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

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41 **Word count:** 350 (Abstract); 5000 (Main text)

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

45

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

47

## 48 **AJOG at a Glance**

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

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

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

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

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

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

64 **Abstract**

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

69 **Data sources:** We followed a prospective protocol (PROSPERO: CRD42022319782) and  
70 searched MEDLINE, EMBASE, PubMed, and Cochrane Library from inception to February  
71 2023.

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

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

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

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

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

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

## 100 INTRODUCTION

101 Around 4% of breast cancer (BC)<sup>1,2</sup> and 15–20% ovarian cancer (OC)<sup>3,4</sup> are caused by known  
102 pathogenic variants (PVs) in a variety of cancer susceptibility genes (CSGs). Common BC/OC  
103 CSGs include *BRCA1* and *BRCA2*, associated with around 69–72% (59–79%) and 67–69%  
104 (51–80%) lifetime BC-risk, and 44–48% (36–65%) and 17–30% (11–46%) lifetime OC-risk,  
105 respectively.<sup>5,6</sup> This compares to the population lifetime risk of 12.9–15% for BC and 1.3–2%  
106 for OC.<sup>7,8</sup> Increasing awareness and acceptability of genetic testing, falling costs, coupled with  
107 changes in clinical practice including increasing genetic testing at cancer diagnosis<sup>3,9</sup> and  
108 recent calls for population testing<sup>10-13</sup> are leading to ever increasing identification of unaffected  
109 women at increased BC/OC risk. Additionally, complex risk algorithms incorporating genetic  
110 (CSGs and polygenic risk score (PRS)) along-with non-genetic (family history  
111 (FH)/epidemiologic/reproductive/hormonal profile/mammographic density) variables are now  
112 available and provide personalised risk prediction for BC and OC.<sup>14-16</sup>

113  
114 Effective strategies which reduce cancer incidence or improve survival are available for women  
115 at increased BC/OC risk and recommended by clinical guidelines. This includes enhanced  
116 screening (BC), medical prevention (selective oestrogen receptor modulators/aromatase  
117 inhibitors for BC, contraceptive pill for OC), risk-reducing mastectomy (RRM), and risk-  
118 reducing salpingo-oophorectomy (RRSO).<sup>17-20</sup> OC screening does not reduce mortality,<sup>21,22</sup>  
119 and surveillance programmes are unavailable for high-risk women. Among these strategies,  
120 risk-reducing surgery (RRS) remains the most clinically effective preventive option whose  
121 uptake has hugely increased over the years.<sup>23</sup>

122  
123 RRM is offered to women with a lifetime BC-risk over 30–40%,<sup>17,24</sup> providing 89–95% cancer  
124 risk-reduction.<sup>25-27</sup> The timing of reconstruction including synthetic implants/autologous tissue

125 (TRAM/DIEP) flaps,<sup>28</sup> can vary, with most preferring immediate reconstruction. RRSO is the  
126 gold-standard OC preventive strategy, reducing OC-risk by 80–97%.<sup>29-31</sup> RRSO has been  
127 undertaken for *BRCA1/BRCA2* carriers, or women with a strong FH of OC. Broadening access  
128 has led to RRSO now being offered to women at >4–5% lifetime OC-risk, including newer  
129 moderate-penetrance OC CSGs and women with a first-degree-relative with high-grade serous  
130 OC.<sup>19,32,33</sup>

131

132 Pre-menopausal oophorectomy leads to premature surgical menopause, impacting quality-of-  
133 life (QoL) outcomes like sexual function and vasomotor/menopausal symptoms.<sup>34,35</sup> It is  
134 associated with long-term detrimental sequelae like coronary heart disease, osteoporosis, and  
135 cognitive decline, although these may be ameliorated by hormone replacement therapy  
136 (HRT).<sup>36</sup> Besides, a higher decision regret rate for pre-menopausal (compared to post-  
137 menopausal) RRSO has been reported.<sup>37</sup> The widespread acceptance of the fallopian tube as  
138 the site of origin of most serous epithelial OC along-with the detrimental health sequelae of  
139 early menopause has supported introduction of a novel two-step strategy of risk-reducing early-  
140 salpingectomy (RRES) and delayed-oophorectomy (DO) (RRESDO).<sup>38-40</sup> This allows pre-  
141 menopausal women wishing to decline/delay RRSO, a degree of OC risk-reduction, whilst  
142 avoiding premature menopause. Given limited outcome data, it is not considered standard of  
143 care<sup>41</sup> and currently offered in clinical trials within USA/Europe.<sup>42-44</sup>

144

145 For women with increased BC/OC risk, the decision of whether and when to undergo RRS is  
146 complex and changes over time. A number of factors may influence this such as, carrying a  
147 PV, cancer risk perception, FH/personal history of cancer, menopause status, fertility wishes,  
148 relationship status.<sup>45</sup> Whilst surgery significantly reduces BC or OC risk and improves cancer-  
149 related worry,<sup>27</sup> it encompasses surgical risks, particularly with complex breast reconstruction.



150 RRM may adversely impact the psychological/physical well-being of patients following  
151 consequent morbidities and body image issues.<sup>46</sup> While HRT may ameliorate outcomes of  
152 premature menopause, it remains contraindicated for many women with BC. RRES is of  
153 unproven benefit, and unlike RRSO will not improve BC mortality in women with BC.<sup>47</sup>

154

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

162

## 163 **OBJECTIVES**

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

169

## 170 **METHODS**

171 We conducted the systematic review and meta-analysis using a prospectively registered  
172 protocol (PROSPERO: CRD42022319782) and reported in line with PRISMA (Preferred  
173 Reporting Items for Systematic Reviews and Meta-analyses).<sup>48</sup>

174

175 *Literature search*

176 We searched MEDLINE, EMBASE, PubMed, and Cochrane Library from inception to  
177 February 2023 for publications in English and human studies, using a predefined search  
178 strategy (Appendix-1, developed by XW/SO/MS). The search strategy was validated<sup>48</sup> by  
179 evaluating whether it could identify a set of four clearly eligible studies identified on  
180 preliminary searches.<sup>49-52</sup> Additionally, reference lists from relevant studies/reviews were  
181 searched manually.

182

183 *Inclusion criteria*

184 We followed a population, intervention, comparison, outcome and study design (PICOS)  
185 framework<sup>53</sup> to specify our inclusion criteria (Figure-1). Population: defined as women at  
186 increased BC or OC risk, including diagnosis of PV in BC or OC CSGs or documented FH of  
187 BC or OC, amounting to a >30–40% or >5% lifetime risk of BC or OC respectively.<sup>19</sup>  
188 Intervention: We focused on RRM for BC prevention, and RRSO or RRESDO for OC  
189 prevention. Comparison: We compared QoL outcomes in women undergoing RRS vs those  
190 who did not. We then compared QoL outcomes across different subgroups: (1) long-term vs.  
191 short-term follow-up: for RRSO or RRESDO  $\geq 1$ -year, and for RRM  $\geq 2$ -years period was  
192 defined as long-term follow-up; (2) women with PVs in BC/OC CSGs (e.g., *BRCA1/BRCA2*)  
193 vs. those with FH-based risk; (3) post-menopausal vs. pre-menopausal RRSO; (4) pre-  
194 menopausal RRSO in HRT users vs. non-users. Outcome: We included studies reporting QoL  
195 outcomes on HRQoL, sexual function, menopause symptoms, body image, cancer-related  
196 distress or worry, anxiety or depression using validated questionnaires/tools. Study design: We  
197 included any study design (prospective/retrospective cohort studies, randomised/non-  
198 randomised trials, or case-series), that follows our PICOS framework.

199

200 *Exclusion criteria*

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

204

205 *Selection process*

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

211

212 *Quality assessment*

213 Two reviewers (XW/SO) independently assessed the methodological quality of included  
214 studies using the Methodological index for non-randomized studies (MINORS), with any  
215 discrepancies resolved by MS. A three-point scale graded the quality of each item, ranging  
216 from 0 (not reported), 1 (reported but inadequate), to 2 (reported and adequate). The maximum  
217 global score is 16 for non-comparative (8 items) and 24 for comparative studies (12 items). A  
218 score  $\leq 12$  for non-comparative and  $\leq 20$  for comparative studies was considered high-risk of  
219 bias.<sup>54</sup> We also assessed the external validity of included studies (representativeness of findings)  
220 based on whether the included population was definitely high-risk for BC or OC (PV in BC/OC  
221 CSGs or confirmed FH). Studies not specifying the high-risk criteria for BC or OC were  
222 deemed as high-risk of bias for external validity.

223

224 *Data extraction*

225 XW extracted Data using predesigned tables, and SO cross-checked this, with any  
226 disagreements resolved by MS/RM. We extracted data on study design, population,  
227 interventions and reported QoL outcomes (HRQoL, sexual function, menopause symptoms,  
228 body image, cancer-related distress or worry, anxiety or depression). For qualitative synthesis,  
229 we summarized the main findings about QoL after RRM, RRSO or RRESDO and the  
230 comparison among pre-designed subgroups.

231

### 232 *Statistical analysis*

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

244

## 245 **RESULTS**

### 246 *Study characteristics*

247 Figure-2 summarises the study selection process. From 11731 citations, we included 34 studies  
248 (N=3762 with RRS vs. N=3002 without RRS) in our qualitative synthesis, which consisted of  
249 16 (N=1102) RRM, 19 (N=2247) RRSO, and 2 (N=413) RRESDO studies. The post-surgery

250 follow-up ranged 1-23 years for RRM, 1-6 years for RRSO and 1-year for RRESDO. RRM  
251 was offered to high-risk women following CSG diagnosis in 3 studies (N=202), or mixed  
252 (CSG/FH-based) or unspecified criteria in 13 studies (N=900). RRSO was offered following  
253 CSG diagnosis in 8 studies (N=621), or mixed/unspecified criteria in 11 studies (N=1626).  
254 RRESDO was offered following CSG diagnosis (2 studies). Table-1 summarises  
255 characteristics of included studies.

256

### 257 *Outcomes reported*

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

263

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

267

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

273

274 Thirteen studies (N=996) reported body image after RRM, 5 studies (N=416) after RRSO and  
275 1 study (N=19) after RRESDO. The commonly used questionnaire was Body Image Scale (BIS,  
276 7 studies). Six other validated/study-specific questionnaires were used by 12 studies.

277

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

284

#### 285 *Quality Assessment*

286 For MINORS score see Figure-3 and Appendix-3. The median MINORS score was  
287 20(IQR:19–21) for 11 comparative and 12(IQR:12–13) for 23 non-comparative studies. Short  
288 (<1-year post-RRSO or <2-years post-RRM) or no reported duration of follow-up, >5% of  
289 participants lost to follow-up, and no sample size calculation were the main potential biases.  
290 Thirteen studies (N=2801) were deemed low-risk of bias for methodological quality, whereas  
291 21 studies (N=4046) were high-risk of bias. Regarding external validity, 9 studies (N=2255)  
292 were deemed high-risk of bias and 25 studies (N=4509) were low-risk of bias.

293

#### 294 *Data synthesis*

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

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

310

311 *QoL outcomes after RRM*

312 -HRQoL

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

322

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

326

327 -Sexual function

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

333

334 Three of four studies provided SAQ data for meta-analysis. Comparing RRM vs. no surgery  
335 found little difference in any SAQ component from the pooled estimates of one study<sup>70</sup> (Table-  
336 3). When comparing different follow-up timeframes (>2-years vs. <2-years), despite little  
337 difference in the pleasure component, an increase of 0.20 (95% CI:0.06,0.34; I<sup>2</sup>=0%; N=92) in  
338 the habit component (more frequent intercourse) and 0.50 (95% CI:0.03,0.97; I<sup>2</sup>=0%; N=92) in  
339 the discomfort component (more discomfort) of SAQ was seen in women >2-years follow-up  
340 (Table-3). However, these results were based on a single study.<sup>56</sup>

341

342 -Body image

343 Women reported satisfactory aesthetic outcomes following RRM with  
344 reconstruction.<sup>49,60,62,63,66,69,70</sup> Women undergoing reconstruction following RRM reported  
345 higher satisfaction with general body shape and appearance than those without  
346 reconstruction.<sup>65</sup> Additionally, women reported better body image with nipple and areola-  
347 sparing RRM than skin-sparing RRM;<sup>64</sup> and higher satisfaction with breasts following



348 autologous reconstruction than implant-based reconstruction.<sup>67</sup> Another three studies<sup>56,57,68</sup>  
349 reported body image problems post-RRM despite reconstruction, with problems persisting  
350 long-term (11.5-years follow-up)<sup>56</sup>. Four studies using BIS lacked SD for meta-analysis.

351

352 -Cancer-related distress

353 Two studies<sup>68,70</sup> reported decreased cancer-related distress after RRM, while two<sup>59,65</sup> 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.<sup>64</sup> Metcalfe<sup>65</sup>  
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<sup>49,57</sup> reported decreased general anxiety, while other studies found little impact on  
362 general anxiety<sup>60,64,70</sup> and depression<sup>49,57,59,60,64,70</sup> post-RRM. Bai<sup>56</sup> 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<sup>34,35,51,71-75</sup> reported HRQoL including physical and mental components was  
372 unaffected after RRSO. Mai<sup>76</sup> and Johansen<sup>50</sup> reported improved HRQoL post-RRSO, and

373 stable HRQoL with screening for women with increased OC-risk. Five studies<sup>52,77-80</sup> reported  
374 short-term deficits (poorer physical/social functioning, more physical role limitations, greater  
375 pain/discomfort, less vitality) following RRSO; Fang<sup>77</sup> reported that despite short-term deficits  
376 in most components (1-month, SF-36), most women recovered to baseline functioning at 6 and  
377 12-months follow-up. Hall<sup>81</sup> concluded that pre-menopausal RRSO did not affect HRQoL,  
378 while the physical component declined amongst post-menopausal women.

379

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

383

384 -Sexual function

385 Decreased sexual pleasure, more sexual discomfort, and less frequent sex were reported after  
386 RRSO in 13 studies.<sup>34,35,50-52,70,72,74,76-78,81,82</sup> This included both pre-menopausal and post-  
387 menopausal women. Four studies<sup>50,52,81,82</sup> showed that HRT may mitigate these risks for pre-  
388 menopausal women but not to pre-surgical levels. Fang<sup>77</sup> reported sexual discomfort improved  
389 after 1-year follow-up compared to 6-months, while Mai<sup>76</sup> concluded sexual function declined  
390 during 5-years follow-up. In contrast, three studies<sup>75,80,83</sup> found little difference in sexual  
391 function post-RRSO vs. no surgery; and also reported little difference in sexual function  
392 between pre- vs. post-menopausal RRSO.<sup>83</sup>

393

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

398 in the discomfort domain (1.12(95%CI:0.93,1.31);  $I^2=0\%$ ; N=1400) in women undergoing  
399 RRSO vs. no surgery. There was a reduction in sexual pleasure (-0.70(95%CI:-1.33,-0.07);  
400  $I^2=0\%$ ; N=313) across different timeframes after RRSO (>1-year vs. <1-year). In pre-  
401 menopausal RRSO, HRT (vs. no HRT) was associated with an increase in sexual pleasure (1.16  
402 (95%CI:0.17,2.15);  $I^2=0\%$ ; N=291) and a decrease in sexual discomfort (-1.20(95%CI:-1.75,-  
403 0.65);  $I^2=0\%$ ; N=157). Little difference was reported across any other comparison.

404

405 -Menopause symptoms

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

411

412 Two of three studies using FACT-ES, and two of three studies using MRS provided data for  
413 meta-analysis. Our meta-analysis showed increased menopause symptoms with RRSO vs. no  
414 surgery, with a reduction in FACT-ES score (-1.96(95%CI:-2.81,-1.10);  $I^2=92\%$ ; N=1745) and  
415 a trend difference of 2.08 ((95%CI:-0.21,4.37);  $I^2=0\%$ ; N=184) for MRS score (Table-4).

416

417 -Body image

418 Four studies<sup>50,51,70,77</sup> reported unaffected body image after RRSO, while women reported being  
419 less physically attractive in one study.<sup>78</sup> Three studies using BIS did not provide SD for meta-  
420 analysis.

421

422 -Cancer-related distress or worry

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

428

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

432

433 -Anxiety or depression

434 Four studies found RRSO had no negative impact on general anxiety<sup>70</sup> and depression<sup>35,70,77,80</sup>.

435 Although Mai<sup>76</sup> reported decreased depression after RRSO, Powell<sup>83</sup> and Stanisz<sup>79</sup> found  
436 increased depressive symptoms post-RRSO. Only one study used HADS, so no meta-analysis  
437 was conducted.

438

439 *QoL outcomes after RRESDO*

440 Nebgen<sup>51</sup>, in a pilot study of 43 pre-menopausal *BRCA1/2* carriers (early-salpingectomy:19,  
441 RRSO:12, screening:12), reported that women undergoing early-salpingectomy  
442 postoperatively experienced decreased cancer-related worry and distress, with unaffected  
443 HRQoL and body image. They described a trend of unaffected sexual function and no  
444 menopausal symptoms after early-salpingectomy.

445

446 The TUBA study<sup>52</sup> recruited 577 pre-menopausal *BRCA1/2* carriers and reported initial 1-year  
447 follow-up outcomes for 548 patients (394 for early-salpingectomy vs. 154 for RRSO). They

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 RRSO vs no RRSO in 1745 women for FACT-ES score (Table-4). While studies

473 indicate HRT can mitigate these symptoms, data could not be meta-analyzed by menopause  
474 status or HRT use. Preliminary data suggested early-salpingectomy did not detrimentally affect  
475 sexual function and had fewer menopause symptoms than RRSO. Most studies reported  
476 decreased cancer-related distress after RRM or RRSO, despite 2 studies<sup>35,71</sup> reporting moderate  
477 to severe cancer-related distress in a small proportion after RRSO. RRM or RRSO did not  
478 negatively impact general anxiety or depression in most studies, although 3 studies reported  
479 increased depressive symptoms after RRM<sup>56</sup> or RRSO<sup>79,83</sup>. For RRM this was supported by the  
480 pooled estimation of 56 women (Table-3).

481

#### 482 *Interpretation*

483 This systematic review can act as a guide/tool (Appendix-5) for clinicians counselling women  
484 about RRS. Where evidence allows, we delineate the actual burden of the impact of RRS on  
485 HRQoL, sexual function, body image, menopause, and psychological well-being. To undergo  
486 RRS or not can be a complex and dynamic decision, which changes with time, and this will be  
487 influenced by other risk factors including presence of a PV in CSGs or a personal history or  
488 FH of cancer.<sup>45</sup> While effective in reducing cancer risk, women need to be made aware that  
489 these operations may detrimentally impact other long-term health outcomes. The summarised  
490 QoL impact of RRS can facilitate improved informed decision-making for women at increased  
491 BC/OC risk to choose between surgical prevention and other available options (BC screening  
492 or BC/OC medical prevention).

493

494 While RRM is a well-established prevention strategy in women at high-risk of BC, apart from  
495 surgical risks,<sup>84,85</sup> a consensus regarding its impact on QoL outcomes is lacking. Despite  
496 unaffected HRQoL post-RRM, it along-with reconstructive surgery has a significant  
497 complication rate and an equivocal impact on body image with several studies reporting no

498 impact<sup>49,60,62,63,66,69,70</sup> and potential deficits with reconstruction<sup>56,57,64,65,67,68</sup>. This is reflected in  
499 the disutility of 0.88 which has been reported for RRM.<sup>86</sup> 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.<sup>65</sup> 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,<sup>65</sup> 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.<sup>19,41,87</sup>  
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<sup>88</sup> and women >4–5% lifetime OC-risk<sup>32,33</sup>, 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.<sup>89</sup> In pre-menopausal women, RRSO increases the  
516 long-term health risks of osteoporosis/osteopenia, heart disease and neurocognitive decline.<sup>36</sup>  
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

523 studies (12/13) found that post-RRSO women reported de-novo or aggravation of menopause  
524 symptoms both in pre- and post-menopausal women. Several studies<sup>50,52,81,82</sup> demonstrated  
525 HRT may mitigate menopause symptoms and improve sexual function, and the latter was  
526 confirmed in our meta-analysis (Table-4). However, HRT cannot fully resolve menopause  
527 symptoms or sexual dysfunction, which remains worse compared to women not undergoing  
528 surgery. Short-term HRT in these women appears safe and (if not contraindicated) is  
529 recommended till age of natural menopause.<sup>19,36</sup> HRT management following premature  
530 surgical menopause is thus critically important for symptom control, sexual function and  
531 ameliorating long-term detrimental health consequences. HRT compliance and satisfaction  
532 appear higher in women managed in specialist centres or high-risk familial cancer clinics.<sup>36,90</sup>  
533 RRSO also alleviates cancer-related distress, worry and has high acceptability and satisfaction  
534 rates (>85%),<sup>72</sup> although the decision regret rate is much higher in pre-menopausal (~9%) than  
535 post-menopausal (~1%) women.<sup>36,37</sup> Women undergoing RRSO should receive non-directive  
536 counselling and support highlighting the pros and cons of surgery to facilitate informed  
537 decision-making. Emerging data suggests women would like to be offered psychological  
538 support and prefer to be managed in specialist clinics.<sup>90</sup> There is an emerging demand for joint  
539 RRSO and RRM procedures undertaken concurrently,<sup>37</sup> but relevant QoL outcome data in this  
540 context is lacking.

541

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



548 RRSO with/without HRT.<sup>52</sup> However, the effect size of OC risk-reduction from early-  
549 salpingectomy and risk of interval cancers remains unknown. Additionally, the long-term  
550 impact on menopause or endocrine function is not established. These issues need addressing  
551 before recommending change in clinical practice guidelines and widespread  
552 implementation.<sup>87,91</sup> RRESDO is not considered standard of care<sup>41</sup> and is currently offered in  
553 the context of clinical trials within USA/Europe.<sup>42-44</sup> UK Cancer genetics Group and RCOG  
554 recommend RRSO as the primary method of surgical prevention and that early-salpingectomy  
555 is best offered in a research setting.<sup>19,87</sup> RRESDO requires comprehensive counselling, ideally  
556 in specialist centres, along with thorough pathology evaluation incorporating the SEE-FIM  
557 protocol<sup>92</sup> and pelvic peritoneal washings, with any serous tubal intraepithelial carcinoma  
558 (STIC) lesions urgently referred for completion surgery and reviewed by a gynaecological  
559 oncology MDT.

560  
561 Our review summarises the QoL outcomes reported (HRQoL, sexual function, body image,  
562 menopause symptoms, psychological well-being) and highlights the various commonly used  
563 tools/questionnaires for each of them (Appendix-2). There is a clear need to establish a unified  
564 approach and develop core outcome sets for reporting QoL outcomes after RRS to optimise  
565 potential evidence synthesis. In addition, the questionnaires/methodologies used precludes the  
566 ability to obtain utility scores of RRS from these studies, although the SF-36 used by some  
567 could be converted to utility scores using algorithms.<sup>93</sup> Utility scores are necessary for cost-  
568 effectiveness analysis to support health policy decision-making. Currently, only Grann<sup>86,94</sup>  
569 investigated the utility scores for RRM and RRSO using time trade-off survey, where  
570 participants did not undergo the relevant surgery. High-quality prospective studies are needed  
571 in women undergoing RRS using an appropriate reporting tool.

572

573 *Strengths and weaknesses*

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

582

583 We recognise a series of limitations. QoL is a heterogenous topic with several outcomes and  
584 many reporting tools/questionnaires. This did not allow a good proportion of the data to be  
585 used for meta-analysis for more robust results. An agreed standardised core outcome set for  
586 RRS outcomes needs developing. We noted substantial heterogeneity ( $I^2 > 75\%$ ) for only two  
587 comparisons (Appendix-4), indicating that differences between study populations or  
588 procedures might affect results. On several occasions aggregate data was not fully available to  
589 include in the meta-analysis, despite contacting the authors. The majority of studies (21/34  
590 studies) were assessed high-risk of bias for methodological quality, including short or  
591 unspecified duration of follow-up,  $>5\%$  participants lost to follow-up, and missing sample size  
592 calculation. This was considered during qualitative synthesis of data to draw conclusions. Most  
593 of our conclusions were compared and found to be in line with the high-quality studies.  
594 Similarly studies that were deemed high-risk for external validity bias (9/34 studies) lacked  
595 clarity on the criteria for high-risk of BC/OC. However, we were unable to undertake  
596 sensitivity analysis for high-quality studies alone given lack of adequate data.

597

## 598 CONCLUSIONS AND IMPLICATIONS

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

608

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610 for the integrity of the data and the accuracy of the data analysis. Xia Wei: Methodology,  
611 Resources, Data Curation, Formal analysis, Writing-Original draft preparation; Samuel Oxley:  
612 Methodology, Resources, Data Curation, Formal analysis, Writing-Original draft preparation;  
613 Michail Sideris: Methodology, Resources, Data Curation, Formal analysis, Writing-Original  
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619 approved the final version, and the corresponding and senior author (Ranjit Manchanda) made  
620 the final decision to submit for publication.

621

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.

Journal Pre-proof

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- 929 Table-1 Study characteristics
- 930 Table-2 Qualitative synthesis of QoL outcomes following RRS
- 931 Table-3 QoL outcomes following RRM
- 932 Table-4 QoL outcomes following RRSO

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Table-1 Study characteristics

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

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

Miseré, 2022 <sup>67</sup>	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 <sup>62</sup>	Germany	Prospective cohort	PV in BC/OC CSGs	RRM	22	2.15 years	No negative impact on HRQoL and sexual function No negative impact on body image with reconstruction
Chae, 2021 <sup>80</sup>	Korea	Cross-sectional	<i>BRCA1/2</i>	RRSO/Controls	30/22	NR	No difference in mental component of HRQoL, sexual function, menopause symptoms, cancer-related distress, and depression Negative impact on physical component of HRQoL
Elit, 2001 <sup>34</sup>	Canada	Retrospective cohort	PV in BC/OC CSGs or FH of OC	RRSO	40	5 years	No negative impact on HRQoL Significant decrease in cancer-related distress Development of menopausal symptoms Negative impact on sexual function
Fang, 2009 <sup>77</sup>	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 Potential impact on short-term sexual function No negative impact on body image and depression
Finch, 2013 <sup>71</sup>	Canada	Prospective cohort	<i>BRCA1/2</i>	RRSO	96	13.7 months	No negative impact on HRQoL Persistent moderate to severe cancer-related distress in a subgroup of women

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



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

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

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934 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;  
935 QoL, quality-of-life; RRESDO, risk-reducing early-salpingectomy and delayed-oophorectomy; RRM, risk-reducing mastectomy; RRS, risk-reducing surgery; RRSO, risk-reducing salpingo-  
936 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 <sup>56</sup>	RRM	Not affected	Decline (habit)	Not applicable	Affected	Not investigated	Not investigated	Not affected	Increased
Brandberg, 2008 <sup>57</sup>	RRM	Not affected	Decline (pleasure)	Not applicable	Affected	Not investigated	Not investigated	Decreased	Not affected
Gahm, 2010 <sup>58</sup>	RRM	Not affected	Decline (sensation, pleasure)	Not applicable	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Gandhi, 2021 <sup>63</sup>	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Not reported	Not reported
Geiger, 2007 <sup>59</sup>	RRM	Not affected	Not investigated	Not applicable	Not investigated	Not affected	Not investigated	Not investigated	Not affected
Gopie, 2013 <sup>68</sup>	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 <sup>70</sup>	RRM	Not investigated	Not affected	Not applicable	Not affected	Decreased	Not investigated	Not affected	Not affected
Herold, 2022 <sup>66</sup>	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Not investigated	Not investigated
Isern, 2008 <sup>60</sup>	RRM	Not affected	Not investigated	Not applicable	Not affected	Not investigated	Not investigated	Not affected	Not affected

Mansour, 2023 <sup>69</sup>	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 <sup>49</sup>	RRM	Not affected	Not affected	Not applicable	Not affected	Not investigated	Not investigated	Decreased	Not affected
Metcalfe, 2004 <sup>65</sup>	RRM	Not affected	Not affected	Not applicable	Improved (with reconstruction)	Not affected	Not investigated	Not investigated	Not investigated
Metcalfe, 2005 <sup>61</sup>	RRM	Not affected	Not investigated	Not applicable	Not investigated	Not investigated	Not investigated	Not investigated	Not investigated
Metcalfe, 2015 <sup>64</sup>	Nipple and areola-sparing RRM vs. skin-sparing RRM	Comparable	Improved sexual well-being	Not applicable	Improved	Comparable	Not investigated	Comparable	Comparable
Miseré, 2022 <sup>67</sup>	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 <sup>62</sup>	RRM	Not affected	Not affected	Not applicable	Not affected (with reconstruction)	Not investigated	Not investigated	Not investigated	Not investigated
Chae, 2021 <sup>80</sup>	RRSO	Decline (physical component)	Not affected	Not affected	Not investigated	Not affected	Not investigated	Not investigated	Not affected
Elit, 2001 <sup>34</sup>	RRSO	Not affected	Decline (desire, vaginal dryness)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Not investigated

Fang, 2009 <sup>77</sup>	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 <sup>71</sup>	RRSO	Not affected	Not investigated	Not investigated	Not investigated	Persistent cancer- related distress in a subgroup	Not investigated	Not investigated	Not investigated
Finch, 2011 <sup>82</sup>	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 <sup>81</sup>	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

				but not to pre-surgical levels					
Heiniger, 2015 <sup>70</sup>	RRSO	Not investigated	Decline (discomfort)	Increased	Not affected	Not affected	Not investigated	Not affected	Not affected
Johansen, 2016 <sup>50</sup>	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 <sup>72</sup>	RRSO	Not affected	Decline (pleasure, discomfort)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Not investigated
Mai, 2020 <sup>76</sup>	RRSO	Improved	Decline (pleasure, discomfort)	Increased	Not investigated	Decreased	Not investigated	Not investigated	Decreased
Michelsen, 2009 <sup>73</sup>	RRSO	Not affected	Not investigated	Not investigated	Not reported	Not investigated	Not investigated	Not reported	Not reported
Nebgen, 2018 <sup>51</sup>	RRSO	Not affected	Trend of decline (discomfort)	Trend of increase	Not affected	Decreased	Decreased	Not investigated	Not investigated

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



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Steenbeek,	RRESDO	Not affected	Not affected	Not affected	Not investigated	Not investigated	Decreased	Not investigated	Not investigated
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2021<sup>52</sup>

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

<i>(1) Intervention</i>	RRM				No surgery				RRM vs. No surgery			
	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>SAQ</b>												
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)
<b>HADS</b>												
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)
<b>(2) Follow-up</b>												
	<2 years follow-up				>2 years follow-up				>2 years follow-up vs. <2 years follow-up			
	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>SF-36</b>												
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)
<b>SAQ</b>												
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%	<b>0.50 (0.03, 0.97)</b>
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%	<b>0.20 (0.06, 0.34)</b>
<b>HADS</b>												
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)

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)
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941 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  
 942 SAQ and HADS; (2) Follow-up: long-term vs. short-term QoL outcomes following RRM. A period of  $\geq 2$ -years was defined as long-term follow-up for RRM, and data was available for SF-36,  
 943 SAQ, and HADS. For each comparison, the effect size of each single arm and the difference between the two arms was calculated.  
 944 HADS, Hospital Anxiety and Depression Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, quality-of-life; RRM, risk-reducing mastectomy; SAQ, Sexual  
 945 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 <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>SF-36</b>												
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)
<b>SAQ</b>												
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%	<b>-1.21 (-1.53, -0.89)</b>
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%	<b>1.12 (0.93, 1.31)</b>
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)
<b>MRS</b>												
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)
<b>FACT-ES</b>												
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%	<b>-1.96 (-2.81, -1.10)</b>
(2) Follow-up	<1 year follow-up				>1 year follow-up				>1 year follow-up vs. <1 year follow-up			
	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>SF-36</b>												
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)
<b>SAQ</b>												
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%	<b>-0.70 (-1.33, -0.07)</b>

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)
<b>MRS</b>												
Overall score	0	0	NA	NA	2	68	0.00%	11.67 (9.85, 13.49)	0	0	NA	NA
<b>FACT-ES</b>												
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)
<b>(3) High-risk definition</b>												
	<b>Diagnosis of PV in BC/OC CSGs</b>				<b>Mixed or unknown basis</b>				<b>Diagnosis of PV in BC/OC CSGs vs. Mixed or unknown basis</b>			
	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Score (95% CI)</b>	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Score (95% CI)</b>	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Difference (95% CI)</b>
<b>SF-36</b>												
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
<b>(4) Menopause status</b>												
	<b>Pre-menopausal RRSO</b>				<b>Post-menopausal RRSO</b>				<b>Post-menopausal RRSO vs. Pre-menopausal RRSO</b>			
	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Score (95% CI)</b>	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Score (95% CI)</b>	<b>Studies</b>	<b>N</b>	<b>I<sup>2</sup></b>	<b>Difference (95% CI)</b>
<b>SF-36</b>												
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)
<b>SAQ</b>												
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)

	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	HRT				No HRT				HRT vs. No HRT			
following pre-menopausal RRSO	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Score (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>SAQ</b>												
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%	<b>1.16 (0.17, 2.15)</b>
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%	<b>-1.20 (-1.75, -0.65)</b>
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)

947 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  
 948 for SF-36, SAQ, MRS, and FACT-ES; (2) Follow-up: long-term vs. short-term QoL outcomes following RRSO. A period of  $\geq 1$ -year was defined as long-term follow-up for RRSO, and data was  
 949 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  
 950 (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  
 951 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,  
 952 the effect size of each single arm and the difference between the two arms was calculated.  
 953 BC, breast cancer; CSG, cancer susceptibility gene; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Subscale; HADS, Hospital Anxiety and Depression Scale; HRT, hormone  
 954 replacement therapy; MCS, Mental Component Summary; MRS, Menopause Rating Scale; NA, not applicable; OC, ovarian cancer; PCS, Physical Component Summary; PV, pathogenic variant;  
 955 QoL, quality-of-life; RRSO, risk-reducing salpingo-oophorectomy; SAQ, Sexual Activity Questionnaire; SF-36, 36-Item Short Form Health Survey.  
 956

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**

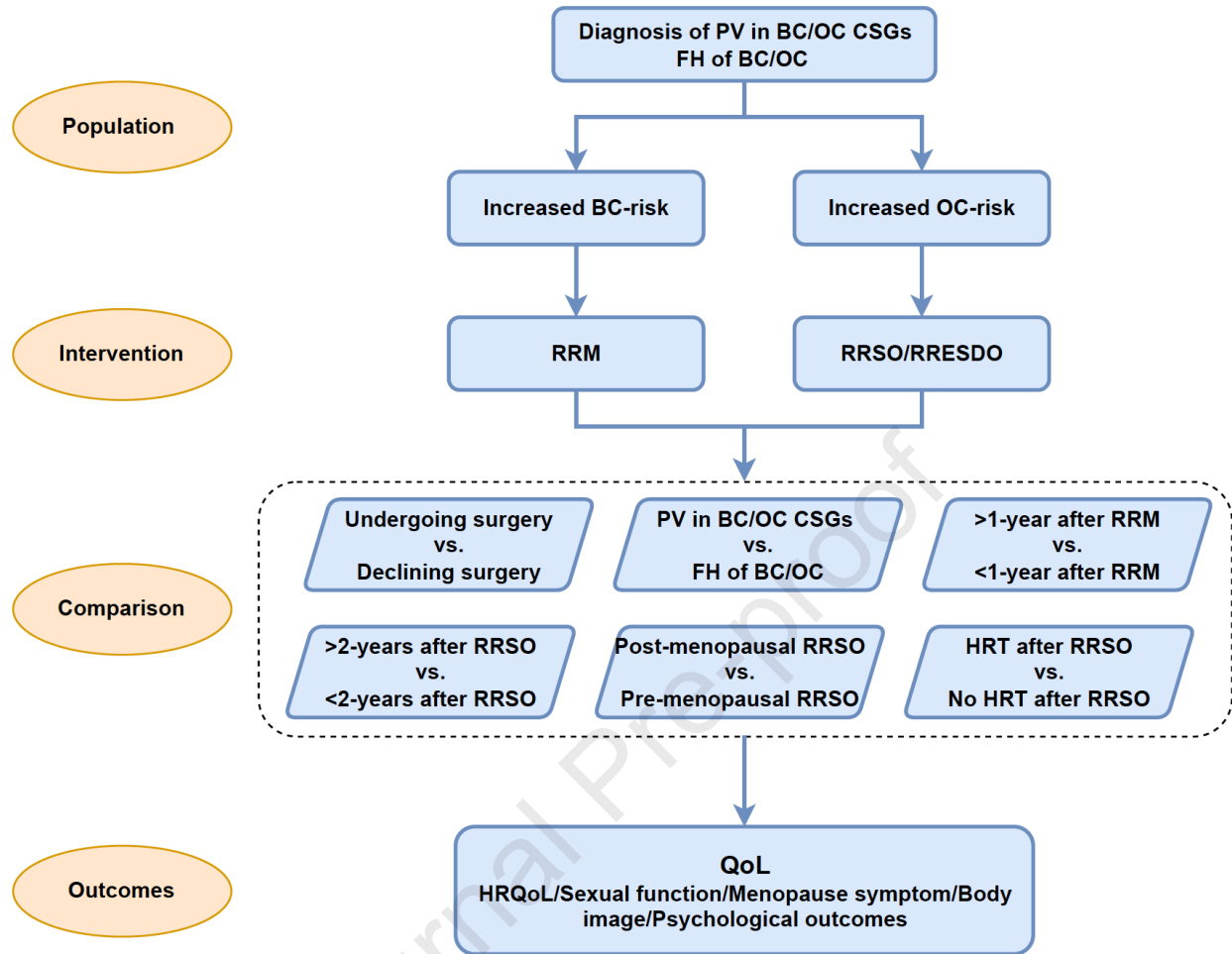
970 **Appendix-3 MINORS checklist score**

971 **Appendix-4 Results comparison between fixed-effects and random-effects model: 4a-**

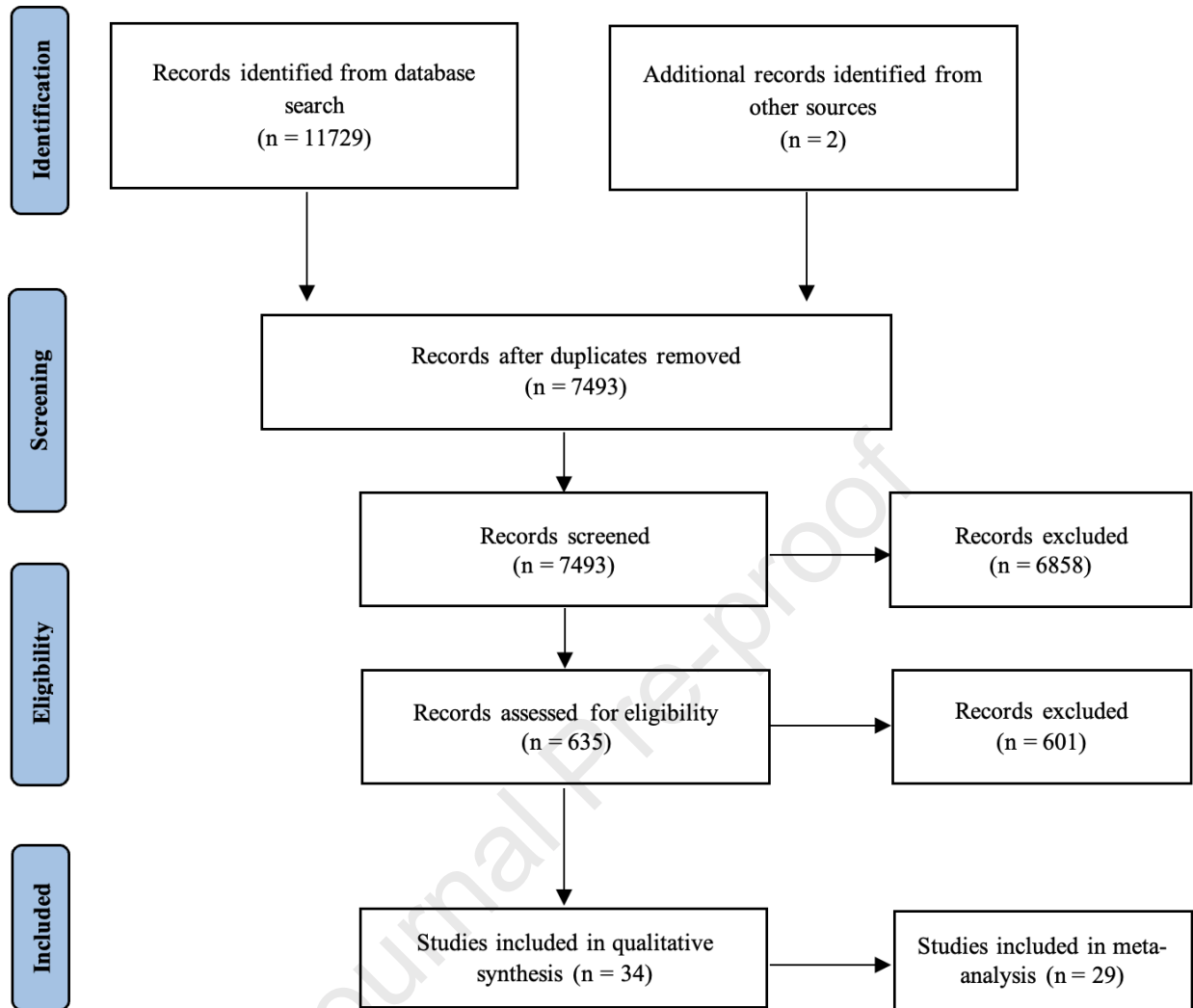
972 **Results comparison between fixed-effects and random-effects model for RRM; 4b-**

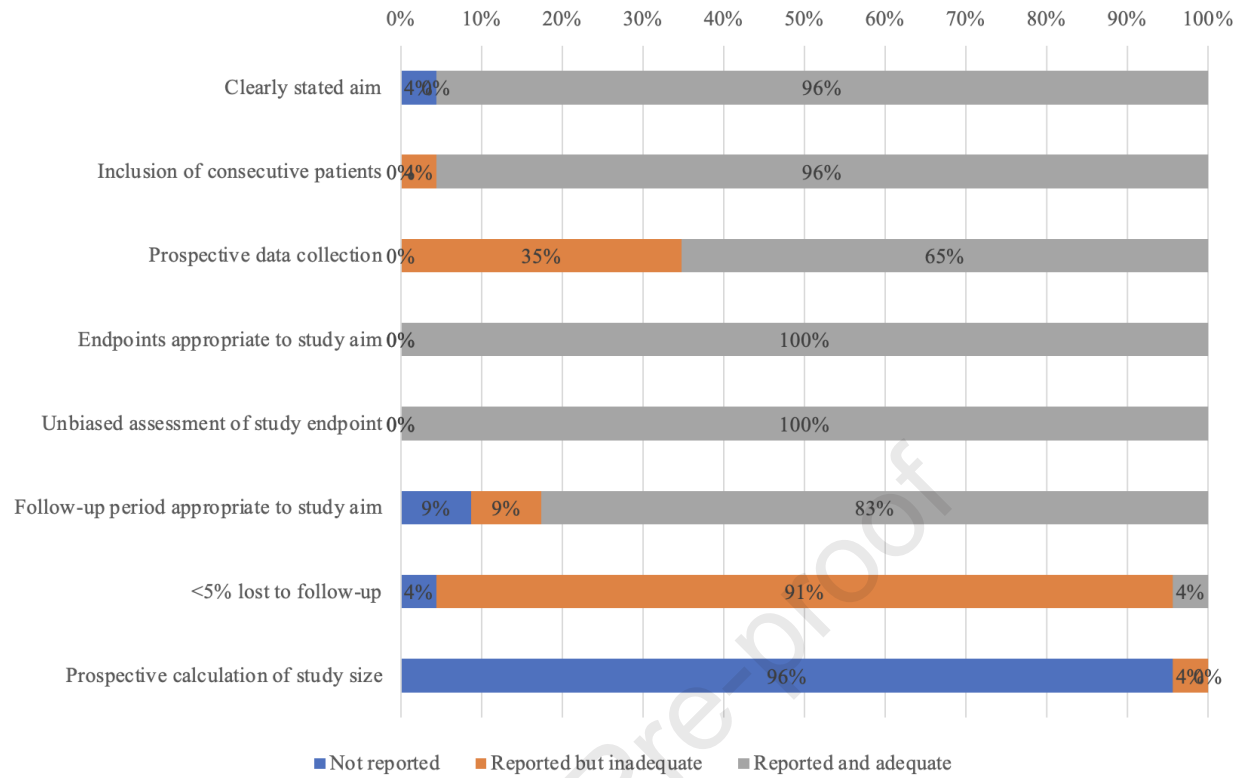
973 **Results comparison between fixed-effects and random-effects model for RRSO**

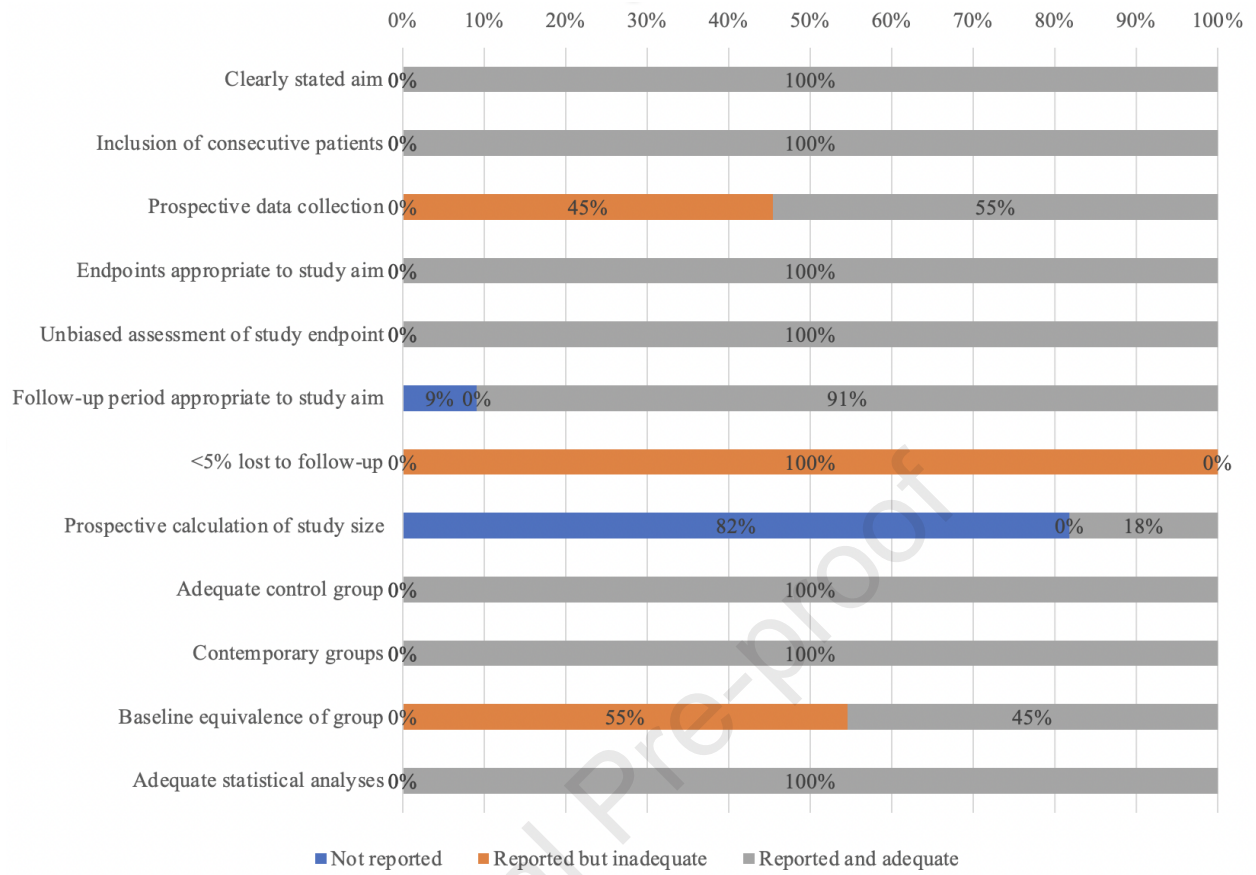
974 **Appendix-5 Summarized findings on quality-of-life following risk-reducing surgery**











## Appendix-1 Search strategy

### 1. Ovid MEDLINE

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

## 2. Embase Classic+Embase

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

### 3. Cochrane Library

ID Search

#1 MeSH descriptor: [Mastectomy] explode all trees

#2 MeSH descriptor: [Salpingo-oophorectomy] explode all trees

#3 MeSH descriptor: [Ovariectomy] explode all trees

#4 MeSH descriptor: [Salpingectomy] explode all trees

#5 MeSH descriptor: [Prophylactic Surgical Procedures] explode all trees

#6 ((prophylac\* or prophylaxis or prevent\* or risk-reduc\* or risk reduc\*) near/5 (surg\* or procedur\* or interven\* or mastectom\* or RRM or salping\* or oophorectomy\* or ovar\* or RRSO or RRESDO)):ti,ab,kw (Word variations have been searched)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Breast Neoplasms] explode all trees

#9 MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees

#10 MeSH descriptor: [Ovarian Neoplasms] explode all trees

#11 MeSH descriptor: [Peritoneal Neoplasms] explode all trees

#12 ((ovar\* or fallopian\* or peritone\* or breast or mammary) near/5 (cancer\* or neoplasm\* or tumor\* or tumour\* or malignan\* or carcinoma\* or adenocarcinoma\*)):ti,ab,kw (Word variations have been searched)

#13 #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Quality of Life] explode all trees

#15 (utilit\* or disutilit\* or quality of life or QoL or health related quality of life or HRQoL):ti,ab,kw (Word variations have been searched)

#16 #14 or #15

#17 #7 and #13 and #16

#### 4. PubMed

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





Appendix-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 <sup>2</sup>	Difference (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>RRM vs. no surgery</b>								
<b>SAQ</b>								
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)
<b>HADS</b>								
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)
<b>&gt;2 years follow-up vs. &lt;2 years follow-up post-RRM</b>								
<b>SF-36</b>								
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)
<b>SAQ</b>								
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%	<b>0.50 (0.03, 0.97)</b>	1	92	0.00%	<b>0.50 (0.03, 0.97)</b>
Habit	1	92	0.00%	<b>0.20 (0.06, 0.34)</b>	1	92	0.00%	<b>0.20 (0.06, 0.34)</b>
<b>HADS</b>								
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.

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

Comparison	Fixed-effects model				Random-effects model			
	Studies	N	I <sup>2</sup>	Difference (95% CI)	Studies	N	I <sup>2</sup>	Difference (95% CI)
<b>RRSO vs. No surgery</b>								
<b>SF-36</b>								
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)
<b>SAQ</b>								
Pleasure	6	3070	0.00%	<b>-1.21 (-1.53, -0.89)</b>	6	3070	0.00%	<b>-1.21 (-1.53, -0.89)</b>
Discomfort	5	1400	0.00%	<b>1.12 (0.93, 1.31)</b>	5	1400	0.00%	<b>1.12 (0.93, 1.31)</b>
Habit	5	2145	5.50%	-0.02 (-0.08, 0.03)	5	2145	5.50%	-0.02 (-0.08, 0.03)
<b>MRS</b>								
Overall score	2	184	0.00%	2.08 (-0.21, 4.37)	2	184	0.00%	2.08 (-0.21, 4.37)
<b>FACT-ES</b>								
Overall score	2	1745	92.00%	<b>-1.96 (-2.81, -1.10)</b>	2	1745	91.97%	-2.13 (-5.17, 0.90)
<b>&gt;1 year follow-up vs. &lt;1 year follow-up post-RRSO</b>								
<b>SF-36</b>								
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)
<b>SAQ</b>								
Pleasure	1	313	0.00%	<b>-0.70 (-1.33, -0.07)</b>	1	313	0.00%	<b>-0.70 (-1.33, -0.07)</b>
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)
<b>MRS</b>								
Overall score	0	0	NA	NA	0	0	NA	NA
<b>FACT-ES</b>								
Overall score	1	313	0.00%	2.10 (0.94, 3.26)	1	313	0.00%	2.10 (0.94, 3.26)
<b>Diagnosis of PV in BC/OC CSGs vs. Mixed or unknown basis (for high-risk definition)</b>								
<b>SF-36</b>								
PCS	0	0	NA	NA	0	0	NA	NA
MCS	0	0	NA	NA	0	0	NA	NA
<b>Post-menopausal RRSO vs. Pre-menopausal RRSO</b>								
<b>SF-36</b>								

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)
<b>SAQ</b>								
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)
<b>HRT vs. No HRT following pre-menopausal RRSO</b>								
<b>SAQ</b>								
Pleasure	3	291	0.00%	<b>1.16 (0.17, 2.15)</b>	3	291	0.00%	<b>1.16 (0.17, 2.15)</b>
Discomfort	1	157	0.00%	<b>-1.20 (-1.75, -0.65)</b>	1	157	0.00%	<b>-1.20 (-1.75, -0.65)</b>
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.

## 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) Mitigated by hormone replacement therapy
✓ Menopause symptoms	Not applicable	Increased 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