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META-OPINION

Postmenopausal hormone therapy in BRCA gene mutation carriers: to whom and which?

Giovanni Grandi [a], Martina Caroli[a], Laura Cortesi[b], Angela Toss[b,c], Giovanni Tazzioli[a,d] and Fabio Facchinetti[a]

[a]Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy; [b]Department of Oncology and Haematology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; [c]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance, University of Modena and Reggio Emilia, Modena, Italy; [d]Oncologic Breast Surgery Unit, Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy

ABSTRACT

Introduction: Risk-reducing-salpingo-oophorectomy (RRSO) inevitably leads BRCA mutation carriers to premature menopause.

Areas covered: To evaluate the existing evidence for use of postmenopausal hormone therapy (HT) in BRCAmc, after RRSO or menopause occurring naturally, for both breast cancer (BC) survivors and those without BC.

Expert opinion: All BC survivors are excluded from any HT treatment: in other BRCAmc, before 51 years of age the benefits of HT overcome the risks after RRSO and/or premature ovarian insufficiency (POF). After 51 years of age, it is important to treat only women with important vasomotor symptoms, after the failure of alternative therapies. Estrogens-only therapy plays a key role in hysterectomized women (HW). In the case of an intact uterus (UW), associations with the lowest dose of progestins/natural progesterone derivatives have to be preferred, as progestins has been shown to play an important role in BC transformation, especially in BRCA1mc. No studies have been performed in BRCAmc with regard to 'progestin-free' HT, in particular the old tibolone (both in HW and UW) and the new tissue-selective estrogen complex (in UW). However, preliminary data obtained from the general population are reassuring about the use of these 'progestin-free' preparations and BC safety.

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1. Introduction

Patients carrying germline mutations in BRCA1 or 2 genes present a life-long increased risk of developing ovarian and breast cancer. In particular, patients with BRCA1 mutations have a 72% lifetime risk of breast cancer (BC) and 44% of ovarian cancer (OC), while the same risk in patients with BRCA2 mutations is 69% and 17%, respectively [1].

Performing risk-reducing-salpingo-oophorectomy (RRSO) for these patients seems to be the best strategy to reduce the risk of OC by up to 96%: it has also been shown to reduce the risk of BC by up to 50% [2], though this protective effect has recently been widely questioned [3]. According to the National Comprehensive Cancer Network (NCCN) guidelines, RRSO is recommended for BRCA1 mutation carriers between the ages of 35 and 40, or when child bearing is complete. The option of delaying RRSO until age 40–45 in women with BRCA2 mutations may be considered as there appears to be a later average age of onset (approximately 8–10 years) than in women with a BRCA1 mutation [4]. However, RRSO inevitably leads patients to premature menopause compared with the average general age of menopause in women (51 years). This involves a number of side effects related to estrogen deprivation, being divided into acute and long-term symptoms. Acute symptoms include hot flushes, insomnia, arthralgia, irritability, a decline in libido, and genitourinary syndrome, while long-term symptoms comprehend an increase in cardiovascular risk, dementia, and early-onset osteoporosis [5]. For these reasons, it is important to offer these patients the possibility of postmenopausal hormone therapy (HT), if no contraindications exist (mainly a previous occurrence of BC), to limit the systemic effects related to early estrogen depletion associated with iatrogenic menopause and to protect them from long-term side effects. Nonetheless, it is mandatory not to forget the increased risk of BC development typically associated with this group of patients, which could be further increased by the use of exogenous hormones. Moreover, some of these women opt for bilateral risk-reducing mastectomy (BRRM) instead of surveillance to further reduce BC risk, although the efficacy of this practice has recently been questioned especially for BRCA2 mutation carriers [6].

Recently, we have discussed the possible use of combined hormonal contraceptives to avoid unintended pregnancies in these women [7]: in this Meta-opinion, we aim to evaluate the existing evidence for the other side of the coin, the systemic postmenopausal HT.

CONTACT Giovanni Grandi, giovanni.grandi@unimore.it Department of Obstetrics, Gynecology and Pediatrics, Obstetrics and Gynecology Unit, Azienda Ospedaliero-Universitaria Policlinico, University of Modena and Reggio Emilia,, Modena, Italy

2. Body

Nowadays, possible postmenopausal HTs can be divided into typical HT formulations [estrogens (E)-only and combined oestro-progestin (EP) HT] or 'progestin-free' HT, with different ways of administration, hormonal components, and regimens (Table 1).

2.1. Typical E and EP treatments

In general, E-only HT is for hysterectomized women, while EP HT is generally offered to women with an intact uterus (Table 1).

Rebbeck *et al*. published a prospective cohort study in 2005 including a sample of 462 BRCA1 and 2 mutation carriers undergoing RRSO, for which the subsequent risk of BC was assessed in relation to the intake of HT. Results showed that, for a median follow-up of 3.6 years, the use of HT (both E and EP combinations) did not influence the protective effect of RRSO on subsequent BC risk [Hazard Ratio: 0.37 (95% CI 0.-14–0.96)] [8]. This was also confirmed by another retrospective study published by Gabriel *et al*. in 2009 which considered the risk of BC in a sample of 73 BRCA1 and 2 mutation carriers undergoing RRSO (and in some cases concomitant prophylactic hysterectomy), of which n = 33 have subsequently started HT (with E, EP or not specified) (median length of HT use: 2.8 years) [9]. It was found that only 3/33 (9.1%) women developed BC in the group of patients undergoing HT, in comparison to 9/29 (31.0%) patients in the group without HT. In particular, all BC cases in the HT group came from the group of patients undergoing E-only treatments, not from the EP group [9]. In contrast, a milestone study concerning HT, published by Anderson *et al*. in 2012 about the Women's Health Initiative (WHI) randomized study data, considered the risk of BC in hysterectomized postmenopausal patients of the general population undergoing therapeutic regimen with equine conjugated estrogen (CE) (E-group) in comparison to placebo. This was the first study showing that CE use alone reduces the risk of BC [Hazard Ratio: 0.77 (95% CI 0.62–0.95)] while, on the contrary, highlighting the role of progestins in BC carcinogenesis, with a Hazard Ratio in the EP group of 1.25 (95% CI 1.07–1.46) in comparison to placebo [10]. This figure had already been demonstrated for BRCA1 mutation carriers. Notably, a matched case–control study performed by Eisen *et al*. in 2008 [11] on 472 BRCA1 mutation carrier postmenopausal women (iatrogenic or not) had been conducted to examine whether the use of HT (E and EP combinations) was associated with a risk of BC. Similarly to [10], they found an inverse correlation between the risk of BC and the use of E-only HT. In this study, the characteristics of hormonal receptors in BCs [Estrogen Receptors (ERs), Progesterone Receptors (PRs)] were also considered in patients undergoing RRSO and subsequent HT. HT use was reported for 12% of patients with ER-positive tumors and for 23% of patients with ER-negative tumors (p = 0.29), confirming the correlation between triple negative cancers and BRCA1 gene mutations, despite the use of HT [11]. Conversely, in BRCA2 mutation carriers, BC cases are more frequently ER+ and PR+ [12].

Finally, a recent prospective cohort study published by Kotsopoulos *et al*. in 2018 [13] considered the risk of BC over time in a sample of 872 BRCA1 mutation carrier women undergoing RRSO (mean follow up: 7.6 years), of which only 377 started E-only or EP HT. Overall, HT use after RRSO was not associated with an increased risk of BC. However, once again, a different incidence of BC was found in the two groups with different HT treatments. In particular, women undergoing E-only HT showed a lower risk than those submitted to EP therapeutic regimens (12% vs. 22%; absolute difference: 10%; log rank p = 0.04). For women who underwent RRSO prior to 45 years of age, each year of E-only HT use was associated with a significant 18% reduction in BC risk (95% CI 0.69–0.97), whereas each year of EP HT was associated with a nonsignificant 14% increase in BC risk (95% CI 0.90–1.46). The potential adverse effect of progestin-containing HT on BC is in line with the emerging role of the PR activation of the nuclear factor κB (RANK)-signaling pathway in BRCA1 BC development [13]. Considering this issue, especially in BRCA1 mutation carriers, the doses of progestins used in HT should be limited, choosing compositions that associate the lowest doses of E with the lowest doses of progestins/natural progesterone derivatives. Only if there is a need to increase the doses of E due to ineffectiveness of HT on symptoms, health-care providers should think about increasing the doses of the progestin components from low to moderate and high doses (Table 2).

Unfortunately, the use of E-only HTs is not allowed in patients with an intact uterus, as estrogenic stimulation of the endometrium without progesterone/progestin-induced inhibition increases the risk of endometrial hyperplasia and endometrial cancer (Table 1). For this reason, BRCA1 mutation carriers should consider the removal of the uterus to avoid the use of progestin-containing HT at the time of RRSO. Moreover, although the overall risk for uterine cancer after RRSO was not increased, the risk of serous endometrial carcinoma was reported to be increased in BRCA1 women [14]. Other advantages of hysterectomy during RRSO included eliminating the small risk of tamoxifen (TAM)-induced endometrial cancer in BC subjects and avoiding the possible, although never clearly reported, tubal carcinogenesis in the uterine interstitial cornua. However, a hysterectomy at the time of RRSO slightly

Table 1. Different ways of administration, hormonal components, and regimens of typical and 'progestin-free' hormone therapy (HT) formulations currently available in Italy today, in relation to possible women users. CE: conjugated estrogen. BZA: bazedoxifene.

'Typical' HT	Possible women users
Estrogen-only (E-only)	Hysterectomized women
Transdermal (patch, gel): estradiol	
Oral: estradiol valerate	
Oestro-progestins (EP) (sequential, combined, continue, cyclic)	Women with an intact uterus
Transdermal (patch): estradiol + levonorgestrel or norethisterone acetate	
Oral: estradiol or estradiol valerate + nomegestrol acetate, drospirenone, dydrogesterone, norethisterone acetate, cyproterone acetate, medroxyprogesterone acetate, dienogest	
'Progestin-free' HT	
Tibolone 2.5 mg/day	Hysterectomized and women with an intact uterus
CE (0.45 mg) and BZA (20 mg)	Women with an intact uterus

Table 2. Low dose or moderate to high dose progestin components currently available in Italy for oestro-progestin EP hormone therapy (HT), ordered by the derivation of the molecule.

	Low dose	Moderate to high dose
Progesterone Derivatives		
Micronized progesterone	100 mg	200 mg
Dydrogesterone	5 mg	10 mg
Nomegestrol Acetate	2.2 mg	5 mg
Medroxyprogesterone acetate	5 mg	10–20 mg
Testosterone Derivatives		
Norethisterone acetate	0.1 mg	0.5–2.5 mg
Levonorgestrel	0.75 mg	–
Intrauterine levonorgestrel	Intrauterine systems releasing 8, 9 or 20 µg daily.	–
Dienogest	2 mg	–
Spironolactone Derivatives		
Drospirenone	2 mg	–

increases surgical risks and short-term morbidity. Hysterectomy should be considered as an optional part of prophylactic surgery for BRCA mutation carriers, and the decision of whether to perform it should be on the basis of correct personalized counseling on the basis of individual factors, associated uterine diseases, and the patient's wishes, especially in BC survivors [15].

2.2. 'Progestin-free' treatments

In addition to the classic HT regimens, characterized by the administration of E-only or EP combinations, there are also other therapeutic alternatives, in particular tibolone (T) (available since 1988) and a new TSEC (Tissue Selective Estrogen Complex), composed of CE and bazedoxifene (BZA), a selective modulator of estrogen receptors (SERM, Selective Estrogen Receptor Modulator) (available since 2014). However, in relation to these other types of 'progestin-free' HT, we do not have specific studies specifically performed in the BRCA mutation carrier setting.

T is a synthetic steroid whose metabolite activities are partly estrogenic, partly androgenic and partly progesterone-like, depending on the tissue in which they act, approved for therapy in both hysterectomized women and those with an intact uterus (Table 1). In particular, T inhibits the enzyme sulphatase, which reduces the desolfatation of estrone (E3) sulfate and blocks cell proliferation in the breast, stimulating apoptosis [16]. T was associated with the least breast epithelial proliferation (evaluated by proliferating cell nuclear antigen immunohistochemistry), but also the least apoptosis (by caspase-3 immunohistochemistry) in comparison to other EP treatments [17]. Several studies have also shown a reduction in breast density during T treatment, in contrast with 'typical' E-only or EP HTs [18,19]. The Million Women Study in 2003 showed that the magnitude of BC risk during HT was substantially greater for EP than for T or E-only treatments in the general population [20]. When we consider the risk of OC in the general population undergoing T therapy, the results are controversial: a study performed in Denmark showed an increased Relative Risk of 1.42 (95% CI 1.01–2.00) [mainly serous cancer with a Relative Risk of 2.21 (95% CI 1.48–3.32)] in comparison to those who had never used T therapy [21]. This result was disproved by another case–control study conducted in Finland in 2013 that considered the risk of OC in patients undergoing various types of HT formulations, showing that the use of T did not significantly increase the risk of OC in contrast to other EP regimens [Odds Ratio for >1 year of use: 1.01 (95% CI 0.64–1.60)], especially in a sequential scheme [22]. However, this effect should not be important after RRSO in BRCA mutation carriers, as it is not the case for the other possible HTs [8,9,11,13]. On the other hand, T use may increase the risk of endometrial cancer [21].

The pharmacological association between CE (0.45 mg) and BZA (20 mg) has been recently approved as HT only in women with an intact uterus (Table 1). The peculiarity of this formulation is the presence of BZA, a molecule belonging to the class of SERM, like another well-known protective molecule used in oncology (TAM). It is able to act as an E agonist or antagonist in different tissues. In particular, this molecule has an E agonist action in the bone tissue, while it acts as an E antagonist in both breast and endometrial tissue, reducing the risk of BC, endometrial hyperplasia and endometrial cancer [23,24]. Several preclinical studies have shown a reduction in breast and endometrial cell proliferation during TSEC treatment in both mice and some primates [25,26], and TSEC has demonstrated a direct antiproliferative effect on human BC cells [27]. Its clinical studies are reassuring with regard to its safety on breast tissue. The 'Selective estrogens, Menopause, And Response to Therapy' (SMART) 1, a multicentre double-blind study involving 3,397 menopausal women from the general population treated with CE/BZA at different dosages (CE 0.45 mg/BZA 20 mg or CE 0.625 mg/BZA 20 mg) or placebo for 2 years, showed that the incidence of BC between the different treatment groups was similar (0.4% for CE 0.45 mg/BZA 20 mg; 0% for CE 0.625 mg/BZA 20 mg, 0.2% for placebo) [28]. Moreover, the 1-year subgroup of the SMART 5 trial [29] compared BZA 20 mg plus CE 0.45 or 0.625 mg, placebo, BZA 20 mg, and CE (0.45 mg) plus medroxyprogesterone acetate (MPA) (1.5 mg) in 940 women from the general population with technically acceptable digital mammograms at screening and at 1 year. TSEC demonstrated noninferiority to placebo in breast density modification. Mammographic breast density decreased from baseline with TSEC, while the EP HT combination tested (CE+MPA) significantly increased breast density from baseline in comparison to placebo. No clinical data about OC risk during TSEC treatment are presently available, but this effect should not be important after RRSO in BRCA mutation carriers.

3. Expert opinion

It is reasonable to think that HT might be safely prescribed in postmenopausal BRCA mutation carriers with different therapeutic opportunities, although there is currently an important

skepticism in the general population, and often also still in many clinicians, both gynecologists, breast surgeons, and oncologists. The benefits of HT are linked to the prevention of cardiovascular risk, dementia, and early onset of osteoporosis associated with the estrogen depletion. This is particularly important when menopause arises suddenly (iatrogenic menopause) and at an earlier age of the 'physiological' event, as in the case of BRCA mutation carriers who are subjected to early RRSO according to NCCN guidelines [4]. With regard to BRCA mutation carriers who are facing spontaneous menopause at a 'physiological' age (51 years old), HT should only be considered in cases where the woman exhibits highly disabling vasomotor symptoms. Other therapeutic evidence-based non-hormonal possibilities are available for women with mild symptoms [selective serotonin reuptake inhibitors (SSRI), SSRI/serotonin–norepinephrine reuptake inhibitor (SNRI) low-dose, clonidine, gabapentin, pregabalin, phytooestrogens]. It is also important to know that all BRCA mutation carriers with a personal history of BC are excluded from the possibility of any HT, as numerous studies have shown that HT use is related to the recurrence of BC [30].

The possible scenarios of BRCA mutation carriers unaffected by BC needing HT are reported in Figure 1. In general, before 51 years of age, the benefits of HT overcome the risks after RRSO and/or premature ovarian insufficiency (POF). After 51 years of age, it is important to treat only women with important vasomotor symptoms, after the failure of alternative therapies, with a carefully shared evaluation of the benefits/risks ratio, especially in the case of RRSO refusal (HT can potentially increase the risk of both OC and BC), after detailed counseling to the women.

Among the therapeutic alternatives for BRCA mutation carriers, E-only therapy plays a key role in hysterectomized women. In the case of an intact uterus, associations with low-dose progestins/natural progesterone derivatives have to be preferred, as progestins has been shown to play an important role in BC transformation, especially in BRCA1 mutation carriers.

Presently, no studies have been performed in the population of BRCA mutation carriers with regard to 'progestin-free' HT, in particular the old T and the new TSEC. However, preliminary data obtained from the general population are reassuring about the use of these 'progestin-free' preparations and BC safety. Considering the good safety profile on both breast (better than EP HT combined regimens) and ovarian tissue, T can be a reasonably valid therapeutic alternative in this population, both in hysterectomized women and women with an intact uterus. TSEC, due to the role of E antagonism on breast tissue linked to BZA similarly to TAM, could be another interesting option in women with an intact uterus. Nevertheless, well-conducted studies about their use and safety as HT after RRSO in BRCA mutation carriers are urgently needed.

Among limitations, the next studies have to clarify the role of HT in BRCA mutation carriers who have already undergone BRRM, because these patients have been excluded from the larger studies considered in this review [8,11,13]. Furthermore, we have not considered the possible use of modern topical or oral hormonal treatments for genitourinary syndrome, such as promestriene, estriol, estradiol, prasterone, and ospemifene, especially in BC survivors.

To conclude, the interest in safe HT preparations for BRCA mutation carriers, for both BC survivors and those unaffected by BC, must be heavily funded and encouraged to improve their quality of life, to limit the oncological risk and to prevent the long-term side effects of menopause after RRSO or occurring physiologically.

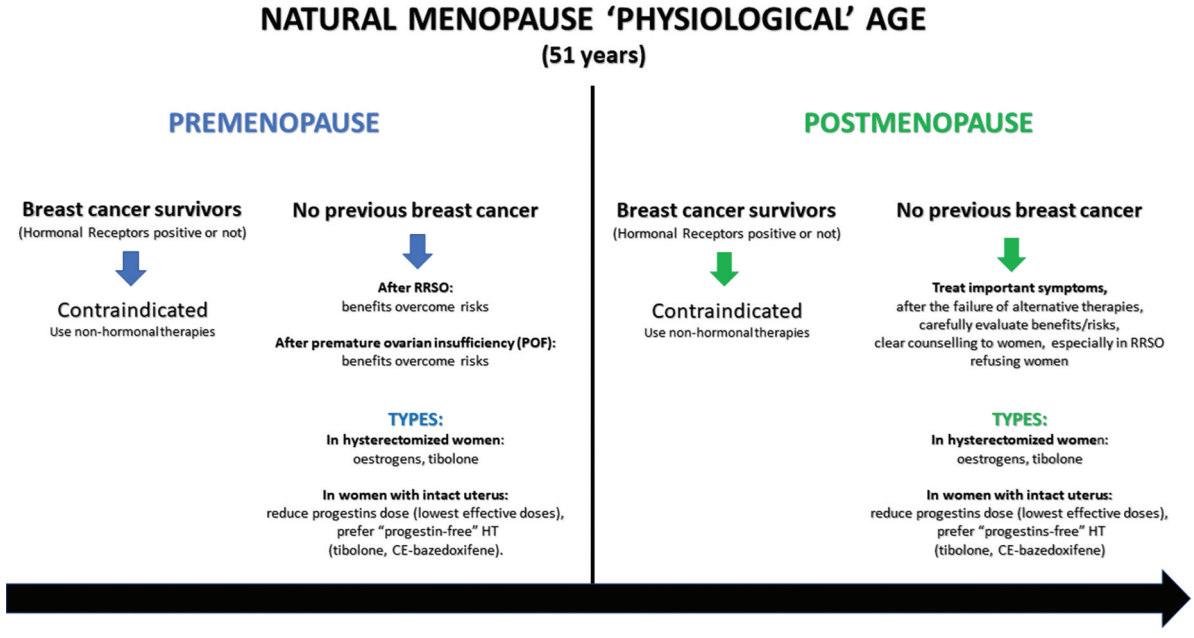

Figure 1. Possible scenarios of HT treatment in BRCA mutation carriers during the reproductive lifespan in relation to RRSO, previous breast cancer and age of menopause occurrence. CE: conjugated estrogen.

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ORCID

Giovanni Grandi http://orcid.org/0000-0002-3567-3278

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