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Review Article

Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with *BRCA1* or *BRCA2* mutations; a systematic review of risks and benefits

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HIGHLIGHTS

- Hormone replacement therapy use improves endocrine symptoms and sexual function after premature surgical menopause.
- In *BRCA* mutation carriers, breast cancer risk is not altered by estrogen replacement therapy after oophorectomy.
- Progestin containing hormonal regimens may have a less favorable breast cancer risk profile for *BRCA* mutation carriers.

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ABSTRACT

Women with germline *BRCA1* or *BRCA2* (*BRCA*) mutations, are recommended risk-reducing salpingo-oophorectomy (RRSO) prior to menopause. Surgical menopause has significant impact on patients' health and well–being. Subsequently, concerns about surgical menopause influence uptake of RRSO in high risk women. The role of hormone replacement therapy (HRT) in *BRCA* mutation carriers undergoing RRSO has been controversial. In the general population, premature surgical menopause is associated with worse quality of life and cognitive function, and increased risk of bone and cardiovascular disease; HRT continued until the natural age of menopause is shown to alleviate a number of these effects. Conflicting information has been published on HRT and breast cancer risk. For *BRCA* mutation carriers, potential augmentation of already elevated breast cancer risk is of great concern. In this article, we provide a review of the literature on HRT in this high-risk population, including effects on quality of life, cardiovascular, bone, and brain health. We also review impact of HRT on breast cancer risk, with a discussion of HRT formulation and surgical approach. Though evidence is limited, HRT after RRSO has a number of reported benefits and does not appear to impact breast cancer risk reduction in *BRCA* mutation carriers. This information is critical when discussing RRSO with patients, as providers should review risks of early menopause and treatment options. This review provides information to assist with counseling this specific population.

Contents

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1. Introduction

In women with inherited breast cancer susceptibility gene mutations, *BRCA1* or *BRCA2* (*BRCA*), the lifetime risk of breast and ovarian cancers is markedly increased. In patients with *BRCA1* mutations, cumulative risk of breast and ovarian cancer by age 80 is about 72% and 44% respectively; for *BRCA2* mutations, that risk is about 69% and 17% respectively [1,2]. Risk reducing salpingo-oophorectomy (RRSO) is the current standard of care for prevention of ovarian and fallopian tube carcinoma in patients with *BRCA* mutations. Per the National Comprehensive Cancer Network (NCCN) guidelines, women with *BRCA1* mutations are recommended RRSO between age 35 to 40, and upon completion of child bearing [3]. Onset of ovarian cancer in patients with *BRCA2* mutations occurs on average 8 to 10 years later than in *BRCA1* mutation carriers; therefore it is reasonable to delay RRSO until age 40 to 45 in patients with *BRCA2* mutations [3].

For women with *BRCA* mutations, overall mortality is significantly decreased if they undergo RRSO at the recommended age [4–8]. Among women with *BRCA* mutations, those who underwent RRSO have lower risk of ovarian cancer compared with women who did not undergo RRSO, including women with a history of breast cancer (hazard ratio (HR) 0.14, 95% confidence interval (CI) 0.04–0.59) and those without a history of breast cancer (HR 0.28, 95% CI 0.12–0.69) [4]. Women who underwent RRSO also had a lower risk of first diagnosis of breast cancer in *BRCA1* mutation carriers (HR 0.63, 95% CI 0.12–0.69), and in *BRCA2* mutation carriers (HR 0.63, 95% CI 0.41–0.96). All-cause mortality was lower for *BRCA* carriers who underwent RRSO (HR 0.40, 95% CI 0.26–0.61), as well as breast cancer specific (HR 0.44, 95% CI 0.26–0.76), and ovarian cancer specific mortality (HR 0.21, 95% CI 0.06–0.80) [4]. The largest reduction in mortality after RRSO was due to a decrease in ovarian cancer specific mortality, which was the predominant reason for improved all-cause mortality in these women. Other studies quote the relative risk of ovarian/fallopian tube/peritoneal cancer after RRSO as 0.04 (95% CI 0.01–0.16) [6] and 0.25 (95% CI 0.08–0.74) [7].

In contrast, women without pathogenic mutations who undergo bilateral salpingo-oophorectomy (BSO) before age 45 and do not use hormone replacement therapy (HRT) have an increased overall mortality [9,10]. In an analysis of long term outcomes in the Nurses' Health Study, over 24 years of follow-up for women with hysterectomy and BSO compared with ovarian conservation, the multivariate HRs were 1.12 (95% CI 1.03–1.21) for total mortality, 1.17 (95% CI 1.02–1.35) for fatal plus nonfatal coronary heart disease, and 1.14 (95% CI 0.98–1.33) for stroke [9]. These results differed with and without HRT, all cause mortality was increased in those under age 50 who had never used HRT (HR 1.41, 95% CI 1.04–1.92), but was not increased in women who were past or current HRT users (HR 1.05, 95% CI 0.94–1.17), this difference was significantly different (p for interaction = 0.03). Rocca et al. found that mortality is significantly higher in women who had undergone bilateral oophorectomy before age 45 than in referent women without oophorectomy (HR 1.67, 95% CI 1.16–2.40, p = 0.006) [10]. These results differed by use of HRT, women who had premature oophorectomy and who did not take estrogen had almost twice the risk of death compared with referent women, HR 1.93 (95% CI 1.25–2.96, p = 0.003); in contrast to those who did take estrogen up to age 45 with HR 1.27 (95% CI 0.67–2.39, p = 0.46) [10].

In addition to increased mortality, surgical menopause can have significant effects on quality of life (QOL). Women who have early menopause may have bothersome symptoms including hot flashes, sleep disturbances, mood changes, and vaginal dryness; these symptoms may be alleviated with HRT. Adverse effects on cognition, mood, cardiovascular, bone and sexual health are also reported with premature or early menopause. HRT may lessen some of these risks, therefore many medical societies recommend providing HRT at least until natural age of menopause [11–15].

The role of HRT in *BRCA* mutation carriers after RRSO is controversial with the main concern being potential augmentation of an already high risk of breast cancer. Much of the data related to risks and benefits of HRT in the general population come from studies of older women undergoing natural menopause, and these data are not necessarily relevant to the question of HRT following premature menopause. For example, the average age of entry into the Women's Health Initiative (WHI) was 63 [16], while RRSO is recommended between age 35 to 45 for *BRCA* mutation carriers. For the purpose of this review, we will mostly restrict our survey to studies of women undergoing premature surgical menopause.

Studies evaluating HRT and surgical menopause are limited by variations in type, compliance and duration of HRT. Johansen et al. published a cross sectional study comparing women at increased risk of hereditary breast and ovarian cancer after RRSO to average-risk control women who had undergone bilateral salpingo-oophorectomy (BSO) [17]. Among women less than age 52 without history of breast cancer, only 52% of RRSO and 49% of BSO controls reported current use of HRT (odds ratio 1.13, 95% CI 0.72–1.76).

For *BRCA* mutation carriers, the decision to use HRT is complex and should be discussed in detail before surgery. Some *BRCA* mutation carriers undergoing RRSO are not candidates for HRT due to a personal history of hormone sensitive breast cancer. For the remainder, the risks of HRT must be balanced against the impact of early menopause on long-term health and quality of life. The goal of this review is to systematically review and present the available data regarding HRT after RRSO in patients with pathogenic *BRCA* mutations, including the impact on QOL, sexual function, breast cancer risk, cardiovascular, brain and bone health. We also discuss the formulation of HRT and consideration of surgical approaches to risk reduction.

2. Methods

A review using The National Library of Medicine (PubMed) Database was performed. Over 15 search terms were used, with three main concepts: "hormone replacement", "*BRCA*", and "risk reduction". The initial search returned over 1000 studies. Articles were included if they examined hormone replacement in women who had undergone RRSO. Only articles published in English were reviewed. Abstracts were reviewed for relevance and all potentially relevant articles were reviewed for inclusion. These articles as well as articles that were referenced were considered for review. Approximately 100 articles were reviewed in full. There are no randomized controlled trials studying HRT in *BRCA*

mutation carriers; therefore, observational and retrospective studies were included.

3. Results

3.1. Quality of life (QOL) and sexual function

HRT improves menopause symptoms (e.g. vasomotor symptoms, sexual function, vulvo-vaginal atrophy) and QOL after premature surgical menopause in the general population [13,18–20]. As expected, similar improvements in QOL have been noted in high-risk women and *BRCA* mutation carriers taking HRT after RRSO. In a retrospective cohort study, Madalinska et al. described the impact of HRT use on endocrine symptoms and sexual functioning in high-risk premenopausal women (total $N = 164$, 78% *BRCA* mutation carriers) who had undergone RRSO [21]. Participants completed a questionnaire on endocrine symptoms (Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES)) and sexual functioning (Sexual Activity Questionnaire (SAQ)), 47% of these women were current HRT users [21]. HRT users reported significantly fewer endocrine symptoms ($p < 0.05$) and similar levels of sexual functioning in comparison with non-HRT users after RRSO [21]. A 2016 retrospective cohort study by Johansen et al. compared sexual activity and functioning after RRSO between HRT users and nonusers [22]. Of 201 sexually active women in the RRSO group, 92 (46%) were current users of HRT; women who used systemic HRT had significantly lower discomfort scores than HRT nonusers ($p = 0.005$). No significant difference was found in pleasure score between HRT users and nonusers within the RRSO group ($p = 0.12$).

Prospective studies on QOL, menopause symptoms and sexual function have found similar results. In 2011, Finch et al. published a prospective observational study using the Menopause- Specific Quality of Life (MENQOL) questionnaire before surgery and one year post surgery [23]. Of the 114 women who completed the questionnaires, 75 were premenopausal at the time of surgery, and 29 (39%) of those women reported taking HRT. Women taking HRT had significantly fewer vasomotor symptoms ($p = 0.0003$) and better sexual functioning ($p = 0.015$) after surgery than those not taking HRT [23]. In another prospective observational study, 57 premenopausal women who underwent RRSO completed the FACT-ES and SAQ questionnaires about endocrine and sexual symptoms before surgery, 3 months and 9 months post-surgery [24]. All premenopausal women had a decline in sexual function after surgery; but women on HRT had significantly less short- and long-term vasomotor symptoms ($p = 0.001$, $p < 0.001$, respectively) and better sexual function ($p < 0.001$) after surgery than those not using HRT [24].

In a cross-sectional study by Tucker et al., premenopausal women report higher sexual distress ($p = 0.020$), dissatisfaction with their sex life ($p = 0.011$), greater psychological distress ($p = 0.005$), and poorer emotional functioning ($p = 0.052$) than post-menopausal women following RRSO [25]. HRT was found to reduce rates of dyspareunia ($p = 0.027$), and the severity of sexual menopause symptoms (change in sexual desire, vaginal dryness, and avoiding intimacy; $p = 0.030$). Interestingly, in this study, topical vaginal estrogen decreased the rates of sexual dysfunction (OR 0.22, 95% CI 0.05–0.95, $p = 0.043$), but systemic HRT did not ($p = 0.130$) [25].

Together, the studies on QOL and sexual function after RRSO for high-risk patients point to clear benefits of HRT (Table 1). Clinicians can reassure women without contraindications to HRT that their menopausal symptoms, QOL and sexual function after RRSO will be better, but not necessarily baseline, if they take HRT. This information may assist women amenable to taking HRT not to delay RRSO for these reasons.

3.2. Bone health

In the general population, premature menopause clearly has a negative impact on long-term bone health [11,13]. Two studies have been published specifically looking at bone health following RRSO and use of HRT. Garcia et al. published a retrospective chart review examining the current management of osteoporosis in *BRCA* carriers after RRSO [26]. They included 225 women who underwent RRSO, 99 (44%) of who had at least one dual-energy X-ray absorptiometry (DXA) scan. Of these women, 56% had results consistent with osteopenia and 12% had results consistent with osteoporosis. Only 14 (25%) women who had RRSO used some form of HRT. Women with normal DXA results were no more likely to have taken HRT than women with bone disease (defined as osteopenia or osteoporosis). The small percentage of women using HRT and getting DXA scans and the potential confounding bias of low bone density leading to HRT use limited the ability of these investigators to assess the effect of HRT on bone health [26].

Challberg et al. reviewed use of HRT in women with *BRCA* mutations after RRSO performed before age 48, specifically evaluating menopause symptoms and bone health [27]. In their sample, only 36% of women

Table 1
Studies evaluating quality of life and sexual function in premenopausal women undergoing RRSO.

Study	Design	Population studied	Number of proven *BRCA* mutation carriers	Mean age at RRSO (range)	Number who used HRT after RRSO (n, %)	Measurement tool	Key results and conclusions
Madalinska [21]	Cross sectional observational	Premenopausal women at risk for hereditary breast/ovarian cancer	128	43 (NS)	77 (47%)	FACT-ES, SAQ	Fewer vasomotor symptoms in HRT users ($p < 0.05$), but comparable levels of sexual functioning in users vs. nonusers
Johansen [22]	Retrospective cohort	Women who had RRSO because of an increased cancer risk	NS	48 (31–76)	119 (44%)	SAQ	In subanalyses of the RRSO group, users of systemic HRT reported less discomfort ($p = 0.001$) than did nonusers
Finch [23]	Prospective observational	Women who elected to undergo RRSO due to a *BRCA* mutation	114 total, 75 premenopausal	47.5 (35–69)	33 (29%)	MENQOL	Premenopausal RRSO was associated with an increase in vasomotor symptoms and decrease in sexual functioning, which was improved by HRT, but not to pre-surgical levels
Vermeulen [24]	Prospective observational	Premenopausal women with increased risk of breast and ovarian cancer	50	NS	27 (47%)	FACT-ES, SAQ	HRT use in the first year after RRSO in premenopausal women had beneficial effects of minimizing endocrine and sexual symptoms
Tucker [25]	Cross sectional observational	Women who had undergone RRSO	32	50 (33–69)	33 (28%)	FSFI, SAQ, FDS-R, RAS, BISC, MENQOL, SF-36, IES	HRT use reduced dyspareunia ($p = 0.027$), and the severity of sexual menopause symptoms ($p = 0.03$)

RRSO, risk reducing salpingo-oophorectomy; HRT, hormone replacement therapy; NS, not specified; FACT-ES, Functional Assessment of Cancer Therapy- Endocrine Symptoms; SAQ, Sexual Activity Questionnaire; MENQOL, Menopause- Specific Quality of Life; FSFI, Female Sexual Function Index; FSDS-R, Female Sexual Distress Scale Revised; RAS, Relationship Assessment Scale; BISC, Body Image Self-Consciousness Scale; SF-36, Short Form Health Survey; IES, Impact of Event Scale.

ever had a DXA scan; only 5 of 31 (16%) women with HRT use had osteopenia, while 37 of 78 (47%) women with >24 months of estrogen deprivation had osteopenia ($p = 0.03$). The impact of premature surgical menopause on bone health should be incorporated into the discussion of the plan for HRT post RRSO (Table 2). Women with existing osteopenia or other risk factors for osteoporosis (smoking, family history, chronic steroids) and women who do not take HRT should be monitored for bone health and density.

3.3. Cardiovascular health and cognitive function

Early menopause has adverse effects on cardiovascular (CV) health and cognitive function in the general population. In a meta-analysis by Atsma et al., the pooled effect of BSO increased the risk of CV disease compared with women who were premenopausal (RR 2.62, 95% CI 2.05–3.35) [28]. The pooled effect on CV disease was 4.55 (95% CI 2.56–8.01) for women who underwent BSO before age 50 compared with BSO after age 50. Rivera et al. showed that in the general population, women who underwent BSO before age 45 had increased mortality associated with cardiovascular disease compared to women who had not undergone any oophorectomy (HR 1.44, 95% CI 1.01–2.05, $p = 0.04$) [29]. Women who were not treated with estrogen after BSO through at least age 45 had significantly higher mortality due to CV disease (HR 1.84, 95% CI 1.27–2.68, $p = 0.001$); women treated with estrogen after BSO were not statistically different than women not undergoing BSO (HR 0.65, 95% CI 0.30–1.41, $p = 0.28$).

In the general population, premenopausal BSO for benign conditions is associated with increased risk of cognitive impairment or dementia later in life. The Mayo Clinic Cohort of Oophorectomy and Aging demonstrated that bilateral oophorectomy before menopause had an increased risk of cognitive impairment or dementia compared to those without oophorectomy (HR 1.46, 95% CI 1.13–1.90) [30]. The risk was higher for women undergoing BSO before age 49 that were not treated with estrogen until age 50 (HR 1.89, 95% CI 1.27–2.83, $p = 0.002$). In women who took estrogen until age 50, risk of cognitive impairment or dementia was not significantly different (HR 0.79, 95% CI 0.25–2.54, $p = 0.69$) [30].

Specifically looking at *BRCA* mutation carriers, there was no significant difference in rates of hypertension, diabetes mellitus, hypercholesterolemia, or coronary artery disease between patients who underwent RRSO before age 50 and those who underwent RRSO after age 50 [31]. The number of events was very small and follow up was short; for example, only 5 had a diagnosis of coronary artery disease/myocardial infarction, and 4 had diabetes mellitus. Much larger numbers are necessary to address the effect of RRSO on CV events in a high risk population.

The effect of RRSO on CV disease specifically in patients with *BRCA* mutations is not well studied (Table 2). Results from the general population of premenopausal BSO suggest that early surgical menopause is associated with increased CV risk, decreased cognitive function, and these effects may be alleviated with HRT.

3.4. Breast cancer risk

Women with inherited *BRCA* mutations are at very high risk of developing breast cancer. Numerous prospective studies in the general population have shown an increased risk of breast cancer in postmenopausal women on extended hormone replacement therapy, particularly the combination of progestin and estrogen, raising concerns about using HRT in women already at high risk of breast cancer [13,16,32]. In 2002, the WHI stopped the trial of estrogen plus progestin (E + P) versus placebo after 5.2 years of follow up because of increased risk of breast cancer exceeding the stopping boundary; the global index statistic supported risks exceeding benefits [16]. The estimated HR for breast cancer was 1.26 (95% CI 1.00–1.59) for E + P versus placebo when the study was stopped. Hazard ratios for breast cancer increased with number of years of postmenopausal hormone use. Given WHI participants had an average age at enrollment of 63, it is unclear how these data apply to women with premature surgical menopause.

Breast cancers in women with *BRCA1* mutations are usually hormone receptor negative as part of a triple negative phenotype, while women with *BRCA2* mutations generally have estrogen and progesterone receptor expressing breast cancer [33,34]. Therefore, it is conceivable that HRT would impact breast cancer risk differentially in *BRCA1* or *BRCA2* mutation carriers, though many studies combine these two groups.

The Prevention and Observation of Surgical Endpoints (PROSE) prospective cohort study, followed 462 women with *BRCA* mutations and no breast cancer history for an average for 3.6 years to evaluate breast cancer risk with and without HRT [35]. The researchers collected

Table 2
Studies on bone, cardiovascular and cognitive health in premenopausal women undergoing RRSO.

Study	Design	Population studied	Number of proven *BRCA* mutation carriers	Mean age at RRSO (range)	Number who used HRT after RRSO (n, %)	Outcome studied	Results	Conclusions
Garcia [26]	Retrospective chart review	All adult women who tested positive for *BRCA* mutation	225	52 (NS)	56 (25%)	Number of women screened for osteoporosis with DXA scan	OR 1.2 (95% CI 0.4–3.7) for bone disease (defined as either osteopenia or osteoporosis) in patients who used HRT	Women with normal DXA results were no more likely to have taken HRT than women with bone disease
Challberg [27]	Retrospective chart review	Women at risk for ovarian cancer who had RRSO at <48 years old	123	41 (24–48)	67 (32%)	DXA scans	Bone loss with a T score of <−1.0 was present in 5/31 (16%) who used HRT and 37/78 (47%) who did not use HRT ($p = 0.03$)	The prevalence of reduced bone mass was far higher among women who had >24 months of estrogen deprivation than in those who had taken HRT
Cohen [31]	Retrospective chart review	Women with *BRCA* mutations who underwent RRSO	226	47.1 (NS)	11 (5%)	Bone health, frequency of hypertension, hyperlipidemia, CAD, MI, diabetes, hypothyroidism and depression	16% (36/226) had hypertension, 17% (39/226) hyperlipidemia, 2% (5/226), CAD or MI, 2% (4/226) diabetes, 13% (29/226) hypothyroidism and 14% (31/226) depression	Despite the risk reduction RRSO offers, attention should be paid to non-cancer end- points, particularly bone health

RRSO, risk reducing salpingo-oophorectomy; HRT, hormone replacement therapy; NS, not specified; OR, odds ratio; CAD, coronary artery disease; MI, myocardial infarction.

information on HRT use, including duration of use, reason for taking, and type of HRT. Average age at RRSO was 42.7 (range 21.5–73.9), only 16 (10.3%) of the 155 RRSO cases underwent RRSO after age 50, and 93 (60%) used HRT. RRSO was significantly associated with breast cancer risk reduction (HR = 0.40, 95% CI 0.18–0.92) and breast cancer risk was not altered by use of HRT (HR 0.37; 95% CI 0.14–0.96). Notably, most women in this study took estrogen-alone, and not E + P [35].

In 2008, Eisen et al. published a matched case-control study of 472 postmenopausal women with a *BRCA1* mutation to examine if use of HRT is associated with breast cancer risk [36]. Those diagnosed with breast cancer were designated as case subjects, while the control subjects were those not diagnosed with breast cancer; a total of 236 matched pairs were identified. The adjusted odds ratio for breast cancer with ever use of HRT as compared to never use was 0.58 (95% CI 0.35–0.96, p = 0.03) [36]. The use of HRT was associated with a decreased breast cancer risk among *BRCA1* mutation carriers [36].

Kotsopoulos et al. published two papers evaluating the effects of HRT on breast cancer risk in *BRCA1* mutation carriers. The first, published in 2016, is a retrospective case control analysis [37]. Pairs of *BRCA1* mutation carriers with and without breast cancer were matched for year of birth (within 2 years), type of menopause (surgical or natural), and age of menopause within 2 years, ($N = 432$ matched pairs). Participants received a questionnaire with demographic information as well as detailed information regarding HRT use including duration and method of administration (e.g., pills, skin patches, or vaginal suppositories). They evaluated HRT use after both natural menopause and RRSO. The mean duration of HRT use was 4.4 years in women who underwent surgical menopause. The adjusted odds ratio for breast cancer in all women who had ever used HRT compared with women who had never used HRT was not significant (OR 0.80; 95% CI 0.55–1.16, p = 0.24). Overall, their findings did not differ by type of menopause (surgical versus. natural), duration of HRT use or formulation of HRT. Therefore, the investigators concluded that a short course of HRT should not be contraindicated for *BRCA1* mutation carriers who do not have a personal history of breast cancer [37].

In 2018, Kotsopoulos et al. published a prospective longitudinal cohort study examining HRT and breast cancer in 872 *BRCA1* mutation carriers after RRSO [38]. Three hundred seventy-seven (43%) used HRT and 495 did not. Of the participants using HRT, 259 used estrogen- alone, 66 used E + P, and another 40 used progestin-alone. Ever use of any HRT after RRSO was not associated with increased risk of breast cancer (HR 0.97; 95% CI 0.62–1.52, p = 0.89). Kotsopoulos concluded that women should not avoid RRSO because of fears associated with estrogen–alone HRT use [38].

The fear of breast cancer risk by patients and providers is often the major deterrent from starting HRT. However, based on the available literature (Table 3), breast cancer risk reduction following RRSO in premenopausal *BRCA* carriers without a history of breast cancer is not changed due to HRT.

3.5. Estrogen and progestin

The type of HRT may impact breast cancer risk; WHI demonstrated an increased risk of breast cancer for women who used combined E + P HRT for more than five years (HR 1.26, 95% CI 1.00–1.59) [16], an association not found for estrogen-only HRT, which was associated with a reduction in rate of breast cancer (HR 0.77, 95% CI 0.59–1.01) [16,39,40]. Whether the hormone formulation impacts breast cancer risk following premature surgical menopause and specifically for women with *BRCA* mutations is less clear.

In the PROSE study of premenopausal *BRCA* carriers who had RRSO, 54 (58%) used estrogen-alone, and 34 (22%) used E + P. Breast cancer risk reduction for women who took progestin with or without estrogen versus women who took estrogen- alone was not significant (HR 2.56; 95% CI 0.08–78.13 for combined therapy), though the small number of women who took combined therapy limited the power to identify differences between subgroups [35]. HRT of any type after RRSO did not significantly alter the risk reduction of breast cancer associated with RRSO (HR 0.40, 95% CI 0.18–0.92 for RRSO without HRT versus HR 0.37, 95% CI 0.14–0.96 for RRSO with HRT). Short term HRT was found

Table 3
Studies assessing breast cancer risk with HRT in *BRCA* mutation carriers.

Study	Design	Population studied	Number of proven *BRCA* mutation carriers	Mean age at RRSO (range)	Number (%) who used HRT	Mean duration of HRT use (range)	Breast cancer risk of HRT	Conclusions
Rebbeck [35]	Prospective cohort	Cases: women who underwent RRSO	155	42.7 (21.5–73.9)	93 (60%)	NS	HR 0.37 (95% CI 0.14–0.96)	Short-term HRT use did not negate the protective effect of RRSO on subsequent breast cancer risk in *BRCA* mutation carriers
		Controls: women without RRSO	307	NA	21 (7%)			
Eisen [36]	Retrospective matched case-control	Cases: women diagnosed with breast cancer	236*	42.3 (28–52)	47 (20%)	4.0y	OR 0.58 (95% CI 0.35–0.96, p = 0.03)	Among postmenopausal women with *BRCA1* mutations, HRT use was not associated with increased risk of breast cancer; rather, it was associated with a decreased risk
		Controls: women without breast cancer	236*	42.6 (28–52)	68 (29%)	3.7y		
Kotsopoulos [37]	Retrospective matched case-control	Cases: women with postmenopausal breast cancer	432*	42.5 (28–53)	80 (18.5%)	4.4y (0.1–25.0)	OR 0.80 (95% CI 0.55–1.16, p = 0.24)	A short course of HRT is not contraindicated in *BRCA1* mutation carriers who have no personal history of breast cancer
		Controls: women who never had breast cancer	432*	43.0 (29–53)	91 (21.3%)	4.3y (0.05–18.0)		
Kotsopoulos [38]	Prospective, longitudinal cohort	Women who used HRT after RRSO	377*	43.0 (30–70)	377 (43%)	3.9 y (0.5–19.0)	HR 0.97 (95% CI 0.62–1.52, p = 0.89)	Use of estrogen after RRSO does not increase the risk of breast cancer among women with a *BRCA1* mutation
		Women who did not use HRT after RRSO	495*	48.4 (29–76)		NA		

RRSO, risk reducing salpingo-oophorectomy; HRT, hormone replacement therapy; NA, not applicable; NS, not specified; HR, hazard ratio; CI, confidence interval; OR, odds ratio.
* *BRCA1* only.

to be safe, but the majority of HRT was estrogen- alone and therefore we cannot definitively comment on other formulations.

In a matched case control study of postmenopausal women with a *BRCA1* mutation, Eisen et al. found that there appeared to be an inverse association with estrogen-only HRT versus no HRT use and breast cancer (OR 0.51, 95% CI 0.27–0.98, p = 0.04) [36]. The association of breast cancer with use of E + P use was not statistically significant (OR 0.66, 95% CI 0.34–1.27; p = 0.21) [36].

In their 2016 matched case-control study, Kotsopoulos et al. reported no adverse effect of estrogen-alone or of combined E + P formulations on breast cancer risk in *BRCA1* mutation carriers after RRSO [37]. A subset of these participants were included in a 2018 prospective, longitudinal cohort study from the same research group; reporting a 10-year actuarial risk of breast cancer to be significantly lower for *BRCA1* mutation carriers who used estrogen-alone compared to those who used E + P (12% versus 22%, p = 0.04) [38]. For each year of estrogen-containing HRT use, there was an 8% reduction in breast cancer risk (HR 0.92, 95% CI 0.83–1.01, p = 0.07). There was a non-significant (8%) increased risk with progestin use (HR 1.08, 95% CI 0.92–1.27, p = 0.34). These associations were stronger for women who underwent RRSO prior to age 45, for whom each year of estrogen-containing HRT was associated with a 18% reduction in breast cancer risk (HR 0.82, 95% CI 0.69–0.97, p = 0.02) while each year of progestin-containing HRT (progestin-alone or E + P) was associated with a non-significant (14%) increase in breast cancer risk (HR 1.14, 95% CI 0.90–1.46, p = 0.28) [38].

Based on the available data, it seems that estrogen-only HRT is preferred over progestin-containing methods in *BRCA* mutation carriers (Table 4). For *BRCA* mutation carriers with at risk breast tissue, minimizing systemic progestin exposure seems preferable. For women taking E + P, options to minimize systemic progestin include intermittent progestin withdrawal every 3 months [41–43] or use of a progestin containing IUD [44–47].

3.6. Surgical approach

Consideration of which HRT regimen to use is different depending on the presence or absence of a uterus. After hysterectomy, women may take estrogen replacement therapy without progestin, while women who retain their uterus should take combined E + P, to decrease the risks of unopposed estrogen on the uterus. Risks of unopposed estrogen include endometrial hyperplasia and endometrial cancer.

Hysterectomy is not universally recommended as a risk reducing surgery in patients with *BRCA* mutations since *BRCA* carriers do not have an overall increased risk of endometrial cancer [48]. There is some debate regarding the role of hysterectomy for a small but increased risk of serous uterine cancer in *BRCA1* carriers [49–52]. There is also uncertain data regarding a more pronounced increased risk of uterine cancer in *BRCA* carriers on tamoxifen [51,53].

One argument for hysterectomy at the time of RRSO is to allow patients the opportunity to take estrogen-alone HRT, which may be more favorable for their breast cancer risk profile compared to E + P. Some authors have argued a theoretical benefit to hysterectomy of more complete removal of the fallopian tube, though there are no case reports in *BRCA* mutation carriers of fallopian tube carcinoma occurring in the isthmic portion of the fallopian tube post RRSO. In 2008, Gabriel evaluated factors associated with hysterectomy and HRT use in *BRCA* carriers after RRSO. Forty of the 73 (55%) patients underwent hysterectomy in addition to RRSO, 17 (43%) of whom used HRT. The remaining 33 (45%) patients underwent RRSO without hysterectomy, and 16 (48%) of these patients used HRT. There was no difference in hormone use following the different surgeries (p = 0.6) [54].

Rebbeck et al. noted that patients undergoing RRSO might benefit from hysterectomy in order to simplify HRT but should be counseled on the increased surgical risk and recovery time [35]. Kotsopoulos et al. encouraged consideration of hysterectomy at time of RRSO to avoid progestin-containing HRT [38].

Hysterectomy at the time of RRSO may be appropriate in some patients and requires careful consideration and individual counseling. The increased expense and morbidity of hysterectomy must be balanced with individual considerations including a potential increased risk of serous uterine carcinoma in *BRCA*1 carriers and the opportunity to avoid progestin exposure in women planning to take HRT. Additionally some women may have other risk factors for uterine or cervical cancer, including history of cervical dysplasia, morbid obesity, and polycystic ovarian syndrome, which should be discussed prior to surgery.

Finally, there has been some consideration of interval salpingectomy with delayed oophorectomy (ISDO) for risk reduction. In theory, this

Table 4
Breast cancer risk by HRT formulation in *BRCA* mutation carriers post RRSO.

Study	Design	Comparison groups	HRT formulation used and number of subjects	Breast cancer risk by formulation	Conclusions
Rebbeck [35]	Prospective cohort	Women who underwent RRSO and used HRT Women without RRSO and did not use HRT	E: 50 E + P: 34 NA	E: HR 0.44 (95% CI 0.12–1.61) E + P: HR 0.43 (95% CI 0.07–2.68)	Breast cancer risk reduction for women who took progestin w/ or w/o estrogen and women who took estrogen- alone was not significantly different
Eisen [36]	Retrospective matched case-control	Cases: women diagnosed with breast cancer Controls: women without breast cancer	E: 28 E + P: 19 E: 40 E + P: 28	E: OR 0.51 (95% CI 0.27–0.98, p = 0.04) E + P: OR 0.66 (95% CI 0.34–1.27, p = 0.21)	An inverse association with breast cancer risk was observed with use of estrogen only; the association with use of E + P was not statistically significant
Kotsopoulos [37]	Retrospective matched case-control	Cases: women with postmenopausal breast cancer Controls: women who never had breast cancer	E: 46, E + P: 28 E: 42 E + P: 41	E: OR 1.0 (95% CI 0.62–1.62, p = 0.11) E + P: OR 0.65 (95% CI 0.38–1.11, p = 0.23)	There is no adverse effect of estrogen-alone or of combined E + P formulations on breast cancer risk in *BRCA1* mutation carriers after RRSO
Kotsopoulos [38]	Prospective, longitudinal cohort	Women who used HRT after RRSO Women who did not use HRT after RRSO	E: 259 E + P: 66 NA	E: HR 0.73 (95% CI 0.41–1.32, p = 0.30) E + P: HR 1.31 (95% CI 0.66–2.57, p = 0.44)	The possible adverse effect of progesterone-containing HRT warrants further study

RRSO, risk reducing salpingo-oophorectomy; HRT, hormone replacement therapy; E, estrogen alone; E + P, estrogen and progestin; NA, not applicable; HR, hazard ratio; CI, confidence interval; OR, odds ratio.

would reduce the adverse consequences of early menopause. Kwon et al. used the Markov Monte Carlo Simulation method to evaluate three strategies for risk reduction for women with *BRCA* mutation: BSO, bilateral salpingectomy, and ISDO. BSO had the lowest cost and highest life expectancy when compared to the other two options. ISDO had the highest quality of life measures. However, the study did not account for the quality of life improvement with HRT, so it may have underestimated their adjusted quality of life expectancy [55].

Beyond simulation, the practice of ISDO is currently being studied. Nebgen et al. recently published a prospective, multicenter, non-randomized pilot study of 43 women with *BRCA* mutations [56]. Participants chose from three arms, 19 (44%) chose ISDO, 12 (28%) chose RRSO, and 12 (28%) chose screening. The RRSO and delayed oophorectomy were timed according to NCCN guidelines, by the age of 40 for *BRCA1* and by the age of 45 for *BRCA2*. Responses to the Cancer Worry Scale indicated worry in the ISDO ($p = 0.01$) and RRSO ($p < 0.0001$) arms were significantly decreased 12 months after surgery. Participants who underwent ISDO indicated decreased anxiety on responses to the State Anxiety Inventory after surgery ($p = 0.02$). Of the 12 patients who underwent ISDO, 3 had completed oophorectomy at the time of publication. Women who chose ISDO were on average 7 years younger than those who chose RRSO, and were >2 years younger than their recommended age for RRSO. The authors suggest that younger women choose ISDO to manage their risk without undergoing permanent menopause. ISDO requires further study to determine efficacy in prevention of ovarian cancer before it can be presented as an alternative to RRSO.

4. Conclusions

The available literature suggests that HRT may provide benefit to *BRCA* mutation carriers after RRSO. RRSO is recommended before the average age of menopause. Early surgical menopause has effects on QOL, sexual function, bone health, cardiovascular health and cognitive function. Studies on QOL show benefit of HRT for *BRCA* mutation carriers after RRSO; HRT users report fewer endocrine symptoms, and better sexual functioning [21–25]. Women who take HRT after RRSO are less likely to have bone disease [26,27]. In regards to CV disease and cognitive function, there are very limited data specifically on *BRCA* mutation carriers, but in the general population HRT mitigates the CV risk seen in women with premenopausal BSO. Understandably, breast cancer risk is of great concern for *BRCA* mutation carriers; available literature shows that breast cancer risk reduction following RRSO in premenopausal women is not changed due to HRT [36,37]. This risk may be affected by the formulation of HRT; studies suggest that estrogen-only HRT is preferred over progestin-containing methods [37,38]. More long-term, well-designed studies are necessary to draw definitive conclusions about risks and benefits of HRT in this high-risk population as well as the optimal duration of use. Premenopausal *BRCA* mutation carriers should be thoroughly counseled on the expected effects of early menopause after RRSO; these women should also be informed of the data about the risks and benefits of HRT. With improved uptake of genetic testing and a growing emphasis on cancer risk-reduction, RRSO is likely to become a more common surgery; data on risks and benefits of HRT are critical.

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Author contribution

SG and ES conceived of the idea, acquired data and wrote the manuscript in consultation with KP, BN, ML, and RY. All authors reviewed the final manuscript.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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