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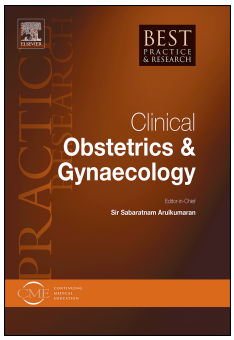

Systematic Review of Acceptability, Cardiovascular, Neurological, Bone Health, and HRT Outcomes following Risk Reducing Surgery in *BRCA* carriers

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PII: S1521-6934(20)30018-3

DOI: https://doi.org/10.1016/j.bpobgyn.2020.01.006

Reference: YBEOG 2005

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 9 November 2019

Revised Date: 19 January 2020

Accepted Date: 21 January 2020

Please cite this article as: Gaba F, Manchanda R, Systematic Review of Acceptability, Cardiovascular, Neurological, Bone Health, and HRT Outcomes following Risk Reducing Surgery in *BRCA* carriers, *Best Practice & Research Clinical Obstetrics & Gynaecology*, https://doi.org/10.1016/j.bpobgyn.2020.01.006.

Systematic Review of Acceptability, Cardiovascular, Neurological, Bone Health, and HRT Outcomes following Risk Reducing Surgery in *BRCA* carriers

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ABSTRACT

Primary surgical prevention in the form of risk-reducing salpingo-oophorectomy (RRSO) is the most effective option and gold standard for ovarian cancer (OC) risk-reduction, particularly given the absence of an effective national OC screening programme. However, premenopausal RRSO leads to premature surgical menopause with detrimental long-term health sequelae particularly in women who do not/are unable to take hormone replacement therapy (HRT). HRT uptake in women undergoing pre-menopausal oophorectomy appears low and is dependent on informed counselling, on the safety of HRT and efficacy in mitigating the health sequelae of premature menopause. Acceptance of a central role for the fallopian tube in OC etiopathogenesis coupled with detrimental consequences of premature menopause, has led to the attractive proposal of early-salpingectomy with delayed oophorectomy as an alternative OC surgical prevention strategy in premenopausal women who have completed their family but decline or wish to delay RRSO. The successful implementation of risk reducing surgery for OC prevention depends on acceptability of surgery to both recipients (e.g. *BRCA1/BRCA2* carriers) and intervention deliverers (healthcare professionals/researchers). Acceptability is also informed by an understanding of health outcomes following risk reducing surgery and the safety of HRT. It is therefore vital to understand the effects of surgery on important health outcomes such as cardiovascular health, neurological function and bone health. We present a comprehensive review of acceptability, selected health outcomes above and HRT safety following risk reducing surgery.

KEYWORDS

Targeted surgical prevention; RRSO; RRESDO; ovarian cancer; *BRCA*; acceptability

INTRODUCTION

Targeted surgical prevention of ovarian cancer

BRCA1/BRCA2 carriers have a ~17%-44% risk of ovarian cancer (OC) and ~65-72% risk of breast cancer (BC).[1-4] Primary surgical prevention in the form of risk-reducing salpingo-oophorectomy (RRSO) is the most effective option and gold standard for OC risk-reduction, particularly given the absence of an effective national OC screening programme. Premenopausal RRSO leads to premature surgical menopause which has detrimental long-term health sequelae (increased risk of heart disease, osteoporosis, vasomotor symptoms, sexual dysfunction, neurocognitive decline) especially if unable to use hormone-replacement-therapy (HRT) due to a personal history of BC.[5-13] RRSO is typically offered from ages 35–40 years for *BRCA1*-carriers and 40–45 years for *BRCA2*-carriers. Decision making is affected by numerous factors. It is a complex and dynamic process and timing needs to be individualised following informed counselling. Much of the literature used to counsel high risk women on the effects of oophorectomy on cardiovascular health, bone health and neurological function is derived from the low risk population. There are many misperceptions on the safety of HRT use in *BRCA* carriers and the counselling received by patients from clinicians is known to be inconsistent.

Acceptance of a central role for the fallopian tube in OC etiopathogenesis coupled with detrimental consequences of premature menopause, has led to risk-reducing early-salpingectomy and delayed oophorectomy (RRESDO) as an attractive two-step alternative OC surgical-prevention strategy in pre-menopausal women who have completed their family but decline or wish to delay RRSO. RRESDO provides some level of risk-reduction whilst conserving ovarian function and avoiding negative health effects of premature menopause. Lack of clarity on several key issues supports offering RRESDO solely within a research setting. Extent of OC-risk reduction and long-term health outcomes with early-salpingectomy including on ovarian-function/premature-menopause remain

unclear. Salpingectomy will not prevent OC arising outside the fallopian tube. Residual fimbrial tissue implants on the ovarian surface after salpingectomy are reported in 9.8% cases,[14] and could become a potential site for malignant transformation. Etiopathogenesis of OC is complex and our current understanding incomplete. Serous-tubular-intraepithelial-carcinoma (STIC) has been described but the natural history, progression-rates, outcomes and rate-limiting step in development of OC associated with different types is unknown.[15] STICs may not be precursors to all HGSOC cases.[16] Concerns exist regarding attrition from delayed-oophorectomy. A proportion who miss delayed-oophorectomy may develop OC. Uncertainties remain around cost-effectiveness. There is also the potential for increased morbidity resulting from two surgeries instead of one.

Acceptability and its importance

Successful implementation of risk-reducing surgery for OC-prevention depends on acceptability of surgery to both recipients (*BRCA1/BRCA2*-carriers) and intervention deliverers (healthcare professionals/researchers).[17, 18] If it is considered acceptable, *BRCA1/BRCA2*-carriers are more likely to adhere to recommendations and benefit from improved clinical-outcomes. From the healthcare professionals perspective, if delivery of risk-reducing surgery to *BRCA1/BRCA2*-carriers has low acceptability, surgery may not be delivered as intended (by intervention designers), impacting overall effectiveness of the strategy. The references to 'acceptability' in UK Medical-Research-Council (MRC) guidance documents on appropriate methods for designing and evaluating complex interventions[19-21] has increased over the years reflecting its growing importance in healthcare, rising from nil in 2000 to fourteen-times in 2015. For the purpose of this review we have measured acceptability in terms of surgical uptake.

We conducted a systematic review on acceptability of 'risk reducing surgery', the effects of surgery on cardiovascular/bone/neurological health and the safety of HRT in *BRCA1/BRCA2* carriers to aid clinicians in counselling high risk women faced with the decision as to whether or not to undergo surgery.

METHODOLOGY

Search-strategy and selection-criteria

Five databases were searched from inception to January-2019 using a common search-strategy (supplementary-table-1): Pubmed, Medline, Embase, CINAHL and PsycINFO. Additionally we searched web-based platforms including specialised journals, Google-searches for grey-literature, conference-proceedings and clinical-trial registries (ISRCTN-registry/ClinicalTrials.gov registry). Searches were not restricted by geographical location, publication-year or study-design, but limited to human studies and English-language. The search was re-run prior to final analyses to capture recently published studies.

Reference-lists of publications retrieved were screened and transferred into reference-management software (EndNote-X8.2, Clarivate-Analytics). Titles/abstracts were screened followed by retrieval and screening of full-text articles fulfilling eligibility-criteria.

Predefined inclusion-criteria were *BRCA1/BRCA2*-carriers undergoing RRSO or RRESDO. Outcome-measures were: uptake; cardiovascular health; bone health; neurological health; HRT-uptake, safety and efficacy (in alleviating the health consequences of premature menopausae).

Exclusions included abstracts/studies that included participants with a personal history of OC, mismatch-repair mutation-carriers (*MLH1/MSH2/MSH6*) and individuals at population level OC-risk.

Data-extraction, Quality-assessment and Analysis

Data were extracted using a standardised, predesigned formatted-sheet (following piloting and refinement) in Microsoft-Excel 2013. Four main categories of data were extracted: methodological characteristics, study-population, surgical-interventions (RRSO/RRESDO), reported outcome-measures. Risk of bias was assessed using the MINORS (Methodological-Index for Non-Randomized-Studies) checklist. Higher scores indicated greater quality studies. No studies were excluded from data synthesis based on quality-assessment scores. We tabulated characteristics and reported outcome-measures of all studies for qualitative synthesis.

RESULTS AND COMMENTARY

Supplementary-figure-1 provides the flow-chart outlining search outcomes and the study-selection process. Searches of electronic databases and reference-lists generated 3547 references. On evaluation of titles and abstracts, 612 articles were potentially eligible for detailed assessment, and 67 met our inclusion-criteria for qualitative-synthesis. Tables 1-3 summarise relevant-studies.

Uptake of surgery

Forty-one studies report on uptake of risk-reducing surgery for OC-prevention in *BRCA1/BRCA2* carriers (Table-1). 39/41[22-60] investigate RRSO uptake and 2/41 RRESDO[61, 62] uptake. Intention to undergo RRSO before *BRCA* carrier status confirmed (putative uptake) ranges from 16-94%[45, 55, 57] and actual uptake (following confirmation of *BRCA* carrier status) ranges from 12-78%.[34-42, 44-49, 51-59, 61-68] RRSO uptake is higher amongst Caucasian population,[39] *BRCA1* (vs *BRCA2*) carriers,[38, 43, 54, 63, 64] older women[38, 45, 63, 68] and women with a personal history of BC.[35, 68, 69] RRSO uptake rates may vary by ethnicity/country.[41 70 28, 30] Both similar and lower surgical prevention rates for RRSO (and risk

reducing mastectomy (RRM)) have been reported in Jewish women, while one study even reports higher RRSO rates (54% v 41%, respectively).[28, 41] It is well recorded that black and minority ethnic (BME) populations experience barriers to accessing healthcare.[70] The same appears to be true amongst BME *BRCA* carriers accessing RRSO. In Cragun et al, uptake of RRSO amongst black and Caucasian women was found to be 28% and 77% respectively.[39] The slightly higher overall RRSO uptake observed in *BRCA1* (42-76%) than *BRCA2*-carriers (28-70%)[32, 38, 43, 54, 63, 64] may be due to the higher lifetime-risk of OC with *BRCA1*. Higher uptake amongst older *BRCA*-carriers[38, 45, 63, 68] suggests that despite OC-risk, many women prefer to delay RRSO until after completing childbearing),[71] the preference of some to delay this till after menopause and the impact of age on risk. 44-72% *BRCA*-carriers undergoing RRSO have a personal history of BC. [35, 68, 69] The positive association of history of BC with RRSO uptake may be linked to earlier reports of reduction in contralateral BC-risk[72, 73] (although recent literature does not support this)[74, 75] and reduction in BC-specific mortality,[75-78] diagnosis of *BRCA*-status following BC, along with personal preferences.

In contrast to earlier reports suggesting *BRCA*-carriers undergo surgery within 12-months of their *BRCA*-result,[51] three time-to-event analyses now show that RRSO-uptake is dynamic and increases with time continuing months/years after initial ascertainment/*BRCA*-diagnosis. 24-38% of *BRCA*-carriers undergo surgery >12months after their initial counselling appointment following results of genetic-testing.[34, 37, 68] Unfortunately, most studies (18/32) do not report mean time from ascertainment of *BRCA*-status to RRSO making it difficult to determine the impact on uptake of RRSO at different time-points or the impact of publication of international RRSO guidelines or key publications on OC/BC-risk and detrimental health sequelae of premature menopause on RRSO rates.

Three longitudinal studies measuring both putative and actual uptake,[45, 55, 57] show actual uptake is lower than putative uptake. Reasons for this discrepancy in uptake were not properly explored.

A pilot prospective, multicentre, non-randomised US study investigating acceptability, surgical outcomes, QoL and psychosocial outcomes of RRESDO as an alternative to RRSO or OC screening, has reported RRESDO uptake as 44% (19/43) and RRSO uptake as 28% (12/43).[61] It is possible that offering pre-menopausal women who have completed their family RRESDO could reduce uptake of pre-menopausal RRSO but may increase the overall number of women undergoing pre-menopausal OC surgical prevention as it offers an alternative option to individuals otherwise declining oophorectomy due to the negative consequences of premature menopause.

Bone health

Reported incidence of osteoporosis and osteopenia diagnosed on DEXA scans in *BRCA* carriers following RRSO (both pre and post-menopausal) is 8-14% and 23-57% respectively (table-2).[6, 65, 79-82] Pre-menopausal RRSO in *BRCA* carriers using E-HRT (oestrogen-HRT) is not associated with an increased risk of osteoporosis/osteopenia. Challberg et al in a retrospective cohort study, found the incidence of osteoporosis and osteopenia to be higher in *BRCA* carriers with no E-HRT use after pre-menopausal RRSO in comparison to women who took E-HRT (osteoporosis: 13% vs 3%, osteopenia: 33% vs 13%).[83] In a Dutch prospective cohort study, bone mass density (BMD) was not found to be lower in *BRCA* carriers undergoing RRSO (pre and post-menopausal) in comparison to an age-matched reference population who had not undergone oophorectomy.[6] However 47% of carriers had a history of E-HRT use and this was not adjusted for in the analysis.[6] Although a prospective cohort study by Cohen et al, evaluated differences between the incidence of osteoporosis/osteopenia in *BRCA* carriers undergoing pre or post-menopausal RRSO, the numbers in

the analysis (n=30) are too small to draw any meaningful conclusion.[80] Overall reported outcomes are in line with findings that E-HRT preserves BMD. Evidence from general population studies show that BMD declines at a significantly greater rate following oophorectomy (trabecular bone loss from the spine 12-19% in the first year) than women who undergo natural menopause (2.5% in the first year).[84] This BMD loss appears to slow down in women using E-HRT following pre-menopausal oophorectomy.

Atraumatic fracture risk post RRSO is 4%.[65] In a prospective cohort study, RRSO in *BRCA* carriers was not found to be associated with an increased risk of atraumatic fracture and this has also been found to be the case in the prospective, observational Nurses' Health Study of 29,380 women at population level risk of OC followed up for twenty-four years.[6, 85] However a prospective Dutch cohort study found a significant increase in bone turnover markers (BTMs): osteocalcin, procollagen type-I N-terminal peptide and serum C-telopeptide of type-I collagen, which have been linked to future fracture risk, at ≥2 years after RRSO, in *BRCA* carriers aged <50 years compared to carriers >50.[7] However, BTMs have limited clinical utility.[86] It is not routinely recommended to use BTMs to select individuals at risk of fractures.[86]

Cardiovascular health

The majority of data pertaining to cardiovascular health following oophorectomy are derived from the low risk population and are used to counsel premenopausal high risk women considering RRSO. Studies have reported premenopausal oophorectomy is associated with an increased risk of coronary heart disease (CHD), [12, 13, 85, 87] with an up to 3% absolute increase in mortality from CHD described in women who have early surgical menopause and do not take HRT.[12] This is in keeping with data suggesting that oestrogens have a cardio-protective effect before menopause, and that

reduction of this protection increases the risk of cardiovascular disease. Although an increased risk of stroke has been reported, this is not statistically significant (HR 1.14, 95%CI 0.98-1.33).[85, 88]

Metabolic syndrome (MetS) has multiple definitions. Key metabolic abnormalities include glucose intolerance, insulin resistance, central obesity, dyslipidaemia and hypertension.[89] In a European prospective cohort study, Hu et al. followed 6156 men and 5356 women aged 30–89 years for a median of 8.8 years.[90] Among women, MetS implied an increased risk of death from all causes (HR 1.38, 95% CI 1.02-1.87) and of death from CVD (HR 2.78, 95% CI 1.57-4.94).[90] Postmenopausal status has been found to be associated with a 60% increased risk of MetS, after adjusting for age, BMI, income and physical inactivity.[91] Data are scarce regarding the association between surgical menopause and MetS. An association between premenopausal oophorectomy performed for benign pathology in women at population level risk of OC and MetS was demonstrated by Dørum et al.[92] They found that patients with bilateral oophorectomy before 50 years of age (n= 263) had a higher prevalence of MetS than age-matched controls (n=789) in a Norwegian population-based health study (38% vs 30% respectively).[92]

Data on CHD following premenopausal oophorectomy in *BRCA* carriers is limited (table-2). A Norwegian case-control study by Michelsen et al compared CHD risk profile (total cholesterol, HDL cholesterol, blood pressure, BMI, waist circumference) and Framingham risk score of cases (326 *BRCA*_carriers and women with a strong FH of OC who have undergone RRSO) and age matched controls (1630 women at population level risk of OC who had not undergone oophorectomy). Baseline cardiovascular morbidity did not differ significantly between cases and controls in terms of prevalence of angina, myocardial infarction, stroke, diabetes mellitus or smoking. Results show cases had a statistically significantly improved CHD risk profile (lower total cholesterol level, higher HDL cholesterol level, lower systolic blood pressure, lower BMI) and lower Framingham total point score

than controls following adjustment for personal history of cancer, education, employment status, cohabitation status, HRT use and level of physical activity. These findings linking RRSO with a favourable CHD profile must be interpreted with caution due to the small sample size and because the comparator group was made up of women at general population risk of OC. Positive health seeking behaviour amongst *BRCA* carriers has been documented in the literature[93] which may have resulted in an improved CHD profile (akin to a healthy volunteer effect) thereby confounding the results.

In a prospective cohort study, Cohen et al (n=226) found no statistically significant difference in hypertension, diabetes mellitus, hypercholesterolaemia, CHD or MI in *BRCA* carriers undergoing pre or post-menopausal RRSO.[80] However HRT use in pre-menopasusal women in that study was only 8%. Advancing age is an independent risk factor for cardiovascular disease[94] and in this study may be a confounder as there was a fifteen year difference between the mean ages of women undergoing pre and post-menopausal RRSO (42 vs 57 years).[80] Also, there were no baseline measurements for comparison, no control group and the follow-up period short (39 months).[80]

Michelsen et al concluded that *BRCA* carriers undergoing RRSO had a more favourable CHD profile than controls (women at population level risk of OC who had not undergone oophorectomy),[95] women undergoing RRSO were significantly more likely to develop MetS (OR 2.12 95%CI 1.26-3.57, P=0.005).[96] The suggested explanation by the authors is the omission of central obesity when evaluating CHD (but included when evaluating MetS) resulted in a more favourable CHD profile in *BRCA* carriers who had undergone RRSO.[95]

There is no data on the effects of RRESDO on cardiovascular health or MetS.

Neurological function

There are no data on neurological function post RRSO/RRESDO in *BRCA* carriers. However there is data from women at general population level risk of OC. The Mayo Clinic Cohort Study of Oophorectomy and Aging included women who underwent pre-menopausal oophorectomy (n=2390) and a group of referent women (n=2390) who did not undergo oophorectomy. Both groups were followed up (median 29.5 years) with the same combination of active and passive methods (direct or proxy interviews, medical records in a records-linkage system, death certificates).[9-11] Data show a statistically significant increased risk of dementia in women undergoing bilateral oophorectomy ≤48 years who do not receive E-HRT until the age of 50 (HR 1.89, 95%CI 1.27–2.83, p=0.002).[9] In women who undergo bilateral oophorectomy ≤48 years but who do receive E-HRT, there is no increased risk of dementia (HR 0.79, 95%CI 0.25–2.54, p=0.69).[9] In the same cohort, there is a non-statistically significant increase in the risk of parkinsonism and Parkinson's disease (PD) in women undergoing pre-menopausal bilateral oophorectomy ≤48 years (HR 2.00, 95%CI 0.97–4.15, p=0.06).[10] However, again in this same cohort study, women who underwent bilateral oophorectomy ≤45 years have been found to have an increased all-cause mortality (HR 1·67, 95%CI 1·16–2·40, p=0·006) as well as mortality specifically associated with neurologic and psychiatric disorders (HR 6·28, 95%CI 1·83–21·5, p=0·003).[11] These findings may suggest that the HRs for parkinsonism/PD could be underestimated if the women who died were at increased risk of parkinsonism/PD (selective censoring). However PD findings from the Mayo Clinic Cohort study are in keeping with other studies including the Nurses' Health Study (n= 77,713) which have shown that bilateral oophorectomy is not associated with an increased risk of PD.[97, 98]

Hormone replacement therapy safety and uptake

Several observational studies have evaluated effect of HRT on BC risk in *BRCA* carriers (table-3).[99-105] Mean duration of HRT use reported varies from 3.6–7.6 years.[99-105] Short term HRT use following RRSO in *BRCA1/BRCA2* carriers has not been shown to significantly increase BC risk.[99-101, 103-105] However sample sizes of these studies are small, follow up short, there is a paucity of data amongst HRT use in *BRCA2* carriers and there are no RCT data.

Authors of the Women's Health Initiative (WHI) Randomized Trials reported an increased risk of developing BC amongst post-menopausal women aged 50-79 years at population level risk of OC in the E+P (oestrogen and progestogen) HRT arm of the trial (HR 1.24, 95%CI 1.01-1.53), and a non-significant reduction in risk among women in the E-HRT group (HR 0.79, 95%CI 0.61-1.02).[106] The Million Women Study (MWS – observational prospective cohort) reported a significantly increased BC risk in post-menopausal women aged 50-64 at population level risk of OC in women using E-HRT (RR 1.30, 95%CI 1.21-1.40, p<0.0001), and E+P-HRT (RR 2.00, 95%CI 1.88-2.12, p<0.0001).[107] However these results are not generalizable to *BRCA* carriers who are a younger cohort of women undergoing premature/surgical menopause as a result of RRSO and have a different (higher) inherent BC risk profile.

Data in *BRCA* carriers have not shown a significant difference in BC risk between E-alone and E+P preparations.[100, 103, 104] A recent multi-centre prospective cohort study (n=872) has shown that progesterone containing HRT (E+P HRT/P-HRT) use following RRSO in *BRCA1* carriers <45 years, resulted in a non-significant increase in BC for each year of progesterone containing HRT use (HR 1.14, 95%CI 0.90-1.46, P=0.28).[102] However the number of women using progesterone containing HRT was small (n=62), menopause status at time of RRSO was not reported, HRT use was determined via patient self-administered questionnaires, 10% of the study sample was lost to follow up and birth cohort effect was not adjusted for. Overall, results of this study are not enough to

change current clinical practice which is to recommend use of short term HRT until the age of fifty-one (average age of menopause) in BC unaffected *BRCA1/BRCA2* carrier undergoing premenopausal RRSO. In women with triple negative BC, HRT may be considered for short-term use following premenopausal RRSO on a case-by-case basis, particularly with good prognostic disease following a multidisciplinary team review involving breast oncologists and menopause specialists.

There are no data on effects of short-term HRT post RRSO until age of natural menopause on endometrial cancer risk in *BRCA* carriers. However the WHI showed a non-significant decrease in the risk of endometrial cancer following E+P HRT use (HR 0.81, 95%CI 0.48-1.36).[106]

HRT use in *BRCA* carriers undergoing pre-menopausal RRSO improves discomfort/dyspareunia and vaginal dryness but does not improve sexual pleasure, habit, satisfaction or libido.[83, 108-110] Although HRT improves certain symptoms of sexual dysfunction, these symptoms are not improved to pre-surgical levels.[109, 110] HRT reduces prevalence and severity of hot flushes following pre-menopausal RRSO.[83, 108, 109, 111] HRT use has also been shown to be protective against bone loss in both pre-menopausal *BRCA* carriers following RRSO[83] as well as women at population level risk of OC[112, 113] and is protective against hip and total fractures in the general population.[106] There is no data on the efficacy of HRT in preventing ischaemic heart disease in *BRCA* carriers undergoing pre-menopausal RRSO. However data from observation studies indicate that HRT reduces the incidence of ischemic heart disease in women at population level risk undergoing premature menopause.[13, 114, 115] HRT use has also been shown to improve QoL following RRSO in *BRCA* carriers.[108-110]

HRT uptake in *BRCA* carriers after pre and post-menopausal RRSO is reported to be between 6-82% (table-3).[54, 57, 104, 111, 116] Specifically uptake of HRT in women undergoing premenopausal RRSO is 8-

75%.[80, 108-110, 117] This wide variation and potentially low uptake rates in premenopausal women is concerning bearing in mind that HRT mitigates the risks of heart disease, osteoporosis, neurocognitive decline, vasomotor symptoms and sexual dysfunction in *BRCA* carriers undergoing premenopausal RRSO.

For *BRCA* carriers undergoing post-menopausal RRSO, HRT uptake is between 0-10%.[80, 110] There is limited data from a case-control studies by Eisen et al (OR 0.68, 95%CI 0.37-1.27, p=0.22) and Kotsopoulos et al (OR 0.72, 95%CI 0.44–1.18, p=0.20)[103] indicating that HRT use following natural menopause does not increase the risk of BC. However sample size for these studies were small and there was no subgroup analysis performed on the effect of type or preparation of HRT on BC risk. Clinicians must be cautious in using systemic HRT in *BRCA* carriers who have reached natural menopause. This is not routinely recommended given paucity and limitations of data in *BRCA* carriers and the findings of the WHI and MWS studies which could potentially impact older *BRCA* carriers who have reached natural menopause.

SUMMARY

Acceptability of targeted surgical prevention of OC is a multifaceted, fluid and dynamic concept that evolves with time and is informed and influenced by counselling received from clinicians on health outcomes following surgery and the safety of HRT. RRSO remains gold standard for preventing OC in *BRCA* carriers with uptake being higher in BRCA1 carriers, Caucasians, women who have completed childbearing and women with a personal history of BC. However when performed in premenopausal *BRCA* carriers it increases risk of osteoporosis/osteopenia, CHD and neurocognitive decline (though *BRCA* specific data on CHD and neurocognitive impact are limited). Use of HRT until natural menopause mitigates risks and there is data supporting safety of short term HRT use in *BRCA* carriers

without a personal history of receptor positive BC. However despite this, HRT uptake in women undergoing premenopausal RRSO remains low highlighting a pressing need for greater education of health professionals on safety of HRT which will in turn improve the accuracy of counselling received by *BRCA* carriers. Acceptance of the central role of the fallopian tube in etiopathogenesis of OC together with health consequences of premature menopause associated with oophorectomy has led to RRESDO being proposed as a two-step surgical alternative for pre-menopausal women who have completed their family but decline or wish to delay oophorectomy. Due to unknown implications of RRESDO on long term health, extent of OC risk reduction and concerns over attrition, it is recommended that it is only offered within the context of a research trial.

ACKNOWLEDGEMENTS

No funding was received for this review.

CONFLICT OF INTEREST

FG is an investigator and study coordinator for the PROTECTOR study. RM declares research funding from Barts and The London Charity and Roseetrees Trust for the PROTECTOR Study and is Chief Investigator. RM declares research funding from The Eve Appeal, Cancer Research UK and from Barts & the London Charity outside this work, as well as an honorarium for grant review from Israel National Institute for Health Policy Research. RM is supported by a NHS Innovation Accelerator Fellowship.

PRACTICE POINTS

- Risk reducing salpingo-oophorectomy is the gold standard for ovarian cancer prevention in *BRCA1* and *BRCA2* carriers. It has high acceptability, though a wide range of uptake rates are reported in the literature.
- Risk reducing early salpingectomy and delayed oophorectomy is a surgical alternative available solely within the context of a research trial for pre-menopausal women declining/wishing to delay oophorectomy.
- Hormone replacement therapy is recommended following premenopausal oophorectomy until the age of fifty-one in women without a personal history of breast cancer. It may be considered in receptor negative breast cancer on a case by case basis.
- Hormone replacement therapy minimises the detrimental consequences of premature menopause.

RESEARCH AGENDA

- Factors affecting the uptake of postmenopausal risk reducing salpingo-oophorectomy in *BRCA1* and *BRCA2* carriers.
- Impact of premenopausal RRSO on CHD and neurocognitive function in BRCA carriers
- Hormone replacement therapy and risk of breast cancer in breast cancer unaffected *BRCA2* carriers undergoing pre-menopausal salpingo-oophorectomy.
- Effect of premenopausal RRSO with and without HRT on fracture risk

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Table-1: Studies reporting uptake of surgical prevention in BRCA carriers

Study	Country	Study design	Sample size (n)	Population	Type of risk reducing surgery	Study findings	Time from ascertainment of carrier status to RRS	Risk of bias
Antill, 2006[1]	Australia	Prospective cohort	266	BRCA1/BRCA2 carriers	RRSO	Uptake overall: 17.3%	3.73 years (mean)	22/24
Beattie, 2009[2]	US	Retrospective cohort	272	BRCA1/BRCA2 carriers	RRSO	Uptake 51% (122/272)	3.7 years (median)	11/16
Botkin, 2003[3]	US	Prospective cohort	26	BRCA1 carriers	RRSO	Uptake overall: 46% (12/26) Uptake by age: 25-39 years 29% (5/17), >40 years 78% (7/9)	NR	22/24
Bradbury, 2008[4]	US	Retrospective cohort	88	BRCA1/BRCA2 carriers	RRSO	Uptake 70% (62/88);	NR	17/24
Chai, 2014[5]	US, UK, Austria, Netherlands, Canada, Israel (PROSE consortium)	Prospective cohort	1499	BRCA1/BRCA2 carriers	RRSO	BRCA1 <50 years 86% BRCA1 >50 years 13% BRCA2 <50 years 71% BRCA2 >50 years 22%	NR	22/24
Cragun, 2017[6]	US	Retrospective cohort	?	BRCA1/BRCA2 carriers	RRSO	Black 28% (32/ Hispanic 91% (11/ Non-Hispanic white 77% (47/	NR	19/24
D'Alonzo, 2018[7]	Italy	Retrospective cohort	79	BRCA1/BRCA2 carriers	RRSO	Uptake 53% (42/79)	NR	11/16
Evans, 2009[8]	UK	Prospective cohort	211	BRCA1/BRCA2 carriers	RRSO	Overall uptake: 45% (96/211) Uptake by mutation status: BRCA1 52% (43/211), BRCA2 28% (29/211) Uptake by age BRCA1/BRCA2: <35 years 12% (8/67), 35-45 years 60% (50/84), >45 years 28% (14/50)	4 years (median)	15/16
Finkelman, 2012[9]	US, UK, Austria, Netherlands, Canada, Israel (PROSE consortium)	Prospective cohort	4649	BRCA1/BRCA2 carriers	RRSO	Uptake in Jewish women: 54% (522/969) Uptake in non Jewish women 41% (1502/3680)	NR	23/24
Flippo-Morton, 2016[10]	US	Retrospective cohort	87	BRCA1/BRCA2 carriers	RRSO	Uptake 78% (68/87)	3.3 years	13/16
Friebel, 2007[11]	US, UK, Austria	Prospective cohort	537	BRCA1/BRCA2 carriers	RRSO	BRCA1 42% (143/339) BRCA2 38% (76/198)	BRCA1 0.9 years (mean) BRCA2 1.5 years	14/16

							(mean)	
Garcia, 2014[12]	US	Retrospective cohort	305	BRCA1/BRCA2 carriers	RRSO	Overall uptake 74% (225/305) Uptake by BRCA status: BRCA1 76% (130/170), BRCA2 70% (95/135)	0.5 years (median)	14/16
Hanley, 2019[13]	Canada	Retrospective cohort	885	BRCA1/BRCA2 carriers	RRSO	BRCA1: 64.7.% BRCA2: 62.2%	2 years	20/24
Harmsen, 2016[14]	Netherlands	Retrospective cohort	580	BRCA1/BRCA2 carriers	RRSO	BRCA1: 98.5% BRCA2: 97.5%	NR	20/24
Holman, 2014[15]	US	Prospective cohort	204	BRCA1/BRCA2 carriers	RRESDO	Expressed intention to undergo RRESDO: 34%	NR	15/16
Kauff, 2002[16]	US	Retrospective cohort	170	BRCA1/BRCA2 carriers	RRSO	Uptake 58% (98/170)	0.3 years (mean)	22/24
Kim, 2016[17]	South Korea	Retrospective cohort	42	BRCA1/BRCA2 carriers	RRSO	52% (22/42)	7.3 months (mean)	14/16
Kram, 2006[18]	Israel	Retrospective cohort survey study	43	Jewish BRCA1/BRCA2 founder mutation carriers	RRSO	Considered RRSO before genetic result 31%; considered RRSO after genetic result 94% Overall actual uptake 78% Actual uptake by age: <50 years 44%, >50 years 89%	NR	14/16
Kwong, 2010[19]	Hong Kong	Retrospective cohort	28	BRCA1/BRCA2 carriers	RRSO	Uptake 14% (4/28)	NR	13/16
Laitman, 2014[20]	Israel	Prospective cohort	179	BRCA1/BRCA2 carriers	RRSO	Uptake 49% in Jewish women	NR	20/24
Lerman, 2000[21]	US	Prospective cohort	39	BRCA1/BRCA2 carriers	RRSO	Uptake 13% (5/39)	NR	20/24
Lodder, 2002[22]	Netherlands	Retrospective cohort	26	BRCA1/BRCA2 carriers	RRSO	Uptake 50% (13/26)	1 year	20/24
Madalinska, 2005[23]	Netherlands	Retrospective cohort	369	BRCA1/BRCA2 carriers or at increased risk because of FH of OC	RRSO	Uptake 72% (265/368)	NR	21/24
Mai, 2017[24]	US, Australia	Prospective cohort	2287	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	Uptake 40% (904/2287)	NR	21/24
Manchanda, 2012[25]	UK	Prospective cohort	1133	BRCA1/BRCA2 (290) carriers and UMS women (873)	RRSO	Uptake 55% in BRCA carriers over 5 years	5 years (mean)	16/16
Meijers-	Netherlands	Retrospective cohort	45	BRCA1/BRCA2	RRSO	Uptake 64% (29/45)	1.75 years	22/24

Heijboer, 2000[26]				carriers			(median)	
Metcalfe, 2000[27]	Canada	Retrospective cohort	56	BRCA1/BRCA2 carriers	RRSO	54% (30/56)	1.4 years (mean)	13/16
Metcalfe, 2007[28]	Canada	Retrospective cohort	672	BRCA1/BRCA2 carriers	RRSO	Uptake 54% (363/672)	4 years (mean)	23/24
Metcalfe, 2019[29]	10 countries*	Prospective cohort	6223	BRCA1/BRCA2 carriers	RRSO	Uptake overall: 64.7% (4023/6223) BRCA1: 62.8% BRCA2: 69.7%	7.5 years (mean)	23/24
Nebgen, 2018[30]	US	prospective, cohort, pilot study	43	Pre-menopausal BRCA1/BRCA2 carriers	RRESDO/RRSO	Uptake: RRESDO 44% (19/43), RRSO 28% (12/43)	NR	22/24
Pezaro, 2012[31]	Australia	Retrospective cohort	276	BRCA1/BRCA2 carriers	RRSO	Uptake: 57% (157/276) Uptake by mutation status: BRCA1 63% (83/142), BRCA2 51% (74/144)	NR	22/24
Phillips, 2006[32]	Australia	Prospective cohort	70	BRCA1/BRCA2 carriers	RRSO	Uptake overall: 29%	3 years	21/24
Ray, 2005[33]	US	Prospective cross-sectional	62	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	Intended uptake: 16% (9/58) Actual uptake: 21% (13/62)	NR	14/16
Reynier, 2011[34]	France	Prospective cohort	101	BRCA1/BRCA2 carriers	RRSO	Uptake overall: 38%	5 years	21/24
Schwartz, 2012[35]	US	Retrospective cohort	100	BRCA1/BRCA2 carriers	RRSO	Uptake 65% (65/100)	5.3 years (mean)	15/16
Sidon, 2012[36]	UK	Retrospective cohort	732	BRCA1/BRCA2 carriers	RRSO	BRCA1: 54.5% BRCA2: 45.5%	5 years	22/24
Singh, 2013[37]	US	Retrospective cohort	136	BRCA1/BRCA2 carriers	RRSO	Uptake overall 52%	Range 1-11 years	20/24
Skytte, 2010[38]	Denmark	Retrospective cohort	306	BRCA1/BRCA2 carriers	RRSO	Uptake 75%	10 years	15/16
Tiller, 2002[39]	Australia	Prospective cohort	83	BRCA1/BRCA2 carriers or at increased risk because of FH of OC	RRSO	Expressed intention to undergo RRSO at baseline: 24% (20/83) would opt for RRSO, 29% (24/83) would decline RRSO, 47% (39/83) unsure; Actual uptake at 3 years: 5/20, 0/24, 5/39	NR	24/24
Uyei, 2006[40]	US	Retrospective cohort	132	BRCA1/BRCA2 carriers	RRSO	Uptake 36% (48/132)	NR	13/16
Westin, 2011[41]	US	Retrospective cohort	182	BRCA1/BRCA2 carriers or	RRSO	Uptake 34% (62/182)	NR	21/24

strong FH of OC

NR – not reported, RRSO – risk reducing salpingo-oophorectomy, RRESDO – risk reducing early salpingectomy with delayed oophorectomy, OC – ovarian cancer, UMS- unknown mutation status

*Austria, Canada, China, France, Israel, Italy, Norway, Holland, Poland, USA

Table-2: Studies reporting bone and cardiovascular health following surgical prevention in BRCA carriers

Studies	Country	Study design	Sample size (n)	Population	Type of risk reducing surgery	Outcomes	Reported outcome measures	Follow up	Risk of bias
Challberg, 2011[42]	UK	Retrospective cohort	119	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	Osteoperosis; ostepenia	osteopenia 28% osteoporosis 10%	NR	20/24
Chapman, 2011[43]	US	Prospective cohort	51	BRCA1/BRCA2 carriers	RRSO	Osteoperosis; ostepenia	Osteopenia: 23% (7/31) Osteoperosis: 10% (3/31)	6 years (median)	21/24
Cohen, 2012[44]	US	Prospective cohort	226	BRCA1/BRCA2 carriers	RRSO	Osteopenia; osteoporosis; diabetes mellitus; hypercholesterolaemia; CAD/MI;	Pre-menopausal RRSO osteopenia: 61% (54/88); post-menopausal RRSO osteopenia: 52% (33/64) Pre-menopausal RRSO osteoperosis: 9% (8/88); post-menopausal RRSO osteoperosis: 20% (13/64) Pre-menopausal RRSO diabetes mellitus: 1% (1/88); post-menopausal RRSO diabetes mellitus: 4% (3/64) Pre-menopausal RRSO hypercholesterloaemia: 15% (21/88); post-menopausal RRSO hypercholesterolaemia: 18% (15/64) Pre-menopausal RRSO CAD/MI: 1% (2/88); post-menopausal RRSO CAD/MI: 4% (3/64)	NR	20/24
Fakkert, 2015[45]	Netherlands	Prospective cohort	211	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	Osteoporosis; osteopenia	osteopenia: 42% (89/211) osteoporosis: 6% (13/211) Women with RRSO at premenopausal age did not have lower BMD and higher fracture incidences compared to an age-matched population	5 years	20/24
Fakkert, 2017[46]	Netherlands	Prospective cohort	211	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	Fracture risk	increase in bone turnover measured after RRSO which are linked to future fracture risk	5 years	20/24
Garcia, 2015[47]	US	Retrospective cohort	225	BRCA1/BRCA2 carriers	RRSO	Osteoporosis; osteopenia; fractures	osteopenia 55.6% osteoporosis 12.1% Fracture post RRSO: 4% (10/225). RRSO in *BRCA* carriers was not found to be associated with an increased risk of atraumatic	41 months (median)	22/24

							fractures.		
Michelsen, 2009[48]	Norway	Retrospective case-control	338 cases (RRSO), 1690 controls (no RRSO)	BRCA1/BRCA2 carriers or strong FH of OC (cases), BRCA status unknown for controls	RRSO	Osteoporosis	osteoporosis 8 vs. 3%; (p = 0.02) in cases vs controls	6.5 years (mean)	22/24
Michelsen, 2009[49]	Norway	Retrospective case-control	326 cases (RRSO), 679 controls (no RRSO)	BRCA1/BRCA2 carriers or strong FH of OC (cases), BRCA status unknown for controls	RRSO	Metabolic syndrome	RRSO significantly associated with metabolic syndrome according to the 2005 National Cholesterol Education Program Adult Treatment Panel III criteria (OR 2.46 [95% CI 1.63-3.73]) and according to the International Diabetes Federation criteria (OR 2.49 [95%CI 1.60-3.88])	6.5 years (mean)	22/24
Michelsen, 2010[50]	Norway	Retrospective case-control	326 cases (RRSO), 1630 controls (no RRSO)	BRCA1/BRCA2 carriers or strong FH of OC (cases), BRCA status unknown for controls	RRSO	CHD	Except for a wider waist circumference, cases had a more favourable CHD risk profile including more physical activity, lower levels of total cholesterol (5.8 vs 6.3 mmol/L), higher levels of high-density lipoprotein cholesterol (1.7 vs 1.5 mmol/L), lower systolic blood pressure (128 vs 139 mmHg), and lower BMI (25 vs 27 kg/m^2) compared with controls Cases had a lower mean (SD) Framingham total score compared to the controls (12.9 [5.1] vs 14.5 [5.2]; P = 0.02)	6.5 years (mean)	22/24
Powell, 2018[51]	US	Prospective cohort	238	BRCA1/BRCA2 carriers	RRSO	Osteoporosis	Premenopausal RRSO: 13% Postmenopausal RRSO: 17%	NR	21/24

NR – not reported, RRSO – risk reducing salpingo-oophorectomy, RRESDO – risk reducing early salpingectomy with delayed oophorectomy, OC – ovarian cancer, CHD – coronary heart disease, BMD – done mass density

Table-3: Studies reporting hormone replacement therapy uptake, safety and efficacy in BRCA carriers

Studies	Country	Study design	Sample size (n)	Population	Type of risk reducing surgery	Outcomes	Reported outcome measures	Follow up	Risk of bias
Challberg, 2011[42]	UK	Retrospective cohort	119	BRCA1/BRCA2 carriers or strong FH of OC	RRSO	HRT efficacy	Less sexual dysfunction in HRT use vs no HRT use group (p=0.09) Fewer vasomotor symptoms in HRT use group vs past use or never use (p= 0.03) Reduced incidence of osteoporosis/osteopenia on DEXA scans with HRT use vs no use (osteopenia 13% vs 33%, osteoporosis 3% vs 13%)	NR	20/24
Cohen, 2012[44]	US	Prospective cohort	226	BRCA1/BRCA2 carriers	RRSO	HRT uptake	Pre-menopausal HRT uptake: 8% (11/144); post-menopausal HRT uptake: 0% (0/82)	NR	20/24
D'Alonzo, 2018[7]	Italy	Retrospective cohort	79	BRCA1/BRCA2 carriers	RRSO	HRT uptake	HRT uptake post RRSO 21% (9/42)	NR	11/16
Eisen, 2008[52]	Canada	Retrospective case-control	236 cases (HRT use), 236 controls (no HRT use)	BRCA1 carriers	N/A	HRT safety	OR for breast cancer associated with ever use of HRT compared with never use was 0.58 (95% CI = 0.35 to 0.96; P = .03).	4 years	21/24
Finch, 2011[53]	Canada	Prospective cohort	114	BRCA1/BRCA2 carriers	RRSO	HRT uptake, HRT efficacy	HRT uptake: pre-menopausal RRSO 39% (29/75), postmenopausal RRSO 10% (4/39) Less sexual dysfunction in HRT use vs no HRT use group (p=0.015) Fewer vasomotor symptoms in HRT use vs no HRT use group (p=0.0003) Greater QoL in HRT use vs no use group as measured by the MENQOL questionnaire	1 year	22/24
Finch, 2013[54]	Canada	Prospective cohort	96	BRCA1/BRCA2 carriers	RRSO	HRT uptake	HRT uptake 30% (29/96)	1 year	21/24
Johansen, 2016[55]	Norway	Retrospective, case-control	294 cases (RRSO), 1224 controls (no RRSO)	BRCA1/BRCA2 carriers or strong FH of OC (cases), BRCA status unknown for controls	RRSO	HRT uptake	HRT uptake 44% (119/294)	NR	21/24
Kotsopoulos, 2016[56]	Canada	Retrospective	432 cases	BRCA1	N/A	HRT safety	The adjusted OR for breast cancer comparing all	4 years	21/24

		case-control	(breast cancer), 432controls (no breast cancer)	carriers			women who ever used HRT to those who never used HRT was 0.80 (95 % CI 0.55–1.16; P = 0.24)		
Kotsopoulos, 2018[57]	Canada	Prospective cohort	872	BRCA1 carriers	N/A	HRT safety	HR 0.97 (95%CI 0.62-1.52; P=0.89) for ever use of any type of HRT vs no use HR 0.73 (95%CI 0.41-1.32; p=0.30) for ever use of E-HRT vs no use HR 1.31 (0.66-2.57; P=0.44) for ever use of E+P HRT vs no use	7.6 years (mean)	21/24
Madalinska, 2006[58]	Netherlands	Retrospective cohort	164	BRCA1/BRCA2 carriers or at increased risk because of FH of OC	RRSO	HRT uptake; HRT efficacy	Pre-menopausal HRT uptake post RRSO 38% (63/164) RRSO HRT users group reported significantly fewer symptoms overall than RRSO HRT nonusers group (P<0.05) RRSO HRT users and RRSO HRT non users groups reported comparable levels of sexual functioning. Compared with the GS group, the RRSO HRT users group reported significantly more discomfort during sexual activities (P<0.01).	NR	21/24
Nebgen, 2018[30]	US	prospective, cohort, pilot study	43	Pre-menopausal BRCA1/BRCA2 carriers	RRESDO/RRSO	HRT uptake (RRSO arm only)	Pre-menopausal HRT uptake in RRSO arm: 2/43 (5%)	12 months	22/24
Pezaro, 2012[31]	Australia	Retrospective cohort	276	BRCA1/BRCA2 carriers	RRSO	HRT uptake	HRT uptake 6% (10/157)	5 years (median)	22/24
Rebbeck, 2005[59]	US	Prospective cohort	462	BRCA1/BRCA2 carriers	RRSO	HRT safety	HRT of any type after RRSO did not significantly alter the reduction in breast cancer risk associated with RRSO (HR 0.37; 95% CI 0.14 - 0.96).	3.6 years	22/24
Tiller, 2002[39]	Australia	Prospective cohort	83	BRCA1/BRCA2 carriers or at increased risk because of FH of OC	RRSO	HRT uptake	HRT uptake post RRSO 82%	3 years	24/24
Tucker, 2016[60]	Australia	Cross-sectional	119	BRCA1/BRCA2	RRSO	HRT efficacy	The risk of sexual dysfunction in those	NR	20/24

				carriers or strong FH of OC			participants using topical vaginal oestrogen was 84% less than those not using it. Greater QoL with HRT use vs no use (p=0.010)		
Vermeulen, 2017[61]	Netherlands	Prospective cohort	57	BRCA1/BRCA2 carriers	RRSO	HRT uptake	Pre-menopausal HRT uptake: 47% (27/57)	9 months	22/24

NR – not reported, RRSO – risk reducing salpingo-oophorectomy, RRESDO – risk reducing early salpingectomy with delayed oophorectomy, OC – ovarian cancer, QoL – quality of life, HRT – hormone replacement therapy, DEXA - dual-energy X-ray absorptiometry

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HIGHLIGHTS

- Acceptability of surgical prevention of ovarian-cancer in BRCA-carriers is a dynamic concept.
- Acceptability is influenced by counselling on health outcomes after surgery and HRT safety.
- Premenopausal oophorectomy increases risk of osteoporosis, heart-disease, neurocognitive-decline.
- HRT use until natural-menopause mitigates risks and data supports safety of short term use in *BRCA*-carriers.