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Hormone therapy replacement in oncological high risk patients: is it possible?

Abstract

Hormone replacement therapy (HRT) has been prescribed for women to avoid or decrease menopausal symptoms, in particular, the presence of hot flashes and night sweats, and to prevent other aging-related conditions, including osteoporosis and cardiovascular disease. Women with a pathogenic variant of BRCA1/2 have a higher lifetime risk of developing ovarian cancer (OC) and breast cancer (BC). It has been shown that risk-reducing salpingo oophorectomy (RRSO) is associated with an OC risk-reduction of approximately 80% and a BC risk-reduction of approximately 50%. Screening for ovarian cancer in high-risk women has not been shown to be reliable. RRSO is currently recommended between the ages of 35 and 40 for BRCA1 mutation carriers and between 40 and 45 for BRCA2 mutation carriers. Despite the well-established reduction in cancer risk, oophorectomy induces surgical menopause and its associated risks. The abrupt decline in circulating sex hormones causes menopausal symptoms, such as vasomotor symptoms, loss of libido, as well as being associated with a decline in cardiac and bone health, and overall bad quality of life among others issues. Many of the side effects can be ameliorated by HRT, but for women with a personal history of breast cancer, exogenous hormones are contraindicated. Although HRT after surgical menopause is prescribed to BRCA mutation carriers without a personal history of breast cancer, the impact on breast cancer risk remains unclear. In this review we discuss a detailed analysis of the updated literature related to the use of HRT in women who undergo RRSO.

Keywords: BRCA 1 mutation, BRCA 2 mutation, risk reducing salpingo oophorectomy, menopausal symptoms, replacement hormone therapy, hot flashes, vasomotor symptoms-osteoporosis

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Abbreviations: HRT, hormone replacement therapy; OC, ovarian cancer; BC, breast cancer; RRSO, risk-reducing salpingo oophorectomy; CV, cardiovascular; BSO, bilateral salpingo oophorectomy; E, estrogen alone; EP, estrogen plus progesterone; ISDO, interval salpingectomy with delayed oophorectomy; USA, United States of America; UK, United Kingdom; NAMS, North American Menopause Society

High oncological risk patients: what do we have for sure?

A germline mutation in BRCA1 or BRCA2 results in a significantly elevated lifetime risk of developing breast cancer (BC) and ovarian cancer (OC). Indeed, more than 90% of hereditary cases of BC and OC are thought to be a result of a mutation in BRCA1/2.[1] In patients with BRCA1 mutations, cumulative risk of BC and OC by age 80 is about 72% and 44% respectively; for BRCA2 mutations, that risk is about 69% and 17% respectively.[2] Therefore, the NCCN Guidelines Panel recommends RRSO for women with a known BRCA1/2 mutation, between the ages of 35 and 40 with a BRCA1 mutation and between 40 and 45 years of age in women with a BRCA2 mutation, since ovarian cancer onset tends to be later in this group[3] RRSO is associated with an OC risk-reduction of approximately 80% and it also seems to reduce BC risk by approximately 50%. All-cause mortality was lower for BRCA carriers who undergo 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.[2] The role of bilateral risk-reducing mastectomy is still controversial.

RRSO: consequences of estrogen deprivation and HRT benefits

Despite the benefit of cancer prevention, prophylactic RRSO in young women results in early menopause. In addition, estrogen loss is associated with other effects that may increase the risks for both morbidity and mortality from other causes, including increased cognitive changes, low sexual desire, genitorurinary syndrome, osteoporosis, and cardiovascular disease. The consequences of hormonal deprivation are widely studied both in general population and in BRCA patients. The Nurses' Health Study[4] included almost 30,000 women who had undergone a hysterectomy for a benign disease predominantly in their fourth decade and reported that oophorectomy was associated with a significant risk of cardiovascular (CV) disease. Over 24 years of follow-up of women who had had a hysterectomy and bilateral salpingo oophorectomy (BSO) compared to women 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. 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). Similarly, the WHI Observational Study[5] included over 25,000 women, all of whom also

had undergone a hysterectomy for benign disease, primarily before the age of 50 years, and found that an elective oophorectomy was associated with a significantly increased risk of all-cause mortality (HR 1.41;95% CI, 1.04-1.92). Rivera et al.[6] showed that in the general population, women who underwent BSO before age 45 had increased mortality associated with CV disease compared to women who had not undergone any oophorectomy (HR 1.44, 95% CI 1.01–2.05, p = 0.04). Women who were not treated with estrogen after BSO until 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). Therefore, for CV disease the cut-off age would appear to be 45 years. Regarding cognitive dysfunction and dementia, studies have reported oophorectomy to be associated with a greater risk in women who undergo this surgery at a younger age than 48 years and 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). 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).[2] In BRCA patients, the prevalence of reduced bone mass was far higher among women who had more than 24 months of estrogen deprivation (36 out of 78, 46%) than in those who had taken HRT to cover any period before 50 years of age (5 out of 31, 16%). The analysis showed a significant difference between those with more than 24 months of estrogen deprivation and those with no deprivation before 50 years (P 1⁄4 0.03).[7] In another study, Michelsen et al.[8] did a retrospective analysis of 326 women from hereditary breast and ovarian cancer families (of whom, 58 were known to have a B1/2 mutation) who had undergone RRSO and compared them to 679 controls without oophorectomy. The women with RRSO had increases in metabolic syndrome, central obesity, altered lipids, elevated fasting glucose and elevated blood pressure.

Data shows that HRT mitigates menopausal symptoms in women with a known mBRCA who have undergone BSO. Madalinska et al.[9] evaluated women who underwent RRSO and were prescribed HRT (N=77) with 2 groups that were not administered HRT: women with a known mBRCA who underwent BSO (N=74) and a control cohort of women without a known mutation who did not undergo RRSO (N = 286). Among mBRCA carriers who underwent RRSO, HRT use was associated with less reports of menopausal symptoms including lower rates of hot flashes (20% vs. 41%), cold sweats (23% vs. 38%), and night sweats (25% vs. 39%). Rebbeck et al.[10] conducted a separate prospective study of 114 mBRCA carriers which included 73 who were premenopausal before RRSO. In this series, women who subsequently took HRT indicated fewer vasomotor symptoms (P=0.0003) and higher sexual functioning (P=0.015) than women who did not. HRT users also reported fewer hot flashes, including lower frequency and severity of symptoms.

What are we concerned about?

The fear of breast cancer risk by physicians and patients is the biggest determinant when/at the moment of prescribing HRT. 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. In 2002, the WHI stopped the trial of estrogen plus progestin (E + P) versus placebo after 5.2 years of follow up because the increased risk of breast cancer exceeded the stopping boundary; the global index statistic supported risks exceeding benefits. 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.[5] However, given WHI participants had an average age at enrollment of 63, it is unclear how these data apply to women with premature surgical menopause. Indeed, in the estrogen-only arm of this study, they observed a reduction of breast cancer rate (HR 0.77, 95% CI 0.59–1.01).

Regarding safety of HRT in BRCA patients, there are several studies. In the study by Armstrong et al.,[11] the use of HRT (both progesterone and estrogen) after RRSO and prophylactic mastectomy until age 50 showed a gain in life expectancy for these patients, which varied by age: there was a gain of 0.78, 0.79, and 0.79 years for a 30-, 35-, and 40-year-old woman, respectively. Rebbeck et al.,[10] in the PROSE Study Group (Prevention and Observation of Surgical Endpoints) included 462 female mBRCA carriers all of whom were followed since the RRSO. 114 women took HRT, 93 of 155 who had a RRSO, and 21 of 307 who did not have a RRSO. Compared with the entire cohort, there was no impact on BC risk with HRT among those who underwent a RRSO (HR 0.37; 95% CI, 0.14-0.96). In addition, it is interesting to note that, even though it is a limited sample size, out of the 93 patients who had a RRSO, 54 patients took estrogen alone and 34 took progesterone with or without estrogen (5 did not specify). There was no significant difference in BC risk reduction between the 2 groups. An additional analysis concentrated on those women who underwent a RRSO before 50 years of age; the authors reported that HRT had no significant impact on the subsequent risk of BC.In another study by Einsen et al.,[12] 472 postmenopausal women with mBRCA1 were examined to compare an increased risk of BC in patients treated with estrogen alone (N=28) or combination estrogen and progesterone (N=19). An inverse association between estrogen use alone (odds ratio [OR] = 0.51; 95% CI, 0.27-0.98) and BC risk was observed, whereas no significant association was seen in combination therapy and risk of breast cancer (OR=0.66; 95% CI, 0.34-1.27). Domcheck et al.[13] presentation described an expansion and follow-up of a study by Rebbeck and associates, that assessed risk of BC in 1,299 previvors carrying BRCA1/2 mutations who had undergone RRSO and compared this risk with mutation carriers who had not. Women using HRT were followed postoperatively for a mean of 5.4 years (range, 0.6-24.4 y). Compared with non-users who had not undergone RRSO, HRT use among women who had undergone RRSO was not associated with an elevated risk for breast cancer. A meta-analysis performed by Marchetti et al.,[14] included both prospective cohort trials and retrospective studies. To be eligible, trials had to estimate BC incidence in BRCA1 and BRCA2 mutation carriers who underwent RRSO and received or not received HRT after prophylactic surgery. Primary endpoint was BC risk. A total of 3 studies were identified 1100 patients. BC risk associated with HRT use after RRSO was 1.01 (95% CI 0.16–1.54) for the entire cohort. Among prospective trials, the BC risk of HRT use was similar, without a negative impact in BRCA mutation carriers who used HRT (HR=0.98; 95% CI 0.63–1.52). A subgroup analysis based on HRT formulation was also performed. In total, among the HRT users, 326 used estrogen alone (E) and 114 used estrogen plus progesterone (EP), for a mean duration of approximately 3.3 years. There was no significant difference in BC risk comparing women who used E regimen and women who use EP

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formulation. But BC risk was lower for women who used E alone versus EP, both in overall population (OR=0.62; 95% CI 0.29–1.31) and prospective studies only (OR=0.53; 95% CI 0.25–1.15).

Clinical practice guidelines also validate the use of HRT in mBRCA after RRSO. ESMO Clinical practice guidelines[15] and NCCN[3] established that short-term HRT in women undergoing RRSO does not negate the reduction in BC risk associated with the surgery. Indeed, the Canadian, Dutch, United States of America (USA), United Kingdom (UK) and Australian guidelines state that HRT can be offered after RRSO for a short period of time in premenopausal women without a history of breast cancer until the age of natural menopause.[16] The NAMS (North American Menopause Society)[17] affirms that, even though the studies that have addressed the effect of HRT use by previvors are limited by their observational design, size, and limited duration of follow-up, they provide some reassurance for clinicians and survivors that use of systemic HRT (whether E or E+T) does not substantially increase breast cancer risk in mBRCA1/2 with intact breasts.

Does the type of HRT makes the difference?

The WHI study[5] 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), an association not found for estrogen-only HRT, which was associated with a reduction of breast cancer rate (HR 0.77, 95% CI 0.59–1.01). However, as we mentioned, this results cannot be applied to women with BRCA mutation who undergo RRSO. Kostopulos et al.[18] conducted the first prospective evaluation of HRT use and breast cancer risk among women with a BRCA1 mutation. The study included 872 BRCA1 mutation carriers of those 377 (43%) women who used HRT after oophorectomy and 495 (57%) women who did not use HRT after oophorectomy. The primary endpoint was invasive BC with 10 years of follow-up. They observed that the use of any HRT following oophorectomy was not associated with an increased risk of developing BC. However, they found a possible protective effect for women who used estrogen-containing HRT alone. Each year of estrogen use was associated with an 8% reduction in breast cancer risk (HR, 0.92; 95% CI, 0.83-1.01), whereas each year of progesterone use was associated with a (nonsignificant) 8% increased risk (HR,1.08; 95% CI, 0.92-1.27). The actuarial 10-year risk were 12% for estrogen-only HRT and 22% for estrogen plus progesterone for all participants combined and were 9% vs 24% for participants who had an oophorectomy prior to age 45. These associations were stronger for women who underwent oophorectomy prior to age 45 years.

What alternatives do we have?

In order to avoid the combined therapy, prophylactic hysterectomy for BRCA mutation carriers would be an option. Moreover, limited data suggest that there may be a slightly increased risk of serious uterine cancer among women with a BRCA1 mutation. The clinical significance of these findings is unclear. Further evaluation of the risk of serious uterine cancer in the BRCA population is needed.[3] However, prophylactic hysterectomy for BRCA mutation carriers is not recommended according to international guidelines to the date.[14] Bilateral salpingectomy, and interval salpingectomy with delayed oophorectomy (ISDO) are also an option, although they should not replace RRSO in this high-risk population.

Conclusion

Given the lack of evidence of an increase in breast cancer risk with HRT use in this group of women, the available data suggests a benefit with its use until the physiological age of menopause. As it is, even if there was a small decrease in the protective effect of RRSO, it would be balanced out by the favorable impact on menopausal symptoms, bone, cardiovascular and cognitive health, as well as the increase in life expectancy. It is important to perform more studies to agree about doses and duration of HRT in women with mBRCA.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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