
| Metcalfe, 2015[64] | Nipple and areola-sparing RRM vs. skin-sparing RRM | Comparable | Improved sexual well-being | Not applicable | Improved | Comparable | Not investigated | Comparable | Comparable |
| Miseré, 2022[67] | RRM with immediate autologous vs. implant-based reconstruction | Improved physical well-being | Comparable | Not applicable | Improved | Not investigated | Not investigated | Not investigated | Not investigated |
| Spindler, 2021[62] | RRM | Not affected | Not affected | Not applicable | Not affected (with reconstruction) | Not investigated | Not investigated | Not investigated | Not investigated |
| Chae, 2021[80] | RRSO | Decline (physical component) | Not affected | Not affected | Not investigated | Not affected | Not investigated | Not investigated | Not affected |
| Elit, 2001[34] | RRSO | Not affected | Decline (desire, vaginal dryness) | Increased | Not investigated | Decreased | Not investigated | Not investigated | Not investigated |

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| Fang, 2009[77] | RRSO | Short-term decline (physical component) Recovered by 6-month | Short-term decline (activity, pleasure, discomfort) | Not investigated | Not affected | Not investigated | Not investigated | Not investigated | Not affected |
| Finch, 2013[71] | RRSO | Not affected | Not investigated | Not investigated | Not investigated | Persistent cancer-related distress in a subgroup | Not investigated | Not investigated | Not investigated |
| Finch, 2011[82] | RRSO | Not investigated | Decline in pre-menopausal women (desire, pleasure, habit, discomfort) Mitigated by HRT, but not to pre-surgical levels | Increased Mitigated by HRT, but not to pre-surgical levels | Not investigated | Not investigated | Not investigated | Not investigated | Not investigated |
| Hall, 2019[81] | RRSO | Decline in post-menopausal women (physical component) | Decline (pleasure, discomfort) Mitigated by HRT, but not to pre-surgical levels | Increased in pre-menopausal women Mitigated by HRT, | Not investigated | Not investigated | Not investigated | Not investigated | Not investigated |

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| | | | | but not to pre-surgical levels | | | | | |
| Heiniger, 2015[70] | RRSO | Not investigated | Decline (discomfort) | Increased | Not affected | Not affected | Not investigated | Not affected | Not affected |
| Johansen, 2016[50] | RRSO | Improved | Decline in pre-menopausal women (pleasure, discomfort) Mitigated by HRT, but not to pre-surgical levels | Not investigated | Not affected | Not investigated | Not investigated | Not investigated | Not investigated |
| Madalinska, 2005[72] | RRSO | Not affected | Decline (pleasure, discomfort) | Increased | Not investigated | Decreased | Not investigated | Not investigated | Not investigated |
| Mai, 2020[76] | RRSO | Improved | Decline (pleasure, discomfort) | Increased | Not investigated | Decreased | Not investigated | Not investigated | Decreased |
| Michelsen, 2009[73] | RRSO | Not affected | Not investigated | Not investigated | Not reported | Not investigated | Not investigated | Not reported | Not reported |
| Nebgen, 2018[51] | RRSO | Not affected | Trend of decline (discomfort) | Trend of increase | Not affected | Decreased | Decreased | Not investigated | Not investigated |

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|---|---|---|---|---|---|---|---|---|---|
| Philp, 2021[78] | RRSO | Short-term decline (memory, social activities) | Decline (habit, interest) | Not investigated | Affected | Not investigated | Decreased | Not investigated | Not investigated |
| Powell, 2020[83] | RRSO | Not investigated | Not affected | Increased in pre-menopause women | Not investigated | Not investigated | Decreased | Not investigated | Increased |
| Robson, 2003[35] | RRSO | Not affected | Decline (discomfort) | Increased | Not investigated | Persistent cancer-related distress in a subgroup | Not investigated | Not investigated | Not affected |
| Stanisz, 2019[79] | RRSO | Decline (sleep problems) | Not investigated | Increased | Not investigated | Decreased | Not investigated | Not investigated | Increased |
| Steenbeek, 2021[52] | RRSO | Short-term decline (physical component) | Decline (function, distress)<br>Mitigated by HRT, but not to pre-surgical levels | Increased<br>Mitigated by HRT, but not to pre-surgical levels | Not investigated | Not investigated | Decreased | Not investigated | Not investigated |
| Touboul, 2011[74] | RRSO | Not affected | Decline (discomfort) | Increased | Not investigated | Decreased | Not investigated | Not investigated | Not investigated |
| Tucker, 2020[75] | RRSO | Not affected | Not affected | Not reported | Not investigated | Not investigated | Not investigated | Not investigated | Not investigated |
| Nebgen, 2018[51] | RRESDO | Not affected | Trend of unaffected | Trend of unaffected | Not affected | Decreased | Decreased | Not investigated | Not investigated |

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|---|---|---|---|---|---|---|---|---|---|
| Steenbeek, 2021[52] | RRESDO | Not affected | Not affected | Not affected | Not investigated | Not investigated | Decreased | Not investigated | Not investigated |

938 HRQoL, health-related quality-of-life; HRT, hormone replacement therapy; QoL, quality-of-life; RRESDO, risk-reducing early-salpingectomy and delayed-oophorectomy; RRM, risk-reducing
939 mastectomy; RRS, risk-reducing surgery; RRSO, risk-reducing salpingo-oophorectomy.

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Table-3 QoL outcomes following RRM

| *(1) Intervention* | RRM | | | | No surgery | | | | RRM vs. No surgery | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **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, 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, 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, 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, 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, 0.49) |
| *(2) Follow-up* | **<2 years follow-up** | | | | **>2 years follow-up** | | | | **>2 years follow-up vs. <2 years 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, 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, 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, 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)** |
| 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)** |
| **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, 1.46) |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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, 1.52) |

Note: The following meta-analyses were conducted for QoL outcomes post-RRM: (1) Intervention: QoL outcomes in women who underwent RRM vs. those who did not. Data was 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 was available for SF-36, SAQ, and HADS. For each comparison, the effect size of each single arm and the difference between the two arms was calculated.
HADS, Hospital Anxiety and Depression Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, quality-of-life; RRM, risk-reducing mastectomy; SAQ, Sexual Activity Questionnaire; SF-36, 36-Item Short Form Health Survey.

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Table-4 QoL outcomes following RRSO

| *(1) Intervention* | RRSO | | | | No surgery | | | | RRSO vs. No surgery | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **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, 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, 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, -0.89)** |
| 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)** |
| 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, 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, 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, -1.10)** |
| *(2) Follow-up* | <1 year follow-up | | | | >1 year follow-up | | | | >1 year follow-up vs. <1 year 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, 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, 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, -0.07)** |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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, 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) |

| ***(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*** | **Pre-menopausal RRSO** | | | | **Post-menopausal RRSO** | | | | **Post-menopausal RRSO vs. Pre-menopausal 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, 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, 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, 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, 0.59) |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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, 0.10) |
| ***(5) HRT use following pre-menopausal 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)** |
| 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, -0.65)** |
| 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, 0.42) |

Note: The following meta-analyses were conducted for QoL outcomes post-RRSO: (1) Intervention: QoL outcomes in women who underwent RRSO vs. those who did not. Data was 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 was 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 (e.g., *BRCA1/BRCA2*) vs. high-risk women based on mixed (CSG or family history) or unspecified criteria. Data was available for SF-36; (4) Menopause status: QoL outcomes following post-menopausal RRSO vs. pre-menopausal RRSO. Data was available for SF-36 and SAQ; (5) HRT use: QoL outcomes in women undergoing pre-menopausal RRSO who took HRT vs. those who did not. Data was available for SAQ. For each comparison, the effect size of each single arm and the difference between the two arms was calculated.

BC, breast cancer; CSG, cancer susceptibility gene; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Subscale; HADS, Hospital Anxiety and Depression Scale; 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; QoL, quality-of-life; RRSO, risk-reducing salpingo-oophorectomy; SAQ, Sexual Activity Questionnaire; SF-36, 36-Item Short Form Health Survey.

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957 **Figure legends**

958 **Figure-1 Structure of the systematic review and meta-analysis** (BC, breast cancer; CSG,
959 cancer susceptibility gene; FH, family history; HRQoL, health-related quality-of-life; HRT,
960 hormone replacement therapy; OC, ovarian cancer; PV, pathogenic variant; QoL, quality-of-
961 life; RRESDO, risk-reducing early-salpingectomy and delayed-oophorectomy; RRM, risk-
962 reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy)

963 **Figure-2 PRISMA flowsheet**

964 **Figure-3 Methodological quality: 3a-Methodological quality of non-comparative studies;**
965 **3b-Methodological quality of comparative studies**

966

967 **Appendix**

968 **Appendix-1 Search strategy**

969 **Appendix-2 Questionnaires used across outcome groups**

970 **Appendix-3 MINORS checklist score**

971 **Appendix-4 Results comparison between fixed-effects and random-effects model: 4a-**
972 **Results comparison between fixed-effects and random-effects model for RRM; 4b-**
973 **Results comparison between fixed-effects and random-effects model for RRSO**

974 **Appendix-5 Summarized findings on quality-of-life following risk-reducing surgery**

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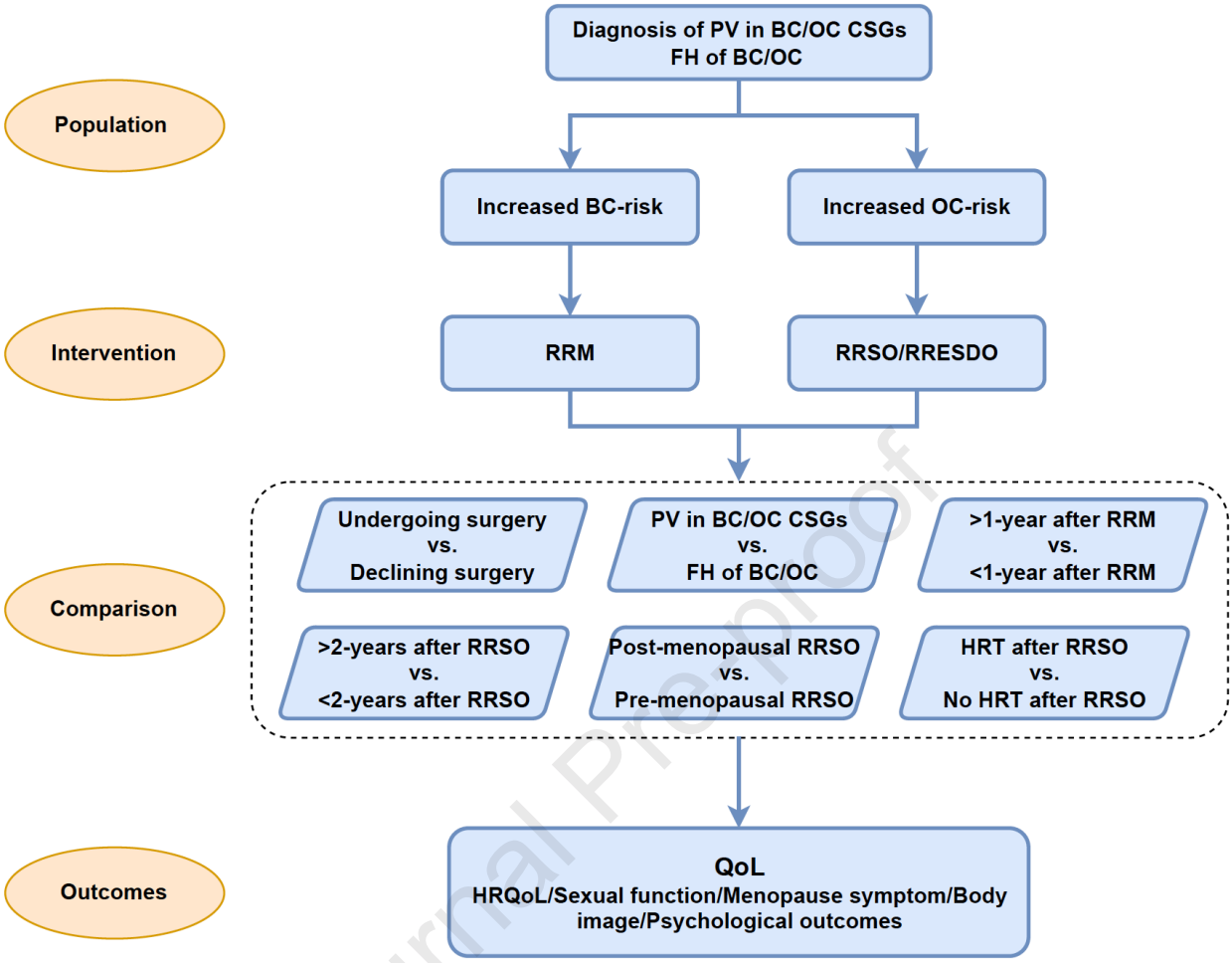


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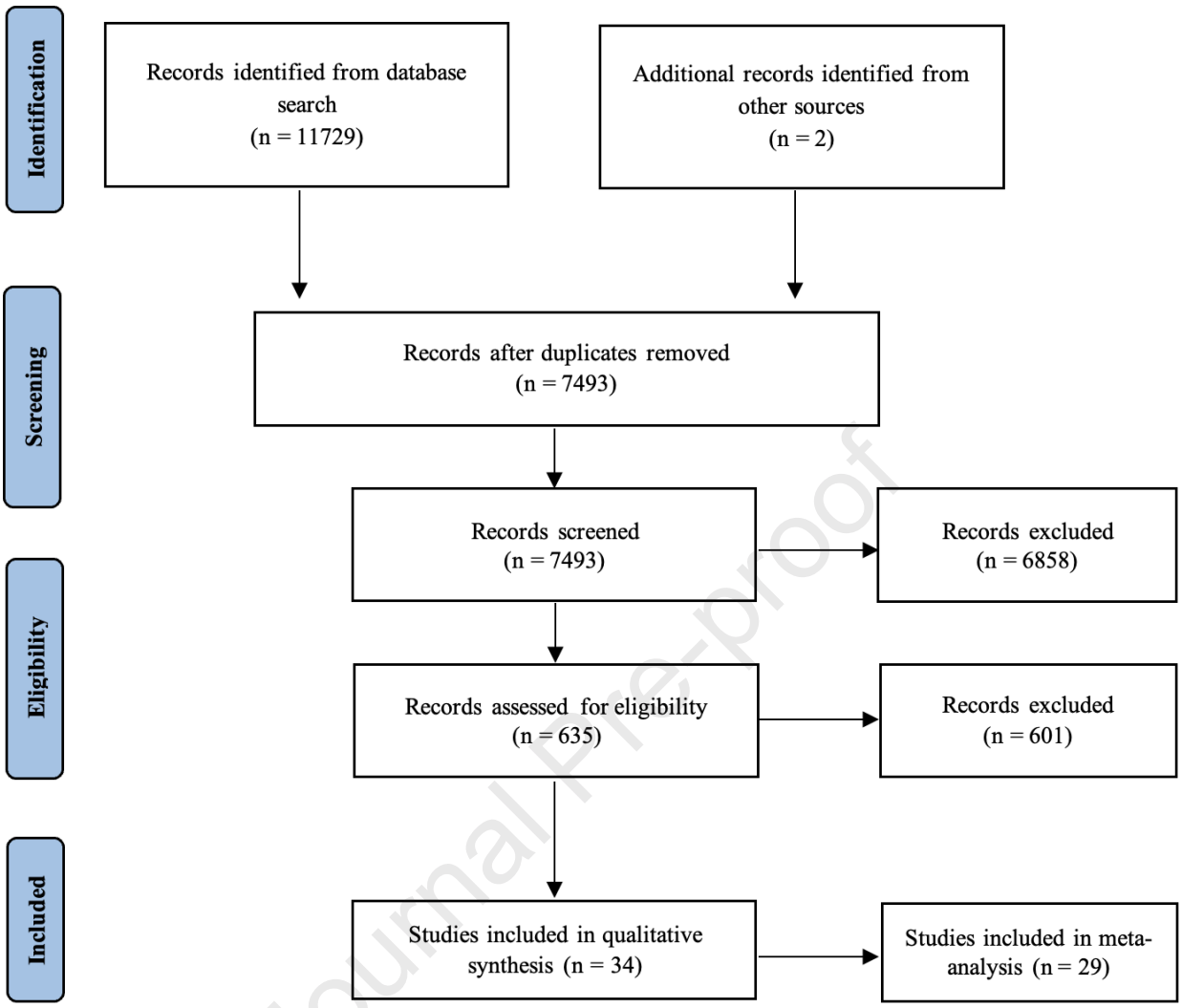


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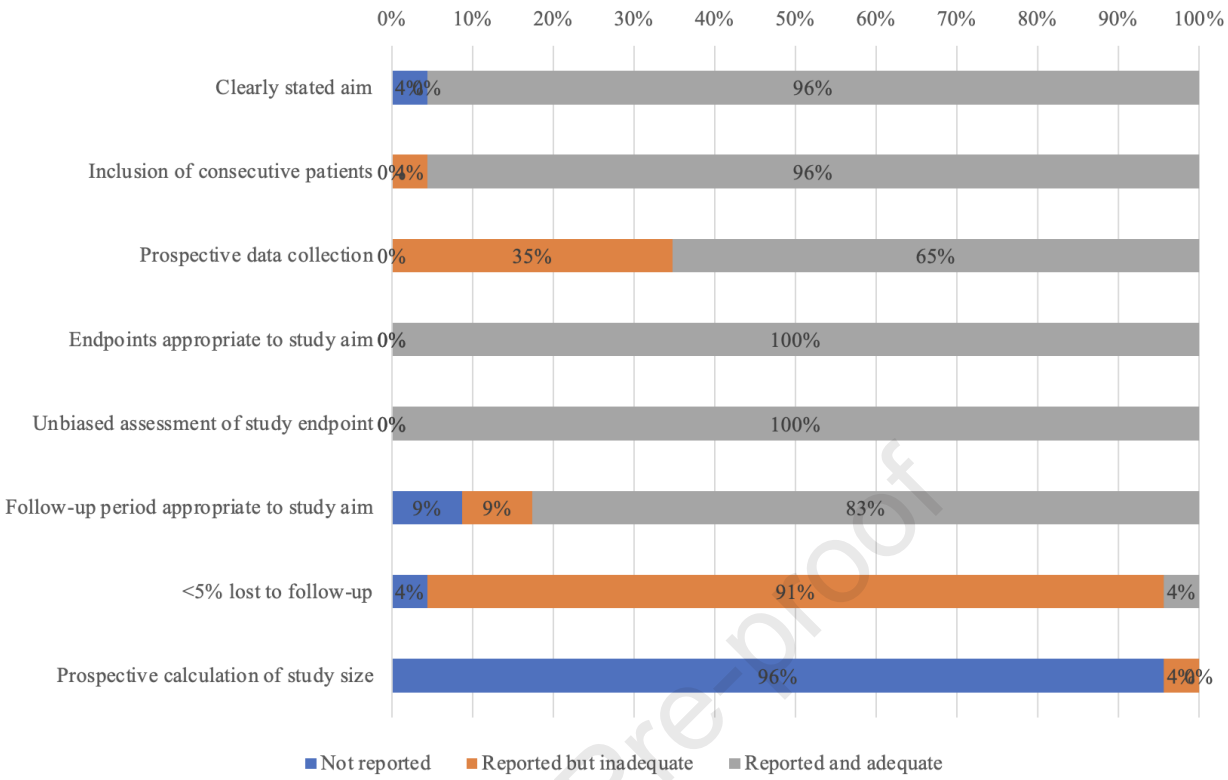


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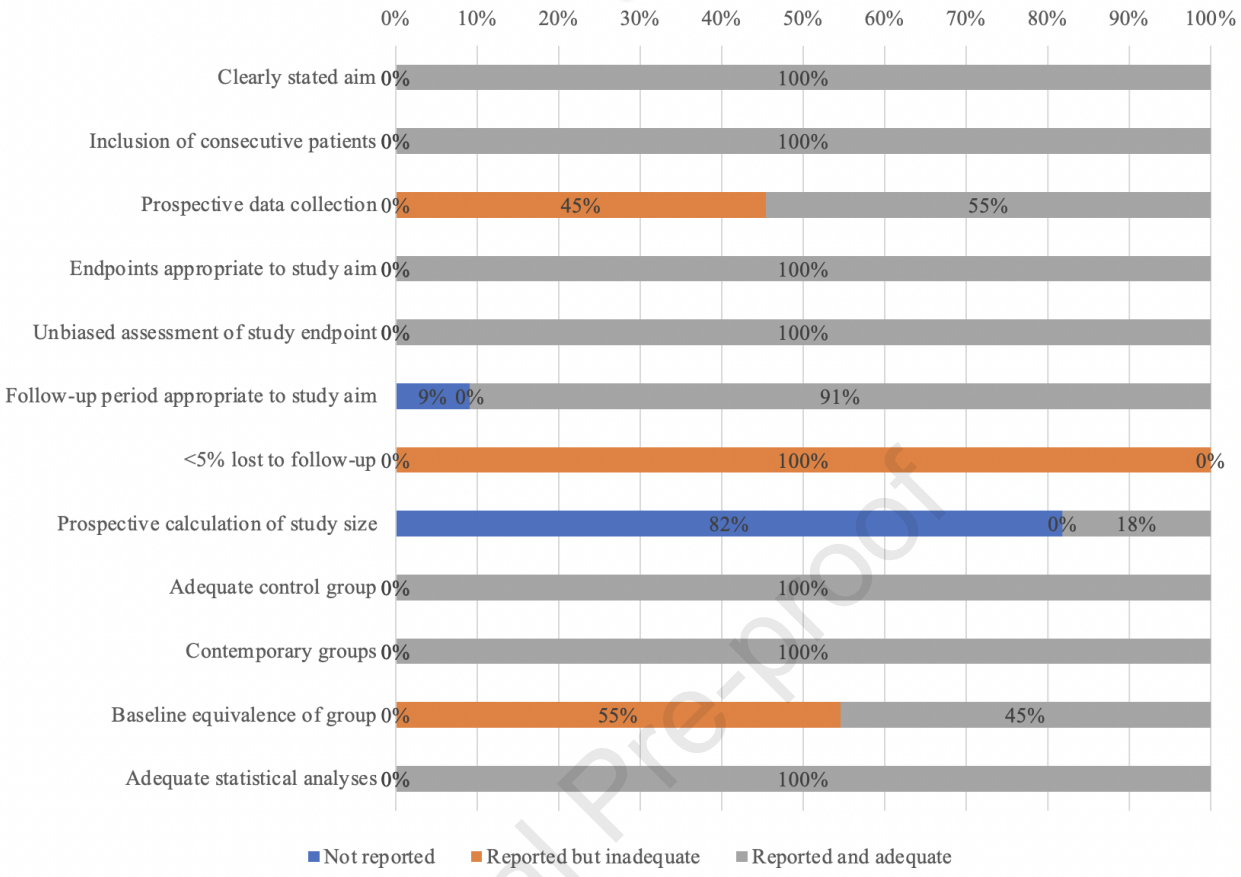


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**Appendix-1 Search strategy**

**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)

Journal Pre-proof

**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)

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**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 |

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**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

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Journal Pre-proof

**Appendix-2 Questionnaires used across outcome groups**

| Studies | RRM | RRSO | RRESDO | HRQoL | | | | | | | | Sexual function | | | | | | | | Menopause symptoms | | | | | | | Body image | | | | | | | | Psychological outcomes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | SF-36 | BREAST-Q | EORTC QLQ-C30 | BSI | PROMIS | EORTC QLQ-BRR26 | QLI | WHQ | SAQ | BREAST-Q | FSFI | CARES | FSDS | SFQ-F | DRQ | Study-specific questionnaire | MENQOL | FACT-ES | MRS | BKI | GCS | MSCL | SCL | BIS | BREAST-Q | BIBC | BPSS | SIBID | EORTC-OV 28 | BODY-Q | Study-specific questionnaire | IES | HADS | STAI | CES-D | BDI | CWS | PHQ-8/9 | GAD-7 | LOT-R | PSS |
| Bai,2019 | 99 | 0 | 0 | 99 | NA | NA | NA | NA | 99 | NA | NA | 99 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 99 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Brandberg,2008 | 90 | 0 | 0 | 90 | NA | NA | NA | NA | NA | NA | NA | 49 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 90 | NA | NA | NA | NA | NA | NA | NA | 90 | NA | NA | NA | NA | NA | NA | NA | NA |
| Chae,2021 | 0 | 30 | 0 | 30 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 30 | NA | NA | NA | NA | NA | NA | 30 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 30 | NA | 30 | NA | NA | NA | 30 | NA |
| Elit, 2001 | 0 | 40 | 0 | 40 | NA | NA | 40 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 40 | NA | 40 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 40 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Fang,2009 | 0 | 38 | 0 | 38 | NA | NA | NA | NA | NA | NA | NA | 38 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 38 | NA | NA | NA | NA | NA | 38 | NA | NA | NA | NA | NA | NA | NA |
| Finch,2011 | 0 | 96 | 0 | 93 | NA | NA | 89 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 70 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Finch,2011 | 0 | 114 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | 83 | NA | NA | NA | NA | NA | NA | NA | 112 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Gahm,2010 | 59 | 0 | 0 | 37 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 55 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Gandhi,2021 | 241 | 0 | 0 | NA | 241 | NA | NA | NA | NA | NA | NA | NA | 241 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 241 | NA | NA | NA | NA | NA | NA | 128* | NA | NA | NA | NA | NA | NA | NA | NA |
| Geiger,2007 | 106 | 0 | 0 | 106 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 106 | NA | NA | 106 | NA | NA | NA | NA | NA | NA |
| Gopie,2013 | 48 | 0 | 0 | 48 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 48 | NA | NA | NA | NA | NA | NA | NA | NA | 48 | NA | NA | NA | NA | NA | NA | 48 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Hall,2019 | 0 | 140 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | 101 | NA | NA | NA | NA | NA | NA | 140 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Heinijger,2015 | 17 | 38 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | 55 | NA | NA | NA | NA | NA | NA | NA | NA | NA | 55 | NA | NA | NA | NA | 55 | NA | NA | NA | 55 | NA | NA | NA | 55 | 55 | NA | NA | NA | NA | NA | NA | NA |
| Herold, 2022 | 43 | 0 | 0 | NA | 43 | NA | NA | NA | NA | NA | NA | NA | 43 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 43 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Isern,2008 | 30 | 0 | 0 | 28 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 30 | NA | 28 | NA | NA | NA | NA | NA | NA | NA | NA |
| Johansen,2016 | 0 | 294 | 0 | NA | NA | 294 | NA | NA | NA | NA | NA | 201 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 292 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Madalinska,2005 | 0 | 369 | 0 | 369 | NA | NA | NA | NA | NA | NA | NA | 277 | NA | NA | NA | NA | NA | NA | NA | 369 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 369 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Mai,2020 | 0 | 562 | 0 | 562 | NA | NA | NA | NA | NA | NA | NA | 391 | NA | NA | NA | NA | NA | NA | NA | NA | 562 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 562 | NA | 562 | 562 | NA | NA | NA | NA | NA | NA |
| Mansour, 2023 | 48 | 0 | 0 | NA | 48 | NA | NA | NA | NA | NA | NA | NA | 48 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 48 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| McCarthy, 2017 | 204 | 0 | 0 | NA | 204 | NA | NA | 204 | NA | NA | NA | NA | 204 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 204 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 204 | 204 | NA | NA | NA |
| Metcalfe,2004 | 60 | 0 | 0 | NA | NA | NA | 59 | NA | NA | NA | NA | 40 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 60 | NA | NA | NA | NA | NA | 57 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Metcalfe,2005 | 60 | 0 | 0 | NA | NA | NA | NA | NA | 59 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Metcalfe, 2015 | 137 | 0 | 0 | NA | 137 | NA | NA | NA | NA | NA | NA | NA | 137 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 137 | NA | NA | NA | NA | NA | 137 | 137 | NA | NA | NA | NA | NA | NA | NA | NA |
| Michelsen,2009 | 0 | 301 | 0 | NA | NA | 301 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 301* | NA | NA | NA | NA | NA | NA | NA | 301* | NA | NA | NA | NA | NA | NA | NA | NA |
| Miseré, 2022 | 47 | 0 | 0 | 47 | 47 | NA | NA | NA | NA | NA | NA | NA | 47 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 47 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Nebgen,2018 | 0 | 12 | 19 | 31 | NA | NA | NA | NA | NA | NA | NA | 31 | NA | NA | NA | NA | NA | NA | NA | NA | 31 | NA | NA | NA | NA | NA | 31 | NA | NA | NA | NA | NA | NA | NA | NA | 31 | NA | NA | NA | NA | NA | NA | NA |
| Philp,2021 | 0 | 36 | 0 | NA | NA | 36 | NA | 36 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 36 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Powell,2020 | 0 | 223 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | 105 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 223 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 223 | 223 | NA | NA | NA |
| Robson,2003 | 0 | 54 | 0 | 53 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 53 | NA | NA | NA | NA | NA | NA | NA | 53 | NA | NA | NA | NA | NA | NA | NA | NA | 53 | NA | NA | 53 | NA | NA | NA | NA | NA | NA |
| Spindler,2021 | 22 | 0 | 0 | 22 | 22 | NA | NA | NA | NA | NA | NA | NA | 22 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 22 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Stanisz,2019 | 0 | 62 | 0 | NA | NA | NA | NA | NA | NA | NA | 61 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 61 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 61 | NA | 61 | NA | NA | NA | 61 | NA |
| Steenbeek,2021 | 0 | 154 | 394 | 514 | NA | NA | NA | NA | NA | NA | NA | NA | NA | 537 | NA | 537 | NA | NA | NA | NA | NA | NA | 525 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 514 | NA | NA | NA | NA | NA | NA | NA |
| Touboul,2011 | 0 | 112 | 0 | NA | NA | 111 | NA | NA | NA | NA | NA | 59 | NA | NA | NA | NA | NA | NA | NA | NA | 107 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 111 | NA | NA | NA | NA | NA | NA | NA |
| Tucker,2020 | 0 | 76 | 0 | 76 | NA | NA | NA | NA | NA | NA | NA | NA | NA | 76 | NA | NA | NA | NA | NA | 76* | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Total** | **1102** | **2247** | **413** | **2283** | **742** | **742** | **188** | **240** | **99** | **59** | **61** | **1529** | **742** | **613** | **30** | **537** | **53** | **48** | **95** | **292** | **1038** | **116** | **61** | **525** | **223** | **53** | **615** | **742** | **60** | **38** | **55** | **36** | **47** | **30** | **1497** | **409** | **795** | **759** | **91** | **768** | **427** | **204** | **30** | **61** |

BDI: Beck Depression Inventory; BIBC: Body Image after Breast Cancer; BIS: Body Image Scale; BKI: Blatt-Kupperman Index; BODY-Q, Body questionnaire; BPSS: Body Parts Satisfaction Scale; BREAST-Q: Breast questionnaire; BSI: Brief Symptom Inventory; CARES: Cancer Rehabilitation Evaluation System; CES-D: Center for Epidemiological Studies-Depression scale; CWS: Cancer Worry Scale; DRQ: Dutch Relationship Questionnaire; EORTC-OV 28, European Organization for the Research and Treatment of Cancer OV-28 questionnaire; EORTC QLQ-BRR26: European Organisation for Research and Treatment of Cancer Breast Reconstruction Questionnaire;EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FACT-ES: Functional Assessment of Cancer Therapy-Endocrine Subscale; FSDS: Female Sexual Distress Scale; FSFI: Female Sexual Function Index; GAD-7: General Anxiety Disorder 7-Item scale; GCS: Greene Climacteric Scale; HADS: Hospital Anxiety and Depression Scale; HRQoL, Health-related quality-of-life; IES: Impact of Event Scale; LOT-R: Life Orientation Test-Revised; MENQOL: Menopause-Specific Quality of Life; MRS: Menopause Rating Scale; MSCL: Menopausal Symptom Checklist; NA, not applicable; PHQ-8/9: Personal Health Questionnaire-8/9 Item Depression Scale; PROMIS: Patient Reported Outcome Measurement Information System; PSS: Perceived Stress Scale; QLI: Quality of Life Index; QoL: Quality-of-life; SAQ: Sexual Activity Questionnaire; SCL: Symptom checklist; SF-36: 36-Item Short Form Health Survey; SFQ-F: Sexual Functioning Questionnaire-Female; SIBID: Situational Inventory of Body Image Dysphoria; STAI: State-Trait Anxiety Inventory; WHQ: Women's Health Questionnaire.
* results not reported

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**Appendix-3 MINORS checklist score**

| Studies | Clearly stated aim | Inclusion of consecutive patients | Prospective data collection | Endpoints appropriate to study aim | Unbiased assessment of study endpoint | Follow-up period appropriate to study aim | <5% lost to follow-up | Prospective calculation of study size | Adequate control group | Contemporary groups | Baseline equivalence of group | Adequate statistical analyses | Total | Denominator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bai, 2019 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | | | | | 14 | 16 |
| Brandberg, 2008 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 0 | | | | | 12 | 16 |
| Chae, 2021 | 2 | 2 | 2 | 2 | 2 | 0 | 1 | 0 | 2 | 2 | 1 | 2 | 18 | 24 |
| Elit, 2001 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Fang, 2009 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 2 | 2 | 21 | 24 |
| Finch, 2011 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Finch, 2011 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Gahm, 2010 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Gandhi, 2021 | 2 | 2 | 2 | 2 | 2 | 0 | 1 | 0 | | | | | 11 | 16 |
| Geiger, 2007 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 19 | 24 |
| Gopie, 2013 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 0 | | | | | 12 | 16 |
| Hall, 2019 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Heiniger, 2015 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 2 | 2 | 21 | 24 |
| Herold, 2022 | 0 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 11 | 16 |
| Isern, 2008 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Johansen, 2016 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 19 | 24 |
| Madalinska, 2005 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 19 | 24 |
| Mai, 2020 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 23 | 24 |
| Mansour, 2023 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| McCarthy, 2017 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Metcalfe, 2004 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Metcalfe, 2005 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Metcalfe, 2015 | 2 | 2 | 1 | 2 | 2 | 2 | 0 | 0 | | | | | 11 | 16 |
| Michelsen, 2009 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 2 | 2 | 20 | 24 |
| Miseré, 2022 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Nebgen, 2018 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 20 | 24 |
| Philp, 2021 | 2 | 2 | 2 | 2 | 2 | 0 | 1 | 0 | | | | | 11 | 16 |
| Powell, 2020 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 19 | 24 |
| Robson, 2003 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Spindler, 2021 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 0 | | | | | 13 | 16 |
| Stanisz, 2019 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | | | | | 14 | 16 |
| Steenbeek, 2021 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 23 | 24 |
| Touboul, 2011 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |
| Tucker, 2020 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | | | | | 12 | 16 |

Appendix-4a Results comparison between fixed-effects and random-effects model for RRM

| 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, 3.37) | 1 | 56 | 0.00% | 1.00 (-1.37, 3.37) |
| Discomfort | 1 | 56 | 0.00% | 0.00 (-0.89, 0.89) | 1 | 56 | 0.00% | 0.00 (-0.89, 0.89) |
| Habit | 1 | 56 | 0.00% | 0.20 (-0.05, 0.45) | 1 | 56 | 0.00% | 0.20 (-0.05, 0.45) |
| **HADS** | | | | | | | | |
| Anxiety | 1 | 56 | 0.00% | 0.10 (-1.76, 1.96) | 1 | 56 | 0.00% | 0.10 (-1.76, 1.96) |
| Depression | 1 | 56 | 0.00% | -0.90 (-2.29, 0.49) | 1 | 56 | 0.00% | -0.90 (-2.29, 0.49) |
| **>2 years follow-up vs. <2 years follow-up post-RRM** | | | | | | | | |
| **SF-36** | | | | | | | | |
| PCS | 1 | 92 | 0.00% | -1.20 (-3.74, 1.34) | 1 | 92 | 0.00% | -1.20 (-3.74, 1.34) |
| MCS | 1 | 92 | 0.00% | -2.20 (-5.06, 0.66) | 1 | 92 | 0.00% | -2.20 (-5.06, 0.66) |
| **SAQ** | | | | | | | | |
| Pleasure | 1 | 92 | 0.00% | -1.10 (-2.30, 0.10) | 1 | 92 | 0.00% | -1.10 (-2.30, 0.10) |
| Discomfort | 1 | 92 | 0.00% | **0.50 (0.03, 0.97)** | 1 | 92 | 0.00% | **0.50 (0.03, 0.97)** |
| Habit | 1 | 92 | 0.00% | **0.20 (0.06, 0.34)** | 1 | 92 | 0.00% | **0.20 (0.06, 0.34)** |
| **HADS** | | | | | | | | |
| Anxiety | 1 | 92 | 0.00% | 0.30 (-0.86, 1.46) | 1 | 92 | 0.00% | 0.30 (-0.86, 1.46) |
| Depression | 1 | 92 | 0.00% | 0.70 (-0.12, 1.52) | 1 | 92 | 0.00% | 0.70 (-0.12, 1.52) |

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.

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Appendix-4b Results comparison between fixed-effects and random-effects model for RRSO

| Comparison | Fixed-effects model | | | | Random-effects model | | | |
|---|---|---|---|---|---|---|---|---|
| | **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, 0.50) | 4 | 1050 | 94.70% | 1.24 (-7.63, 10.12) |
| MCS | 4 | 1050 | 0.00% | -0.14 (-1.33, 1.04) | 4 | 1050 | 0.00% | -0.14 (-1.33, 1.04) |
| **SAQ** | | | | | | | | |
| Pleasure | 6 | 3070 | 0.00% | **-1.21 (-1.53, -0.89)** | 6 | 3070 | 0.00% | **-1.21 (-1.53, -0.89)** |
| Discomfort | 5 | 1400 | 0.00% | **1.12 (0.93, 1.31)** | 5 | 1400 | 0.00% | **1.12 (0.93, 1.31)** |
| Habit | 5 | 2145 | 5.50% | -0.02 (-0.08, 0.03) | 5 | 2145 | 5.50% | -0.02 (-0.08, 0.03) |
| **MRS** | | | | | | | | |
| Overall score | 2 | 184 | 0.00% | 2.08 (-0.21, 4.37) | 2 | 184 | 0.00% | 2.08 (-0.21, 4.37) |
| **FACT-ES** | | | | | | | | |
| Overall score | 2 | 1745 | 92.00% | **-1.96 (-2.81, -1.10)** | 2 | 1745 | 91.97% | -2.13 (-5.17, 0.90) |
| **>1 year follow-up vs. <1 year follow-up post-RRSO** | | | | | | | | |
| **SF-36** | | | | | | | | |
| PCS | 2 | 351 | 0.00% | 0.64 (-0.69, 1.98) | 2 | 351 | 0.00% | 0.64 (-0.69, 1.98) |
| MCS | 2 | 351 | 0.00% | 1.19 (-0.15, 2.52) | 2 | 351 | 0.00% | 1.19 (-0.15, 2.52) |
| **SAQ** | | | | | | | | |
| Pleasure | 1 | 313 | 0.00% | **-0.70 (-1.33, -0.07)** | 1 | 313 | 0.00% | **-0.70 (-1.33, -0.07)** |
| Discomfort | 0 | 0 | NA | NA | 0 | 0 | NA | NA |
| Habit | 1 | 313 | 0.00% | 0.05 (-0.05, 0.15) | 1 | 313 | 0.00% | 0.05 (-0.05, 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 |
| MCS | 0 | 0 | NA | NA | 0 | 0 | NA | NA |
| **Post-menopausal RRSO vs. Pre-menopausal RSSO** | | | | | | | | |
| **SF-36** | | | | | | | | |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PCS | 1 | 90 | 0.00% | -3.19 (-7.54, 1.16) | 1 | 90 | 0.00% | -3.19 (-7.54, 1.16) |
| MCS | 1 | 90 | 0.00% | -0.60 (-4.95, 3.75) | 1 | 90 | 0.00% | -0.60 (-4.95, 3.75) |
| **SAQ** | | | | | | | | |
| Pleasure | 3 | 414 | 65.03% | -0.13 (-1.00, 0.74) | 3 | 414 | 62.74% | -0.59 (-2.19, 1.02) |
| Discomfort | 1 | 223 | 0.00% | 0 (-0.59, 0.59) | 1 | 223 | 0.00% | 0 (-0.59, 0.59) |
| Habit | 3 | 414 | 0.00% | -0.04 (-0.17, 0.10) | 3 | 414 | 0.00% | -0.04 (-0.17, 0.10) |
| **HRT vs. No HRT following pre-menopausal RRSO** | | | | | | | | |
| **SAQ** | | | | | | | | |
| Pleasure | 3 | 291 | 0.00% | **1.16 (0.17, 2.15)** | 3 | 291 | 0.00% | **1.16 (0.17, 2.15)** |
| Discomfort | 1 | 157 | 0.00% | **-1.20 (-1.75, -0.65)** | 1 | 157 | 0.00% | **-1.20 (-1.75, -0.65)** |
| Habit | 2 | 134 | 0.00% | 0.16 (-0.09, 0.42) | 2 | 134 | 0.00% | 0.16 (-0.09, 0.42) |

BC, breast cancer; CSG, cancer susceptibility gene; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Subscale; HADS, Hospital Anxiety and Depression Scale; 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; QoL, quality-of-life; RRSO, risk-reducing salpingo-oophorectomy; SAQ, Sexual Activity Questionnaire; SF-36, 36-Item Short Form Health Survey.

Journal Pre-proof

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

34 studies | 6,764 women | 12 countries

- Risk-reducing mastectomy and salpingo-oophorectomy reduce cancer distress with unaffected health-related quality of life
- Women and clinicians should be aware of body image problems post mastectomy, and sexual dysfunction and menopause symptoms post salpingo-oophorectomy

| | Risk-reducing mastectomy | Risk-reducing salpingo-oophorectomy |
|---|---|---|
| ✓ Health-related quality of life | Unaffected (short-term physical deficits) | Unaffected (short-term physical deficits) |
| ✓ Sexual function | Affected in a small number of studies | Affected (pleasure/discomfort/frequency)<br>Mitigated by hormone replacement therapy |
| ✓ Menopause symptoms | Not applicable | Increased<br>Mitigated by hormone replacement therapy |
| ✓ Body image | Affected in some studies | Unaffected |
| ✓ Cancer distress or worry | Reduced in most studies | Reduced in most studies |
| ✓ Anxiety or depression | Not negatively affected in most studies | Not negatively affected in most studies |

- Preliminary data demonstrates better profile for sexual function and menopause-specific quality of life with risk-reducing early-salpingectomy, while long-term outcome data on cancer risk reduction is awaited

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