Surgical Menopause in Patients with BRCA Mutation, the Role of Hormone Therapy

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ABSTRACT

Introduction: women with BRCA1/2 (mBRCA) mutation have an increased risk of developing breast (BC) and ovarian (OC) cancer. Bilateral salpingo-oophorectomy (BSO) is associated with an 80% risk reduction for OC and 50% for BC. The recommended age for this procedure is 35 to 40 years. The consequence is premature menopause, which hurts the quality of life due to the presence of climacteric symptoms, increased risk of cardiovascular disease, osteoporosis, and a higher risk of cognitive impairment. Hormone therapy (MHT) is the most effective treatment for preventing these symptoms.

State of the art: different studies have shown an increased risk of BC in postmenopausal women receiving MHT, particularly with combined therapy, estrogen + progesterone (E+P). According to the meta-analysis by Marchetti et al., in women carrying mBRCA who received MHT, there was no difference in the risk of BC compared to E alone with E+P. In the Kostopoulos study, there was also a possible protective effect in those who used E alone. Another study in healthy carriers showed that in women younger than 45 years at the time of BSO, MHT did not affect BC rates. However, in women older than 45 years, BC rates were higher. As the E+P scheme is associated with a higher RR of BC, the doses of progestogens should be limited, choosing natural progesterone byproducts of intermittent use to decrease systemic exposure. According to various international guidelines, healthy mBRCA carriers undergoing BSO should be offered MHT until the average age of menopause.

Conclusion: premature menopause decreases life expectancy, which is why one of the tools to improve and prevent deterioration of quality of life is MHT. Short-term use of MHT appears safe for women with mBRCA who undergo BSO before age 45 as it does not counteract the reduction in the risk of MC obtained by surgery.

Key words: BRCA - breast cancer - bilateral salpingo-oophorectomy - early menopause - menopausal hormone therapy

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INTRODUCTION

Women with BRCA1/2 (mBRCA) gene mutation have an increased risk of developing breast cancer (BC) and ovarian cancer (OC). More than 90% of hereditary breast and ovarian cancers result from mutation in these genes, which is more frequent in patients of Ashkenazi Jewish ancestry, with a prevalence of 2.5% in this population[1].

The cumulative risk of cancer at age 80 in patients with BRCA1 mutation is up to 72% for MC and up to 44% for OC, while for BRCA2 mutation, the risk of cancer at age 80 is 69% and up to 17%, respectively[2].

Bilateral risk-reducing mastectomy is the most effective procedure for reducing the risk of MC in mBRCA1/2 carriers, decreasing the risk of MC to almost 90%[1]. Bilateral salpingo-oophorectomy (BSO) is associated with nearly 80% risk reduction for OC. The role of BSO in reducing the risk of MC has been evaluated in multiple studies, mostly reporting a risk reduction.

However, there may be an overestimation of this reduction due to selection bias in existing observational studies. The magnitude of the MC risk reduction and its clinical implications are not well-defined[2].

Early menopause and abrupt post-surgical estrogen decline cause a decrease in quality of life due to menopausal symptoms, and it can also increase the risk of cardiovascular disease, osteoporosis, and cognitive impairment. In premature menopause, the climacteric symptoms are often more intense than in natural menopause[3].

There is some evidence that BSO in the general population is associated with increased mortality, especially if done at an early age if menopausal hormone therapy (MHT) is not prescribed. MHT is the most effective treatment for the control of vasomotor symptoms and for improving the quality of life of symptomatic women.

However, MHT use in mBRCA carriers after BSO is debatable, the main concern being the potential increased risk of MC.

METHODOLOGY

Online search of literature in PubMed for the following terms: BRCA mutation, breast cancer, ovarian cancer, bilateral salpingo-oophorectomy, hormone replacement therapy. Twenty-four relevant articles were found.

STATE OF THE ART

Time to perform the BSO

Several international guidelines recommend performing BSO to reduce cancer risk in patients with mBRCA. The European Society for Medical Oncology (ESMO)[1] recommends performing it between 35-40 years of age, while the American College of Obstetricians and Gynecologists (ACOG)[4], the Society of Obstetricians and Gynecologists of Canada (SOGC)[5] and the Spanish Society of Medical Oncology (SEOM)[6] differentiate between both types of mutation, recommending it between 35-40 years of age in patients with mBRCA1 and between 40-45 years of age in women with mBRCA2; maximum protection against MC comes when oophorectomy takes place early. The SOGC mentions that women with mBRCA2 can defer surgery until age 50, but the maximum benefit in MC risk reduction occurs when the surgery is performed before age 45[5].

The NCCN (National Comprehensive Cancer Network)[7] and the RCOG (Royal College of Obstetricians and Gynecologists)[8] recommend performing it between the ages of 35 and 40 after completion of childbearing. With patients who are mBRCA2 carriers, it is reasonable to defer it until age 45. However, RCOG guidelines state that the reduction in MC risk is more significant when BSO occurs before age 40.

Consequences of BSO

MHT has been shown to improve the quality of life after BSO in mutation carriers. In a prospective observational study involving 178 premenopausal women at high risk of hereditary OC, we assessed climacteric symptoms with the FACT-ES (Functional Assessment of Cancer Therapy Endocrine) questionnaire and sexual function with the SAQ (Sexual Activity Questionnaire) in women who underwent BSO with or without subsequent MHT. Women who performed MHT had significantly fewer vasomotor symptoms ($p = 0.001$, $p < 0.001$, respectively) and better sexual function ($p < 0.001$) after surgery relative to women not using MHT. We conclude that MHT use in the first year after BSO in premenopausal women has a beneficial effect by minimizing climacteric symptoms and improving sexual function[9].

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women in the Western world, and premature menopause is associated with an increased risk of CVD, as demonstrated in the Nurses' Health Study. That study included 29 380 women aged 30 to 55; 55.6% had undergone an adnexal hysterectomy (AHT) or hysterectomy without oophorectomy, 44.4% for benign pathology, with follow-up for 24 years. Results showed that women with AHT had higher total mortality (HR 1.12, 95% CI 1.03-1.21), higher risk of fatal and non-fatal coronary heart disease (HR 1.17, 95% CI 1.02-1.35), and increased risk of stroke (HR 1.14, 95% CI 0.98-1.33)[10].

In another study comparing women with oophorectomy vs. ovarian preservation, women with bilateral oophorectomy performed before age 45 had higher mortality from cardiovascular disease (HR 1.44; 95% CI 1.01-2.05; P = 0.04). In turn, mortality was significantly higher in women who did not receive estrogen treatment before age 45 (HR 1.84; 5% CI: 1.27-2.68; P = 0.001), but this did not occur in women treated with MHT (HR 0.65; 95% CI: 0.30-1.41; P = 0.28)[1]. However, data from studies in the general population indicate that MHT reduces the risk of CVD.

MHT use also proved to protect against bone loss in the general population and in women who are

mBRCA carriers after BSO. Evidence from studies in the general population shows that bone mineral density (BMD) decreases at a significantly higher rate after oophorectomy (spinal trabecular bone loss 12-19% during the first year) relative to women with natural menopause (2.5% in the first year). This loss is less in women using MHT after surgery[12].

Challberg et al.[13], in a retrospective cohort study, showed that the incidence of osteoporosis and osteopenia was higher in mBRCA carriers who did not use MHT after BSO compared with women who underwent MHT (osteoporosis: 13% vs. 3%, osteopenia: 33% vs. 13%, respectively). 3%, osteopenia: 33% vs. 13%, respectively). The Mayo Clinic study on oophorectomy and aging included women who underwent oophorectomy during premenopause (n = 2390) and a group of control women (n = 2390). Both groups were followed for a mean of 29.5 years. The data show a statistically significant increased risk of dementia in women younger than 48 years undergoing bilateral oophorectomy who do not receive MHT until age 50 (HR 1.89, 95% CI 1.27 -2.83, p = 0.002), whereas in women undergoing bilateral oophorectomy before age 48 but who received MHT, we found no increased risk of dementia (HR 0.79, 95% CI 0.25-2.54, p = 0.69)[12].

According to a retrospective cohort study of 12,837 women with premature surgical menopause, only 55.3% received MHT, and 47.9% used it for less than one year[14]. Those who undergo early surgical menopause and do not receive MHT are at risk for adverse long-term health consequences.

Risk of MC with MHT

One of the concerns regarding the use of MHT is the possibility of an increased risk of MC. Several prospective studies of the general population have demonstrated an increased risk of MC in postmenopausal women receiving MHT, especially with the combined therapy, estrogen + progesterone (E+P).

Chlebowski et al. (2020)[15] evaluated the association of MHT with long-term incidence and mortality of MC from the Women's Health Initiative (WHI) study. In that WHI study, one arm involved 16 608 women without hysterectomy; 8506 women were randomized to receive 0.625 mg/d equine conjugated estrogens (ECE) plus 2.5 mg/d medroxyprogesterone acetate (MPA) and 8102 placebo, while in the other arm involving 10 739 women with hysterectomy 5310 were randomized to receive 0.625 mg/d ECE alone and 5429 placebo, with a mean treatment duration of 5.6 and 7.2 years, respectively. After more than 20 years of cumulative follow-up, the ECE alone group compared with placebo was associated with a statistically significantly lower incidence of MC (238 cases vs. 296 cases HR, 0.78; 95% CI: 0.65-0.93; P = 0.005).

In contrast, in the arm receiving ECE+MPA compared with placebo, a higher incidence of MC was found (584 cases vs. 447 cases; HR, 1.28; 95% CI:1.13-1.45; P < 0.001). The results of this study suggest that combined and continuous use of E+P MHT in combined and continuous form increases the risk of MC in the general population during and after treatment, in contrast to estrogen replacement therapy alone, which significantly reduces the incidence of M.

A recent meta-analysis of 58 studies[16] also demonstrated a significant increase over time in the risk of MC associated with MHT, where the increase was steeper with the E+P combination. In that study, 108 647 postmenopausal women developed MC at the mean age of 65 years; 55 575 (51%) had received MHT with a mean duration of 10 years in current users at diagnosis and approximately seven years in previous users.

All types of MHT, except vaginal estrogens, were associated with an excess in cases of MC. It is worth mentioning that the risk increased over time: it was higher for the E+P combination than when using E preparations alone and even more so when using the daily progestin. Among current users, the relative risk (RR) during the first four years of use for E+P was 1.60 (95% CI 1.52-1.69), and for E alone, RR was 1.17 (95% CI 1.10-1.26).

With MHT use for 5-14 years was E+P RR 2.08 (95% CI 2.02-2.1) and for E alone RR 1.33 (95% CI 1.28-1.37). It fits to clarify that when discriminating the type of progestogen used in MHT, the risk does not change.

In short, the use of MHT for five years after 50 years of age would increase the incidence of MC between 50 and 69 years of age in approximately one out of every 50 users of E+P who use a continuous regimen, one out of every 70 users of E+P with intermittent use, and one out of every 200 users of E-only preparations.

In any case, the data are the result of the use of MHT in postmenopausal women, so extrapolating these results to women with premature surgical menopause, younger and with an already increased baseline risk of breast cancer, such as patients with mBRCA, would not be entirely accurate.

MHT in women with mBRCA and risk of cancer

Women with mBRCA1 are usually hormone receptor-negative, while women with mBRCA2 are usually hormone receptor-positive[8]. Several studies evaluating patients with mBRCA who used HRT did not find an association between its use and the risk of MC. Marchetti et al., in their meta-analysis[17] based on three cohorts (Kotsopoulos et al., 2018; Gabriel et al., 2009; Rebbeck et al., 2005) aimed to clarify whether MHT after BSO might hurt the risk of MC in women carrying mBRCA1/2. They included 1100 women with mBRCA1/2 who had undergone BSO. Among the MHT users after surgery, 326 used E alone, and 114 used E+P for a median duration of approximately 3.3 years. The results showed that the risk of MC associated with MHT use after BSO was 1.01 (95% CI: 0.16-1.54) for the entire cohort. There was no significant difference in the risk of MC when comparing women using E and women using E+P formulation.

When analyzing the Kotsopoulos et al.18 study individually, we found a possible protective effect in those women who used E. Including 872 mBRCA1 carriers, 377 women used MHT after oophorectomy, with a mean

duration of 3.9 years. When we considered the 10-year MC risk between women with MHT and those who did not use it, no significant difference appeared, diagnosing 92 (10.6%) cases of MC at follow-up. The HR was 0.97 (95% CI: 0.62-1.52; P = 0.89) for any form of MHT. However, the effects of E alone and combined hormonal therapy were different.

The 10-year risk of MC was significantly lower for women who used E alone compared with women who used E+P (12% vs. 22%; absolute difference, 10%; P = 0.04). This effect was higher in women who underwent oophorectomy before age 45 (9% vs. 24%; P = 0.009). For each year of use of MHT with E alone, there was an 8% reduction in the risk of MC (HR, 0.92; 95% CI, 0.83-1.01; P = 0.07). In contrast, the HR for each year of E+P use was 1.08 (95% CI, 0.92-1.27), but this was not statistically significant (P = 0.34). If these results are analyzed, MHT would appear to be a safe therapeutic option in carriers of this mutation.

In a retrospective study by Michaelson-Cohen et al. (2021) 19, 306 healthy female mBRCA1/2 carriers who had undergone BSO were followed for 7.26 years and compared the incidence of MC over time in carriers who received MHT for four years versus those who did not. According to the results, there were 36 diagnoses of MC, 20 of 148 patients (13.5%) in the MHT group, and 16 of 155 (10.3%) in the non-MHT group (OR 1.4; 95% CI 0.7-2.7). In women who were 45 years of age or younger at the time of BSO, MHT did not affect the rate of MC. However, in those older than 45 years who underwent BSO, the rates of MC were higher in users of MHT (OR 3.43, p < 0.05, 95% CI 1.2-9.8). The authors concluded that MHT use after short-term BSO was associated with a 3-fold increased risk of MC in carriers older than 45 years. These results suggest that the risk may be related to the timing of exposure to MHT around the natural age of menopause, even among BRCA1/2 carriers. This result is consistent with studies in the general population where MHT in postmenopausal women increases the risk of MC.

Armstrong et al.20 demonstrated that women with mBRCA1/2 who undergo prophylactic oophorectomy between the ages of 30 and 40 would experience a significant gain in life expectancy, regardless of their decision about MHT after oophorectomy. That effect depends on the duration of MHT use, age at the point of surgery, and the presence or absence of concurrent mastectomy.

How to Decrease the Risk of MC with MHT

E+P schemes are generally associated with a higher RR of MC. However, not all combined esque mas carry the same risk. MPA, levonorgestrel, and norethisterone acetate are associated with a higher risk than micronized progesterone (RR in the range of 1.5-2 and between 1.1-1.3, respectively)[21]. The potential adverse effect of MHT with progestogens concerning MC would be due to the activation of the nuclear factor -B (RANK) signaling pathway[22]. Given this problem, especially in carriers of such mutations, the doses of progestogens should be limited, choosing compositions associating lower doses or natural progesterone derivatives with intermittent use or levonorgestrel-releasing intrauterine device to decrease systemic exposure. The Dutch Hereditary and Familial OC guideline differentiates between women who did or did not undergo risk-reducing mastectomy. Tibolone is the first-line treatment when breasts are present, as it allows for better mammographic interpretation. After prophylactic mastectomy, they recommend combined therapy, and after hysterectomy, estrogen-only therapy is the first option[23].

The American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the International Menopause Society (IMS) recommend the use of micronized progesterone as a safe alternative[24]. According to various studies, estrogens alone have a more favorable risk profile than combined E+P therapy. However, all women who retain their uterus need progesterone to counteract the estrogenic effect on the endometrium. That will lead to whether prophylactic hysterectomy is warranted at the time of BSO to avoid using progesterone; however, hysterectomy alone to obviate the need to take progesterone is not without risk. According to SOGC5, the hysterectomy is recommended when there are risk factors for uterine cancer, other uterine pathologies, and the use of tamoxifen. It is doubtful whether the recommendation of hysterectomy for serous uterine cancer risk reduction in patients with mBRCA1 is feasible. For their part, ACOG4 and NCCN7 state that the decision to perform a hysterectomy should be individualized, and the risk of high-grade uterine cancer in mBRCA1 carriers should be discussed with the patient and decided according to her preferences.

Current recommendations

The North American Menopause Society (NAMS) states that MC risks do not increase with using systemic HT in menopausal mBRCA carriers and that young survivors with or without breasts should not postpone or avoid risk-reducing BSO because of concerns about the potential increase in MC with MHT[25]. The National Cancer Institute, according to the latest 2020 recommendations, suggests the use of MHT in patients with BSO younger than 45 years who are mBRCA1/2 carriers with no history of MC. The duration of MHT could be up to 4 years. In patients with a history of BC, MHT is contraindicated[26].

According to SOGC5, ACOG, and RCOG8, women with BRCA receiving BSO should be offered MHT until the average age of menopause. While local estrogen is an option for women undergoing BSO, nonhormonal options should be the first choice. According to ACOG4 and NCCN7, short-term hormone therapy does not significantly elevate the risk of MC. Brief treatment with MHT after BSO is safe for healthy mBRCA carriers, while MHT after MC should be avoided. So far, no evidence exists contraindicating the use of HRT in women with mBRCA. If compound selection is considered, the schedule, route of administration, and dose should be individualized according to each patient's profile (Table 1).

Table 1. Possible scenarios after a risk-reducing BSO

Patients with mBCRA after BSO, MC survivors	Patients with mBCRA after BSO, without a history of MC
Hormone therapy is contraindicated	The benefits of hormone therapy outweigh the risks
	It should be offered to any patient with premature surgical menopause, up to an average age close to menopause

CONCLUSION

Premature menopause decreases the life expectancy of women through deleterious cardiovascular and bone tissue effects. That is why one of the tools to improve and prevent the deterioration of the quality of life is MHT, even in women who do not present climacteric symptoms. Using MHT in the short term seems safe for women carriers of BRCA who undergo BSO before the age of 45 as it does not counteract the reduction in the risk of MS obtained thanks to surgery. For those hysterectomized women, estrogen alone may be the safest and most reasonable option. It is imperative to explain to each particular woman the risks and benefits based on the literature evidence and individual interests and expectations. Ultimately, with adequate information, the decision will always be an individualized and consensual decision with the patient.

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