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Bilateral salpingo-oophorectomy and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers: Assessing the evidence

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Abstract

Without preventive interventions, women with germline pathogenic variants in *BRCA1* or *BRCA2* have high lifetime risks for breast cancer (BC) and tubo-ovarian cancer. The increased risk for BC starts at a considerably younger age than that for tubo-ovarian cancer. Risk-reducing bilateral salpingo-oophorectomy (rrBSO) is effective in reducing tubo-ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers, but whether it reduces BC risk is less clear. All studies of rrBSO and BC risk are observational in nature, and subject to various forms of bias and confounding, thus limiting conclusions that can be drawn about causation. Early studies supported a statistically significant protective association for rrBSO on BC risk, which is reflected by several international guidelines that recommend consideration of pre-menopausal rrBSO for BC risk reduction. However, these historical studies were hampered by the presence of several important biases, including immortal person-time bias, confounding by indication, informative censoring, and confounding by other risk factors, which may have led to over-estimation of any protective benefit. Contemporary studies, specifically designed to reduce some of these biases, have yielded contradictory results. Taken together, there is no clear and consistent evidence for a role of pre-menopausal rrBSO in reducing BC risk in *BRCA1* or *BRCA2* mutation carriers.

Introduction

Women who have inherited pathogenic variants in the *BRCA1* or *BRCA2* genes (hereafter called mutation carriers) are at high risk of developing breast cancer (BC) and tubo-ovarian cancer [1]. Risk-reducing bilateral salpingo-oophorectomy (rrBSO) is highly effective at reducing the risk of tubo-ovarian cancer [2-3]. In contrast, the role of rrBSO in mitigating BC risk in mutation carriers, while previously widely accepted and incorporated in clinical guidelines (see table 1), is now less clear and challenged by emerging contradictory evidence [4-10]. This paper reviews the literature on rrBSO and subsequent risk of first BC for mutation carriers and suggests modifications to existing guidelines based on compilation of new evidence from recent studies.

Cancer Risks for *BRCA1* and *BRCA2* Mutation Carriers

Without preventive interventions, the average cumulative lifetime risk of BC for women harbouring a *BRCA1* or *BRCA2* mutation is 72% (95% CI 65%-79%) and 69% (95% CI 61%-77%), respectively [1] compared to 13% in the general United States (US) population [11]. However, the location of the mutation within the gene, common genetic variants across the genome, family history, lifestyle-related factors, and age all influence risk for individual mutation carriers [1,12-20]. For women with these mutations, BC risk increases rapidly with age from early adulthood and then plateaus to remain at a relatively high constant level throughout the remaining lifetime. This plateau is reached between 31 to 40 years for *BRCA1* mutation carriers (incidence 23.5 per 1,000 person-years, 95% CI 19.1-28.9) and about 10 years later for *BRCA2* mutation carriers (incidence 27.5

per 1,000 person-years, 95% CI 21.6-35.1) [1]. Phenotypically, *BRCA2*-associated BCs are usually estrogen receptor (ER)-positive and progesterone receptor (PgR)-positive. Conversely, *BRCA1*-associated BCs are usually ER and PgR-negative [21], although preclinical studies suggest that female hormones do play an important role in the aetiology of *BRCA1*-associated BCs [22-28].

In contrast to BC risk, tubo-ovarian cancer risk does not become elevated above the low population level until after age 35 years for *BRCA1* mutation carriers or 50 years for *BRCA2* mutation carriers [1,2]. In the largest prospective pooled cohort study of mutation carriers, the average risk to age 50 was 8% (95% CI 6-12%) for *BRCA1* mutation carriers and 0% (95% CI 0-2%) for *BRCA2* mutation carriers. In that study, mutation carriers of either gene were most likely to develop tubo-ovarian cancer when aged 61-70 years [1], although another study suggested that peak incidence may be a decade earlier for *BRCA1* mutation carriers [2].

Risk-reduction Options

Mutation carriers have several options available to reduce their cancer risk. All major evidence-based guidelines recommend consideration of risk-reducing bilateral mastectomy (rrBM) and chemoprevention to reduce BC risk, and rrBSO to reduce tubo-ovarian cancer risk (see table 1). The recommendations regarding age for rrBSO to reduce tubo-ovarian cancer risk vary between guidelines, and by mutation type (see table 1). For example, the US National Comprehensive Cancer Network (NCCN) (https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf) and

Australian eviQ (https://www.eviq.org.au/cancer-genetics/adult/risk-management/3814-brca1-or-brca2-risk-management-female##cancer-risk-management-guidelines) suggest that rrBSO should only be performed from age 35 for *BRCA1* mutation carriers, and from age 40 for *BRCA2* mutation carriers, and only after family completion. Conversely, the United Kingdom (UK) National Institute of Health and Care Excellence (NICE) (https://www.nice.org.uk/guidance/cg164) provides little guidance regarding the appropriate age for the procedure, and the European Society of Medical Oncology (ESMO) [29] and the American College of Obstetricians and Gynecologists (ACOG) (https://www.acog.org/womens-health/faqs/brca1-and-brca2-mutations) suggest consideration between ages 35-40 years without distinguishing between *BRCA1* and *BRCA2*.

In contrast, there is no consensus regarding the use of rrBSO to reduce BC risk. ACOG recommends a discussion regarding pre-menopausal rrBSO to reduce BC risk, while the NCCN, and NICE recommend a discussion of rrBSO to reduce BC risk after completion of childbearing. These recommendations do not vary by mutation type (see table 1). In contrast, ESMO [29] and eviQ do not recommend rrBSO for BC risk reduction.

Types of Bias in Observational Studies of rrBSO and Breast Cancer Risk

Evidence for an association between rrBSO and BC risk is based on observational studies [3,4-10,30-43], which contain inherent biases that must be considered when interpreting their results and applying them to clinical practice. These biases

have been discussed since 2003 [4,44-46] (see table 2) with most leading to an overestimation of any protective association between rrBSO and BC risk in mutation carriers.

Studies of rrBSO and Breast Cancer Risk

Historical Studies

A meta-analysis by Rebbeck et al. [3], published in 2009, evaluated four case-control or cohort studies with non-overlapping participants that addressed this question [31,32,34,35]. These studies included 3,066 *BRCA1*, 1,116 *BRCA2* and a further 1,669 mutation carriers where the specific gene not stated. The results suggested a statistically significant protective association between rrBSO and BC risk for *BRCA1* (HR 0.47, 95% CI 0.35-0.64) and *BRCA2* mutation carriers (HR 0.47, 95% CI 0.26-0.84), and when the specific gene mutated was not stated (HR 0.49, 95% CI 0.37-0.65) [3]. These findings were supported by several subsequent studies with similar results [36,37], however analysed datasets were overlapping. Not surprisingly, these results impacted clinical practice.

Pivotal Study

It has recently become clear that the findings of these older studies may be spurious due to the presence of several biases [4,43]. Heemskerk-Gerritsen et al. assessed the association between rrBSO and BC risk by analysing new data from the Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON) nationwide cohort [4]. They first replicated the eligibility criteria and analyses of

the four major historical studies [30-32,36] (two of which [31,32] were included in the meta-analysis by Rebbeck et al. [3]). The results were similar to the findings of the original studies with hazard (HR) or odds ratios varying from 0.36 to 0.62, lending support to the intervention. To demonstrate the impact of bias, they reanalysed the HEBON data using a statistical design that minimised several biases. To reduce cancer-induced testing bias, they started the observation period at receipt of genetic test result or age 30, whichever came last and excluded women diagnosed with BC before the start of observation. To reduce immortal person-time bias they treated rrBSO as a time-dependant variable, allocating all person-years of observation before rrBSO, as well as the three months following rrBSO, to the non-rrBSO group. Utilising data from 589 *BRCA1* and 233 *BRCA2* mutation carriers, with 75 and 14 incident breast cancers respectively, and a median follow-up of 3.2 years, they found no statistically significant association between rrBSO and BC risk for mutation carriers combined (HR 1.09, 95% CI 0.67-1.77). The estimates for *BRCA1* and *BRCA2* mutation carriers analysed separately were HR 1.21 (95% CI 0.72-2.06) and 0.54 (95% CI 0.17-1.66), respectively. There was also no statistically significant association between pre-menopausal rrBSO (i.e., before age 51) and BC risk for mutation carriers combined (HR 1.11, 95% CI 0.65-1.90). The median age at rrBSO was 45 years (range 31-67 years). The use of hormone replacement therapy (HRT) was not reported, and data related to other BC risk factors, including parity, were missing (41%), which may have introduced confounding by other risk factors. In addition, confounding by indication, survival bias from competing risk of tubo-ovarian cancer and informative censoring may have been present. Regardless, it was the publication of this pivotal study in 2015 [4] that initiated the ongoing debate and

controversy regarding whether rrBSO reduces BC risk for *BRCA1* and *BRCA2* mutation carriers.

More Recent Studies

Since Heemskerk-Gerritsen's analysis [4,43], six further, larger cohort studies have been published that address this question [6-11] (see table 3). These studies attempted to minimise bias; however, most have potential residual methodologic issues (see supplementary table 1). Taken together, these studies do not help reach consensus on whether rrBSO is associated with reduced BC risk.

Kotsopoulos et al. published a prospective cohort study of 2,969 *BRCA1,* 725 *BRCA2* and 28 *BRCA1 or BRCA2* (specific gene unknown) mutation carriers with no prior BC diagnosis, to evaluate the effect of rrBSO on BC risk [5]. Of the 3,722 women studied, 857 underwent rrBSO before cohort enrolment and 695 underwent rrBSO after enrolment. The observation period commenced either at completion of the baseline questionnaire or receipt of genetic testing result, whichever was later, to limit cancer-induced testing bias. The mean age at rrBSO was 46.3 years (range 13-78). With 350 incident BCs observed during a mean follow-up period of 5.6 years, there was no statistically significant association between rrBSO and BC risk for *BRCA1* (HR 0.97, 95% CI 0.73-1.29, p=0.85) or *BRCA2* mutation carriers (HR 0.68, 95% CI 0.38-1.21, p=0.19). rrBSO was also not statistically significantly associated with reduced risk for BC diagnosed under age 50 years for *BRCA1* mutation carriers (HR 0.84, 95% CI 0.58-1.21, p=0.34), however, rrBSO was associated with an 83% lower risk of BC diagnosed under

age 50 years for *BRCA2* mutation carriers (95% CI 0.05-0.61, *p*=0.006). It is unclear why this analysis was limited to BCs diagnosed before age 50, rather than examining the effect of rrBSO before age 50 on risk of BC over the entire follow-up period. In light of Heemskerk-Gerritsen et al.'s publication, Kotsopoulos et al. treated rrBSO as a time-dependent variable, mitigating immortal person-time bias and adjusted for parity and other well-described risk factors in a multivariable analysis. They attempted to reduce potential confounding by indication, informative censoring, and survival bias by adjusting for cancer family history (i.e., number of first-degree relatives affected by BC). However, this approach fails to consider more subtle components of family history that affect cancer risk, such as age at BC diagnosis and affected status of more distant relatives (of particular importance where there is paternal inheritance) and therefore provides only partial mitigation.

Following on from Kotsopoulos et al., Terry et al. analysed data from 716 *BRCA1* and 573 *BRCA2* mutation carriers from the Prospective Family Study Cohort, encompassing the Breast Cancer Family Registry (BCFR) and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) [6]. In their sample, the median age of rrBSO was 44 years for *BRCA1* and 46 years for *BRCA2* mutation carriers. Incident BC was diagnosed in 116 *BRCA1* and 80 *BRCA2* mutation carriers during a median follow-up of 10.7 years. To demonstrate the importance of treating rrBSO as a time-dependant variable, Terry et al. first treated it as a fixed exposure and observed a statistically significant association between rrBSO and reduced BC risk similar to Rebbeck et al.'s meta-analysis (*BRCA1*: HR 0.40, 95% CI 0.26-0.67; *BRCA2*: HR 0.32, 95%

CI 0.17-0.60). However, there was no statistically significant association when rrBSO was treated as a time-dependent variable (*BRCA1:* HR 1.20, 95% CI 0.67-2.12; *BRCA2*: HR 0.86, 95% CI 0.43-1.72). This supported the conclusions of Heemskerk-Gerritsen et al. and emphasises the potential effect of this bias on these observational studies. The study design reduced cancer-induced testing bias by only including women who were unaffected at the start of the observation period, however the observation period did not start at the time of genetic testing, so residual cancer-induced testing bias may have been present. Other potential sources of bias may also have been present including confounding by indication, survival bias from competing risk of tubo-ovarian cancer, informative censoring and confounding by other risk factors. Further, Terry et al. did not report on the effect for mutation carriers undergoing pre-menopausal rrBSO, although an analysis of women in the upper tertile of BC risk (inclusive of mutation carriers and other high-risk women), showed no difference in risk based on age at rrBSO (<45, 45-49, ≥50 years).

More recently, Choi et al. [7] reported findings from further analyses of BCFR data, including 746 women with *BRCA1* and 576 with *BRCA2* mutations, of which 483 and 373 had breast cancer respectively. This newer study had the same methodological issues as Terry et al. [6]. Some of these potential biases were likely exacerbated by the apparent inclusion of prevalent BC cases at cohort recruitment, and of additional retrospective data back to age 16 years [47]. The estimated HRs for *BRCA1* and *BRCA2* mutation carriers overall were 0.57 (95% CI 0.38-0.84) and 0.62 (95% CI 0.41-0.96), respectively, and 0.28 (95% CI 0.10-0.63) and 0.19 (95% CI 0.06-0.71), respectively, in the first 5 years following

rrBSO. No HRs were estimated for the relationship between pre-menopausal rrBSO and BC risk [7].

Mai et al. have also recently addressed this question using data from the US Gynecologic Oncology Group-0199, a multi-institution, prospective cohort study of women at high risk of tubo-ovarian cancer [8]. Considering only women in this study without a personal history of BC (minimising cancer-induced testing bias), there were 242 *BRCA1* and 189 *BRCA2* mutation carriers included in the analysis between rrBSO and BC risk, of whom 120 *BRCA1* and 102 *BRCA2* mutation carriers had rrBSO. rrBSO was treated as a time-dependent variable, mitigating immortal person-time bias. Thirty-eight incident BCs were observed during follow-up: 29 in *BRCA1* and 9 in *BRCA2* mutation carriers. There was no statistically significant protective association between and rrBSO and BC for *BRCA1* or *BRCA2* mutation carriers combined or separately (HR 1.15, 95% CI 0.52-2.54, p= 0.72; *BRCA1* HR 1.22, 95% CI 0.50-3.00, p= 0.66; and *BRCA2* HR 1.09, 95% CI 0.20-6.06, p= 0.92*,* respectively). This held true when the analysis was limited to pre-menopausal rrBSO (combined HR: 0.84, 95% CI 0.40-1.77, p= 0.64*; BRCA1:* HR 0.84, 95% CI 0.37-1.91, p= 0.68; *BRCA2:* HR 0.73, 95% CI 0.11-4.82, p= 0.75), however that analysis also included women with a personal BC history which, if anything, would lead to an overestimate of any association, through cancer-induced testing bias. Despite being a prospective cohort study specifically designed to address this question, the study had a small number of incident cancers and remained subject to several important biases. The authors recognised potential confounding by indication, especially as women in the rrBSO group were less likely to have a first- or second-degree relative diagnosed with

pre-menopausal BC (p= 0.03). Like other contemporary studies, survival bias from competing risk of tubo-ovarian cancer, informative censoring and confounding by other risk factors may have been present.

Mavaddat et al. recently published the largest study addressing this issue, using international, multi-centre prospective pooled cohort data [9]. It included 2,272 *BRCA1* and 1,605 *BRCA2* mutation carriers from three large consortia – the International BRCA1/2 Carrier Cohort Study (IBCCS), the kConFab Follow-up Study and the BCFR. Notably, the IBCCS cohort overlaps with that analysed by Heemskerk-Gerritsen et al. [4] and the kConFab and BCFR cohorts overlap with those in Terry et al. [6] and Choi et al. [7]. Cancer-induced testing bias was minimised by excluding women affected with BC at the start of the observation period and by commencing observation after mutation testing (in 97% of enrolled women). rrBSO was treated as a time-dependent variable, with the addition of a latency period immediately after rrBSO (and at commencement of observation). During 5.4 and 4.9 years of follow-up respectively, a total of 269 and 157 incident BC cases were diagnosed in *BRCA1* and *BRCA2* mutation carriers respectively. In the primary analysis, there was no statistically significant association between rrBSO and BC risk in *BRCA1* (HR 1.23, 95% CI 0.94-1.61) or *BRCA2* (HR 0.88, 95% CI 0.62-1.24) mutation carriers. For women with *BRCA2* mutations, the HR for those who underwent rrBSO prior to the age of 45 was 0.68 (95% CI 0.40-1.15), whereas that for rrBSO after age 45 was 1.07 (95% CI 0.69-1.64). There was some evidence of a stronger association with increasing time since rrBSO for *BRCA2* mutation carriers (p-trend = 0.011), with a HR 0.51 five years after rrBSO (95% CI 0.26-0.99, p=0.046) overall, and HR 0.39 (95% CI 0.16-0.97) in women

undergoing rrBSO ≤45 years. These findings should be interpreted with caution as there was substantial variation in this HR between individual cohort studies included in the analysis (*p* value for heterogeneity = 0.005) [9]. Like the others, this study is subject to possible bias from informative censoring. Women undergoing rrBSO were more likely to have a family history of tubo-ovarian cancer (*p*<0.001*)*, suggesting potential confounding by indication, although no statistically significant difference was observed in their family history of BC amongst first- and second-degree relatives and a statistical adjustment was made to account for this. The authors also adjusted for parity, age at first birth and HRT, limiting confounding by other risk factors.

Stjepanovic et al. [10] conducted an analysis of data from five prospectively-maintained registries in Spain and the US, including 444 *BRCA1* and 409 *BRCA2* mutation carriers aged ≤51 years, 337 of whom underwent rrBSO before age 51. During the median 4.3 years of follow-up, 96 women developed incident BC (54 with *BRCA1* mutations and 42 with *BRCA2* mutations). The median age of pre-menopausal rrBSO was 42 years (range 30.5-50.9) in *BRCA1* and 43.5 years (range 33.7-50.9) in *BRCA2* mutation carriers. In contrast to some of the other recent studies, a statistically significant protective association between rrBSO and BC risk was reported for *BRCA1* mutation carriers (HR 0.45, 95% CI 0.22-0.92, *p*= 0.03), but there was no statistically significant association for *BRCA2* mutation carriers (HR 0.77, 95% CI 0.35-1.67, *p*= 0.51). They concluded that this evidence was sufficient to continue to recommend pre-menopausal rrBSO for *BRCA1* mutation carriers [10]. Stjepanovic et al. reduced several biases, including immortal person-time bias by treating rrBSO as a time-dependent variable and

adding a three-month latency after rrBSO. Cancer-induced testing bias was removed by commencing the observation time at receipt of mutation results, or at age 30, whichever occurred later and excluding women with a prior cancer diagnosis [10]. However, the authors were unable to control for differences in family history or other potential confounding and therefore, the threat of confounding by indication and other risk factors persists. A sensitivity analysis that excluded women undergoing rrBM yielded similar results to the primary analysis, although this does not completely exclude the possibility of informative censoring [4]. The authors went on to conduct a meta-analysis of findings from theirs and four published studies [4-6,41] to determine the association between pre-menopausal rrBSO and BC risk. Utilising the two studies that distinguished rrBSO before or after age 50 [5,41] alongside their own data in a subsequent analysis, Stjepanovic et al. observed a HR 0.61 (95% CI 0.36-1.02) for *BRCA1* and HR 0.43 (95% CI 0.18-1.01) for *BRCA2* mutation carriers [10].

Other Options to Reduce Breast Cancer Risk

rrBM is the most effective BC risk reduction intervention for mutations carriers. rrBM was associated with an 87% and 82% reduction in BC risk for *BRCA1* and *BRCA2* mutation carriers respectively in a meta-analysis of four studies [36,37,48-50]. Similar to studies of rrBSO, all rrBM studies were observational and subject to bias, however, there is clear biologic plausibility that rrBM may reduce BC risk. Discussion of rrBM is recommended by NCCN, NICE, ESMO, ACOG and Australian eviQ guidelines however uptake is variable [51-53], so alternatives are desirable.

The use of chemoprevention in women with *BRCA1* and *BRCA2* mutations is also endorsed in guidelines. Unlike rrBM or rrBSO, it has the advantage of being a reversible intervention if women experience side-effects or change their mind.

Despite high-quality data supporting the efficacy of chemoprevention for non-carriers at high risk of BC [54-57], and evidence that the risk reduction persists for many years after cessation of the medication [55-56], data pertaining to mutation carriers are extremely limited. The only randomised trial of aromatase inhibitors for primary BC prevention in carriers was underpowered but reported no protective association between letrozole and BC in post-menopausal women (HR 1.29, 95% CI 0.4-3.9) [58]. The NSABP-P1 study of tamoxifen for BC prevention estimated a risk ratio for BC of 1.67 (95% CI 0.32-10.7) for *BRCA1* and 0.38 (95% CI 0.06-1.56) for *BRCA2* mutation carriers randomised to tamoxifen [59]. This study had limited power due to only 8 *BRCA1* and 11 *BRCA2* mutation carriers identified amongst 288 incident BC cases. Given that the point estimate for *BRCA2* was considerably less than 1 however, these finding are often interpreted to indicate that tamoxifen may be efficacious for risk reduction in this population, although there remains considerable uncertainty. Enrolment of women onto randomised clinical trials of new potential chemopreventive agents is encouraged (https://www.breastcancertrials.org.au/current-clinical-trials/brca-p).

A detailed discussion of lifestyle factors is beyond the scope of this paper, but population recommendations for healthy living, such as maintaining a healthy

weight, participating in regular moderate-intensity exercise, minimising alcohol intake and minimising exposure to combined exogenous estrogen and progesterone, should be applied [14].

Discussion

Despite concerted efforts over twenty years to ascertain whether, and to what extent, rrBSO reduces BC risk in unaffected *BRCA1* and *BRCA2* mutation carriers, there remains uncertainty and no consensus. Yet this question is of critical interest to clinicians and the women they care for, as it underpins advice regarding strategies to reduce BC risk. Randomised trials of premenopausal rrBSO versus no rrBSO are not considered feasible, because women are unlikely to accept such a randomisation. The absence of randomised trial data means that clinical decision making is reliant on data from observational studies which have important limitations. The observational studies to date have contained several types of bias and while some recent studies have made attempts to minimise this problem, residual bias likely persists. Some biases cannot be fully mitigated in an observational study design, and others, such as confounding by indication, have mitigation strategies that are very difficult to achieve without severely limiting the sample size.

Based on the seven recent, more methodologically robust studies [4-10] highlighted in this review (table 3), there is not clear and consistent evidence of a protective effect of rrBSO on BC risk for either *BRCA1* or *BRCA2* mutation carriers. It may be most relevant to focus on studies of pre-menopausal rrBSO,

given that any protective association between rrBSO and BC risk would only be biologically plausible for pre-menopausal rrBSO, because post-menopausal rrBSO does not alter circulating levels of female hormones. Of the four studies [5,8-10] that assessed the association between pre-menopausal rrBSO and BC risk in *BRCA1* mutation carriers (using the average age of menopause in the general population, 50 or 51 years, as a surrogate for actual menopausal status), only Stjepanovic et al. [10] showed a clear protective association. The other three studies reported HRs between 0.84 and 1.11, and confidence intervals including 1. Conversely, all four studies [6,9-11] of rrBSO in pre-menopausal *BRCA2* mutation carriers reported point estimates <1 (HR 0.17-0.77) however, apart from Kotsopoulos et al. [5], the confidence interval included 1 in the other three studies (see table 3). Of note, Kotsopoulos et al. only included BCs diagnosed before age 50, which differs from the design of the other studies. Despite the wide confidence intervals, given that the point estimates for pre-menopausal rrBSO for *BRCA2* were consistently <1, it is plausible that a clear protective association was not demonstrated due to underpowered individual analyses. An individual participant data meta-analysis may help to clarify this point, although the problem of residual confounding and bias will not be overcome by meta-analytical techniques.

Overall, considering the limitations of the published studies and their conflicting results, the current evidence does not support a recommendation that *BRCA1* or *BRCA2* mutation carriers should consider pre-menopausal rrBSO specifically to reduce to their risk of first BC. This review of the evidence does not address the role of BSO for treatment of BC or prevention of a second BC event. Pre-menopausal rrBSO is associated with both long- and short-term morbidities, many

of which are irreversible [60-65]. While some of these may be alleviated by HRT, caution is needed when considering combined HRT for women with *BRCA1* or *BRCA2* mutations who are already at heightened risk of BC. Based on all the evidence presented, we strongly advise that rrBSO should be postponed until the latest possible age at which a woman may still derive the maximum cancer risk reduction from the procedure. Given the uncertainty regarding the reduction in BC risk conferred by rrBSO, the optimal age for the procedure in women with no personal history of BC should be driven by tubo-ovarian cancer risk. For *BRCA1* mutation carriers, tubo-ovarian cancer risk increases above that of the general population from the mid-30s [1] and guidelines recommend rrBSO between age 35 and 40 years, if childbearing is complete. However, for *BRCA2* mutation carriers, tubo-ovarian cancer risk is lower and increases later [1], so unless there is a family history of early-onset tubo-ovarian cancer, rrBSO could reasonably be delayed until age 45 years (which is at the upper end of the age range of 40-45 years recommended by NCCN). Research into the role of salpingectomy and delayed oophorectomy is ongoing (https://clinicaltrials.gov/ct2/show/NCT02321228, https://clinicaltrials.gov/ct2/show/NCT01907789), but such an approach cannot currently be considered a standard of care for reducing tubo-ovarian cancer risk.

Conclusions

No randomised studies of rrBSO and BC risk have been conducted, nor are they likely to be. The protective association between rrBSO and BC risk suggested by early observational studies with designs that exposed them to considerable bias

has not been clearly confirmed in seven subsequent contemporary observational studies with generally, more robust study designs. Thus, although rrBSO is considered optimal for mutation carriers to reduce risk of tubo-ovarian cancer, we contend that it should not currently be utilised specifically to provide protection against first BC and thus, in women without a personal history of BC, rrBSO should be delayed until the age at which tubo-ovarian risk reduction becomes relevant. Meanwhile, rrBM is the most effective way of reducing BC risk, however for women who find rrBM unacceptable, close surveillance together with modification of lifestyle-related risk factors and consideration of chemoprevention (especially for *BRCA2* mutation carriers) and modification of lifestyle-related risk factors, are reasonable options.

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No new data were generated or analysed in support of this research.

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Table 1: Cancer risk reduction guidelines for female BRCA1 and BRCA2 mutation carriers without a personal history of breast cancer

Intervention	NCCN	NICE	ESMO	ACOG	eviQ
Lifestyle modification[a]	Not mentioned	Recommended	Recommended	Not mentioned	Discuss
Chemoprevention	Pre-menopausal - consider Tam Postmenopausal – consider Tam, raloxifene or AI	Pre-menopausal- consider Tam Postmenopausal – consider Tam or AI	Consider Tam	Consider Tam, especially for *BRCA2*	Pre-menopausal - consider Tam Postmenopausal - consider Tam, raloxifene or AI
Risk-reducing mastectomy	Discussion regarding degree of protection	Discussion regarding degree of protection, and potential psychosocial impact	Discuss benefits, limitations, potential complications and psychosocial impact	Discuss	Offer; greatest benefit ≤40 yrs
Risk-reducing salpingo-oophorectomy to reduce tubo-ovarian cancer risk	Consider following completion of family, typically between 35-40yrs for *BRCA1* or 40-45yrs for *BRCA2*, unless age at diagnosis in the family warrants earlier consideration	Discuss risks and benefits, including discussion of negative impact of surgically-induced menopause; consider after completion of family	Discuss, taking into account mutation type, patient preferences and family history to determine appropriate age; recommended between ages 35-40yrs	Discuss between the ages of 35-40yrs and after completion of childbearing	Recommend from 35yrs for *BRCA1* and from 40yrs for *BRCA2*; after family completion
Risk-reducing salpingo-oophorectomy to reduce BC risk	Discuss degree of risk reduction for BC; consider after completion of family	Discuss risks and benefits, including discussion of negative impact of surgically-induced menopause; consider after completion of family	Not recommended for reduction of BC risk	Discuss pre-menopausal rrBSO to reduce risk of BC	Not recommended for reduction of BC risk

[a]Lifestyle modification including maintenance of healthy weight, participation in regular moderate-intensity exercise, minimisation of alcohol intake and exogenous estrogen/progesterone exposure.

NCCN= National Comprehensive Cancer Network, NICE= National Institute for Health and Care Excellence, ESMO= European Society for Medical Oncology, ACOG= The American College of Obstetricians and Gynecologists, rrBSO= risk-reducing bilateral salpingo-oophorectomy, BC= breast cancer, Tam= tamoxifen, AI= aromatase inhibitor, yrs=years

All guidelines also recommend intensified BC screening

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Table 2: Possible Sources of Bias in Studies of rrBSO and Breast Cancer Risk

TYPE OF BIAS	DEFINITION AND EXAMPLE	IMPACT	POSSIBLE MITIGATION STRATEGIES
Confounding by indication	Confounding by indication may be introduced if women who choose rrBSO have a different BC risk to those who do not have rrBSO. For example, within *BRCA1* and *BRCA2* there are areas, of each gene which, when mutated, increase TOC risk and decrease BC risk compared with mutations in other regions. Carriers with an inherently higher risk of TOC and lower risk of BC may be more likely to choose rrBSO because they have a stronger family history of TOC [46].	The potential benefit of rrBSO on BC risk may be overestimated as women opting to undergo rrBSO may do so because of a strong FHx of TOC and may have been at comparatively lower risk of developing BC [46].	The potential impact of confounding by indication may be mitigated by matched sibling cohorts, taking into account the age difference of siblings to prevent introduction of bias associated with start of follow-up (below) [46], however this strategy can substantially reduce sample size. Adjusting for FHx in the analysis offers partial mitigation of this bias.
Survival bias from competing risk of TOC	This bias is closely related to confounding by indication and describes the observation that women, who are at inherently higher risk of TOC than BC, who do not undergo rrBSO, may contribute fewer person-years at risk during follow-up if they die from TOC before censoring for another reason. If these women are over-represented in the control group, the bias introduced by indication and survival is accentuated [46].	Overestimation of the protective association between rrBSO and BC risk, further amplifying confounding by indication [46].	As per confounding by indication.
Informative censoring	When a censoring event, for example, rrBM, depends on the study endpoint (BC risk) then the censoring becomes "informative." Carriers with higher familial BC risk may be more likely to undergo early rrBM, before rrBSO, compared to carriers with lower familial BC risk. The censoring event, rrBM, is considered "informative" because the group of women who undergo rrBM were more likely to develop BC than women who proceed to either rrBSO or other risk-reducing options [4,46].	The potential benefit of rrBSO on BC risk may be overestimated due to an excess of lower-risk women in the rrBSO group.	This may be partially mitigated by adjusting for family history.
Cancer-induced testing bias	Cancer-induced testing bias explains the observation that diagnosis of BC often prompts genetic testing. Women who are then found to carry a *BRCA1* or *BRCA2* mutation may be recommended to undergo rrBSO for TOC risk reduction. Thus, an analysis of BC incidence before and after rrBSO may be enriched for BC events in the non-rrBSO period [4,46].	May lead to overestimation of the association between BC risk and rrBSO.	Exclusion of women with a personal history of BC prior to genetic testing. Starting the observation period at the time of genetic testing [4,46].
Immortal person-time bias	Immortal person-time bias relates to the follow-up period that participants survived BC-free before rrBSO. This bias is introduced if the person-time before rrBSO is not allocated to the non-rrBSO group [4].	Results in misallocation of observation time away from the non-rrBSO group and consequently, an increase in BC events per person-year in this group, biasing towards a protective association between rrBSO and BC [4].	Consider rrBSO as a time-dependent variable and allocate the observation period between the date of genetic testing and rrBSO to the non-rrBSO group [4].
Confounding by other risk factors	Confounding by other risk factors for BC also needs to be taken into account when assessing the efficacy of rrBSO [46]. e.g., parity - parous women may be more likely to undergo rrBSO compared with nulliparous women. If parous carriers are also at lower risk of BC, the association between rrBSO and reduced BC risk may appear spuriously stronger.	May lead to over- or underestimation of the association between rrBSO and BC risk depending on risk factor.	Adjustment for these confounders
Missing data	Due to the nature of observational studies, it is not always possible to collect data points of interest on all patients [45].	Depending on the volume of missing data and its relationship to the main study outcomes, missing data may affect the integrity of the results [45].	Imputation methods [66,67].
Other	Age at rrBSO – if the association between rrBSO and reduced BC risk only occurs for women who have early pre-menopausal rrBSO and not for those who have peri or post-menopausal rrBSO (which is biologically plausible) then including women with peri and post-menopausal rrBSO in the analysis will tend to weaken the association seen between rrBSO and reduced BC risk.	Any association between rrBSO and reduced BC risk may be underestimated or missed	Analyses stratified by age at rrBSO.
	cHRT – women who undergo pre-menopausal rrBSO may be more likely to receive subsequent cHRT than women who do not have rrBSO. If cHRT increases BC risk in carriers, any association between rrBSO and reduced BC risk may be spuriously weaker	Any association between rrBSO and reduced BC risk may be underestimated or missed	Adjustment for use of cHRT

BC=breast cancer; TOC = tubo-ovarian cancer; rrBSO = risk-reducing bilateral salpingo-oophorectomy; rrBM = risk-reducing bilateral mastectomy; FHx = family history; cHRT = combined hormone replacement therapy.

Table 3: Characteristics of contemporary studies of rrBSO and breast cancer risk in BRCA1 and BRCA2 mutation carriers

		Heemskerk-Gerritsen et al. 2015 [4]	Kotsopoulos et al. 2017 [5]	Terry et al. 2019 [6]	Choi et al. 2021 [7]	Mai et al. (GOG-0199) 2020 [8]	Mavaddat et al. 2020 [9]	Stjepanovic et al. 2020 [10]
N	Overall	822	3694	1289	1322	432	3877	853
	BRCA1	589	2969	716	746	242	2272	444
	BRCA2	233	725	573	576	189	1605	409
Median observation time (years)		3.2	5.6[a]	10.7[c]	NR	NR	5.4 *(BRCA1)* [a] 4.9 *(BRCA2)* [a]	4.3
N rrBSO/non-rrBSO	*BRCA1*	246/343	1187/1782	254/462	166/2484[c]	120/122	836/1436	180/264
	BRCA2	100/133	355/370	197/376	144/1781[c]	102/87	381/1108	170/239
Age at rrBSO	Median (range)	45 (31-67)	46.3 (13-78)	*BRCA1:* 44 *BRCA2*: 46	*BRCA1:* 44.5[ac] *BRCA2:* 46.9[ac]	NR[d]	NR	42 (30.5-56.5)
	Pre-menopausal, n (%)	NR	1033[b] (67)	333[b] (74)	NR	535 (57.8)[d]	NR	337 (39.5)
N incident BC diagnosis	*BRCA1/BRCA2* n	75/14	292/57	116/80	483/373	29-Sep	269/147	54/42
	Pre-menopausal	66	NR	118†	NR	NR	NR	NR
	Postmenopausal	23	NR	78[b]	NR	NR	NR	NR
rrBSO and BC risk association , 95% CI) rrBSO/non-rrBSO	Overall	1.09 (0.67-1.77)	0.89 (0.69-1.14)	NR	NR	1.15 (0.52-2.54)	NR	NR
	BRCA1 (all)	1.21 (0.72-2.06)	0.97 (0.73-1.29)	1.2 (0.67-2.12)	0.57 (0.38-0.84)	1.22 (0.50-3.00)	1.23 (0.94-1.61)	See below
	BRCA2 (all)	0.54 (0.17-1.66)	0.68 (0.38-1.21)	0.86 (0.43-1.72)	0.62 (0.41-0. 96)	1.09 (0.20-6.06)	0.88 (0.62-1.24)	See below
	"Pre-menopausal" rrBSO *BRCA1/BRCA2*	1.11 (0.65-1.90)	NR	NR	NR	0.84 (0.40-1.77)	NR	NR
	"Pre-menopausal" rrBSO *BRCA1*	NR	0.84 (0.58-1.21)	NR	NR	0.84 (0.37-1.91)	1.11 (0.80-1.52)	0.45 (0.22-0.92)
	"Pre-menopausal" rrBSO *BRCA2*	NR	0.17 (0.05-0.61)	NR	NR	0.73 (0.11-4.82)	0.57 (0.32-1.01)	0.77 (0.35-1.67)

[a]Mean

[b]Pre-menopausal defined as <50 years old at baseline

[c]Inclusive of *BRCA1* and *BRCA2* mutation carriers, and other high-risk women

[d]Not reported for the subgroup of women without a personal history of breast cancer. Note this subgroup analysis also included women with personal history of BC so not directly comparable to that for the other studies

N= number; rrBSO = risk reducing bilateral salpingo-oophorectomy; NR= not reported; BC=breast cancer; TOC= tubo-ovarian cancer

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Bilateral salpingo-oophorectomy and breast cancer risk for BRCA1 and BRCA2 mutation carriers: Assessing the evidence

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