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REVIEW

Gynecological–endocrinological aspects in women carriers of *BRCA1/2* gene mutations

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ABSTRACT

Women carriers of mutations in the genes *BRCA1* and *BRCA2* coding for tumor suppressor proteins are at high risk of developing breast and ovarian cancers. Hereditary breast and ovarian cancers due to *BRCA* pathogenic mutations occur at earlier ages: mean age 43 years at diagnosis of breast cancer for *BRCA1* mutations; onset of ovarian cancer up to 10–21% by age 50 years. Preventive strategies are then defined in the reproductive years.

The National Comprehensive Cancer Network (NCCN) guidelines define that *BRCA1/2* genetic testing should begin with the affected cancer individual (*BRCA1/2* full sequencing); then, family members should be tested for the specific gene mutation found.

A woman known to be a carrier needs a strict specific surveillance strategy to achieve early diagnosis. The NCCN proposes breast imageneological surveillance beginning at age 25 years; ovarian surveillance beginning at age 30–35 years. Concomitantly, risk-reducing strategies should be analyzed: surgical or pharmacological. When prophylactic bilateral salpingo-oophorectomy is performed before menopause, estrogen replacement therapy could be required.

For *BRCA*, we review the risks of cancer in mutations carriers, criteria for genetic testing, surveillance and risk-reduction strategies, and the safety of prescribing hormone therapy when needed.

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Introduction

Family history of breast or ovarian cancer is common among women diagnosed with these types of cancer, though <10% of breast cancer[1] and around 10–15% of epithelial ovarian cancer[2] are related to hereditary mutations. The most common germline mutations associated with the hereditary early onset breast and ovarian cancers are those that affect the genes *BRCA1* and *BRCA2* that code for BRCA1 and BRCA2 tumor suppressor proteins[3]. Five percent of breast cancer in the USA has been reported to be due to *BRCA1/2* mutations annually[4], and about 84% of hereditary breast cancer and 90% of hereditary ovarian cancer are caused by mutations in *BRCA1* and *BRCA2* genes[5].

A specific concern on preventive strategies in *BRCA1/2* mutations is that they confer the risk of cancer at earlier ages in adulthood. The mean age for diagnosis of breast cancer in *BRCA1* mutations carriers has been described as 43 years, and for *BRCA2* as 47 years, versus age 61 years in the general population[6]. Otherwise, the age of onset of ovarian cancer is 63 years in the general population, but in *BRCA1* mutations the risk is 2–3% by 40 years of age, and up to 10–21% by 50 years[7,8]; in *BRCA2* mutations, this risk occurs later in life: 2–3% by age 50 years[9]. Globally, the decision on preventive strategies should be analyzed during the reproductive stage of a woman's life.

Moreover, in the last years, concern on cancer risk in *BRCA1/2* mutation carriers has grown in women worldwide, after the famous actress Angelina Jolie was diagnosed as a carrier of a *BRCA1* mutation in her late thirties and the discussion of medical choices for risk-reduction procedures in the press[10].

Amongst the risk-reduction strategies, the most effective for increasing survival is bilateral mastectomy plus bilateral salpingo-oophorectomy (when childbearing is completed). The latter, though, implies the consequences of surgical menopause at an early age on quality of life, sexual function, bone loss, and increase of cardiovascular risk[11,12].

In this article we review the risk of developing cancer in *BRCA* mutation carriers, the criteria for genetic testing, the surveillance and the risk-reduction strategies that affected women must or can be offered, and the safety of prescribing hormone therapy (HT) when needed.

BRCA genes and BRCA proteins

BRCA1 and *BRCA2* are tumor suppressor genes involved in a multitude of fundamental cellular processes; among others,

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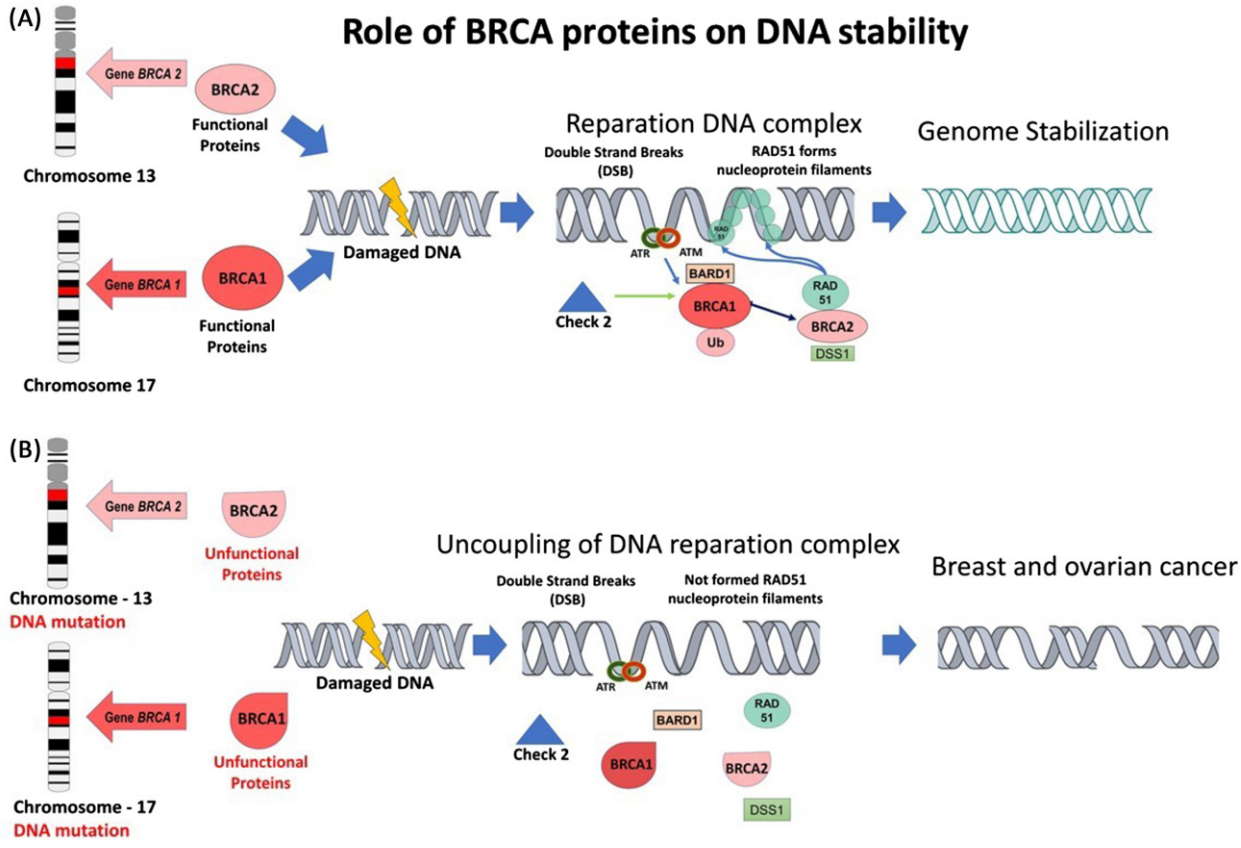

Figure 1. Role of BRCA proteins in DNA stability. Normally, when DNA mutations or alterations occur, both BRCA1 and BRCA2 proteins can stop the replication fork, or the breaks in the double strand of DNA, by triggering the homologous recombination that takes place, forming a complex between BRCA2 and the recombinase RAD51 and other enzymes and stabilizing proteins. This complex recognizes the DNA lesion and proceeds to repair the damage (A). On the other hand, when *BRCA1* and/or *BRCA2* genes suffer mutations, the generated dysfunctional BRCA1 and BRCA2 proteins will not form the complex, and thus the damage in DNA will not be repaired and will be perpetuated (B).

they are required to maintain chromosome stability protecting the genome from damage[13,14].

The germline mutations that inactivate or truncate the BRCA proteins lead to genomic instability and tumorigenesis, this by double-strand DNA damage during DNA replication or during exposure to ionizing radiation and other genotoxic compounds[15]. The tumors originated by mutated BRCA1 or BRCA2 proteins are defective in homologous recombination-mediated DNA repair[15,16].

When DNA mutations or alterations occur, BRCA1 and BRCA2 proteins can stop the damage of breaks in the double strand of DNA, as well as stop damage in the replication fork (the replication fork is the location where DNA replication occurs), by triggering homologous recombination. Both genes, *BRCA1* and *BRCA2*, mediate homologous recombination: BRCA1 protein participates by modulating signal transduction pathways that are involved in homologous recombination; BRCA2 protein participates directly by forming a complex with the recombinase RAD51 (enzyme involved in the homologous recombination and repair of DNA)[15,16].

More than 1600 different mutations have been described in the *BRCA1* gene, the majority of which promote frameshifts resulting in non-functional protein. In the case of *BRCA2*, more than 1800 mutations have been identified including insertions, deletions, and missense mutations that lead to truncated or unfunctional protein[17,18]. The absence of an effective DNA repair mechanism permits DNA damage to occur at different sites; in consequence, mutations in the *BRCA1* and *BRCA2* genes predispose to tumorigenesis: breast and ovarian cancers, and others.

Figure 1 shows the mechanisms by which *BRCA1* and *BRCA2* maintain genome integrity. Normally, when DNA mutations or alterations occur, both BRCA1 and BRCA2 proteins can stop the replication fork, or the breaks in the double strand of DNA, by triggering the homologous recombination that takes place, forming a complex between BRCA2 and the recombinase RAD51 and other enzymes and stabilizing proteins. This complex recognizes the DNA lesion and proceeds to repair the damage (Figure 1A). On the other hand, when the *BRCA1* and/or *BRCA2* genes suffer mutations, the generated dysfunctional BRCA1 and BRCA2 proteins will not form the complex, and thus the damage in DNA will not be repaired and will be perpetuated (Figure 1B)[19].

Risk of developing cancer in *BRCA1/2* gene mutation carriers

The mutation prevalence among the general population is 1 1 per 400 to 1 per 800. In specific ethnic groups such as Ashkenazi Jewish and Icelanders the prevalence is as high as 1 per 40 and 1 per 167, respectively[20]. If one copy of *BRCA1*

or *BRCA2* is mutated on the germline, the mutation will be inherited in an autosomal dominant manner[7].

The most common targets of these mutations are the breast and the ovary, which are subject to important growth signals by hormonal stimulation in fertile women. About 84% of hereditary breast cancer and 90% of hereditary ovarian cancer are caused by mutations in the *BRCA1* and *BRCA2* genes[5,21]. Otherwise, the cumulative risk of breast cancer at the age of 70 years ranges from 57 to 65% in *BRCA1* mutation carriers and from 45 to 49% in *BRCA2* mutation carriers[21,22]. For ovarian cancer, the cumulative risk is 39–49% and 11–18% for *BRCA1* and *BRCA2* mutation carriers, respectively[23].

BRCA1-associated breast cancer is commonly triple negative (negative for both estrogen and progesterone receptors, and human epidermal growth factor receptor 2 negative). It is noteworthy that in a triple-negative breast cancer, the risk of *BRCA* gene mutation is as high as 20%[24]. *BRCA2*-related breast cancers, though, are similar to the sporadic subtypes[15]. Ovarian carcinomas associated with *BRCA1/2* gene mutations tend to be of serous or endometrioid histology and of high grade[25].

The age of presentation of breast cancer in *BRCA1* mutation carriers is earlier than in *BRCA2* mutation carriers, with a mean age of diagnosis of 43 versus 47 years, respectively[6]. The age of onset of ovarian cancer is rarely before age 40 years in both *BRCA* mutations[7,8].

BRCA1 and *BRCA2* mutations are also associated with pancreatic, stomach, laryngeal, fallopian tube, melanoma, and prostate cancers. Noteworthy, men with breast cancer have a risk of *BRCA2* mutation of 14% and less frequent for *BRCA1* mutation[26]; the lifetime risk of breast cancer is 6.8 and 1.2% in *BRCA2* and *BRCA1* mutated males, respectively[27].

Criteria for genetic testing

The National Comprehensive Cancer Network (NCCN) recommends *BRCA1* and *BRCA2* genetic testing for patients with one or more of the following criteria[28]:

- Individual from a family with a known *BRCA1* or *BRCA2* gene mutation
- Personal history of breast cancer if:
  - diagnosed at age 45 years or less
  - diagnosed at age 50 years or less with one or more of the following:
    - an additional primary breast cancer
    - ≥1 blood relative with breast cancer at any age
    - ≥1 relative with pancreatic or prostatic cancer
    - an unknown or limited family history
  - diagnosed at age 60 years or less if the breast cancer is triple negative
  - diagnosed at any age with one of the following:
    - ≥1 blood relative with breast cancer diagnosed at 50 years or younger,
    - ≥2 blood relatives with breast cancer diagnosed at any age,
    - ≥1 blood relative with ovarian carcinoma,
    - ≥2 blood relatives with pancreatic or prostate cancer at any age,
    - a close male blood relative with breast cancer
    - ethnicity with high risk of mutation (Ashkenazi Jewish)
- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of metastatic pancreatic cancer
- Personal history of pancreatic or prostate cancer (Gleason score ≥7) at any age, with:
  - ≥1 blood relative with ovarian cancer at any age or breast cancer at 50 years or less, or
  - 2 relatives with breast, pancreatic or prostate cancer at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* pathogenic mutation detected by tumor profiling
- Family history only (appropriated affected family member unavailable for testing):
  - first or second-degree blood relative meeting any of the above criteria
  - third-degree blood relative who has breast cancer and/or ovarian carcinoma and who has 2 or more close blood relatives with breast cancer and/or ovarian cancer.

Other institutions, such as the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors, suggest similar criteria for genetic testing for *BRCA* mutations[29].

Genetic testing should begin with the affected cancer individual, by full sequencing of *BRCA1* and *BRCA2* genes. Once a specific mutation is found, family members should be tested for the specific gene mutation[28].

Breast and ovarian surveillance

Once a woman is known to be a *BRCA* mutation carrier, a strict and specific surveillance must be made to achieve early diagnosis in consideration of the high risk of early onset breast or ovarian cancer.

The NCCN suggests the following for breast surveillance in BRCA mutation carriers[28]:

- Starting at 18 years of age: self-examination for breast awareness;
- Starting at age 25 years: clinical breast examination should be performed every 6–12 months;
- Ages 25–29 years: annual breast magnetic resonance imaging (MRI) screening or mammogram if MRI is not available;
- Ages 30–75 years, both MRI and mammogram should be performed every year;
- From 75 years onward, management is individualized.
- If a breast cancer diagnosis before age 30 years is present in the family history, then the age at which to begin screening may be individualized.

For ovarian surveillance, the NCCN suggests clinical examination, transvaginal ultrasound, and serum CA-125 as screening tests, starting at age 30–35 years[28]. It has also been suggested to begin this surveillance 5–10 years earlier than the age of the younger relative when diagnosed with ovarian cancer[25]. This should be done every 6 or 12 months according to the clinician's discretion, since this strategy has not shown to be sensitive or specific regarding an impact on ovarian cancer mortality[25].

It has been reported that only 16% of physicians in the USA recommend the NCCN screening to their patients with *BRCA* mutation[30].

The choice between preventive surgery and regular surveillance requires knowledge of the effectiveness of each.

Efficacy of breast surveillance in *BRCA1/2* mutation carriers

The effectiveness of imaging screening has limitations in high-risk women, especially in *BRCA1/2* mutation carriers, differing from the general population, and these are considered in the planning of a screening method for this group of women[31]. The sensitivity is affected by the fact of being young women with dense breasts, and also by the occurrence of breast cancers with different histological subtypes: in *BRCA1* mutation carriers, cancers are generally ductal type, typically triple negative, with a faster rate of growth; in *BRCA2* mutation carriers, infiltrating invasive lobular carcinoma occurs more frequently, this histological type being more difficult to diagnose with mammography. In particular, in carriers of *BRCA1/2* mutations, interval cancers (cancer that becomes palpable between one screening round and another) occur more frequently than in the normal risk population, with an approximate 40–60% rate[31].

Hence, breast resonance was introduced as an additional method to screening mammography or in combination with clinical examination or ultrasound. Results of different prospective clinical trials have been published in the last 15 years and, in all, the sensitivity of breast resonance is higher in this high-risk group, approximately twice the sensitivity of mammography[32–34].

The benefits described with breast resonance screening in the group of high-risk patients are: early diagnosis with smaller tumor size, lower involvement of lymph nodes, lower appearance of interval cancers, longer metastasis-free time, and in some studies longer survival. Nevertheless, this examination is less specific, with the highest false positive rate and a greater number of unnecessary biopsies; thus, women should be informed and accept the risk of false positives before undergoing this or any screening method[35,36].

Otherwise, for women with *BRCA* mutations who have been already treated for breast cancer, screening of the remaining breast tissue should continue with annual breast imaging[28].

Cancer risk-reducing strategies in BRCA1/2 mutation carriers

Risk-reducing strategies for breast cancer and for ovarian cancer include surgery and/or chemoprevention.

In the case of breast cancer, a risk-reducing mastectomy (RRM) has been shown to decrease the cancer risk by up to 90–95% in *BRCA* mutation carriers[3,25]. The recommended age to perform this surgery has not been established. A survival analysis, comparing screening surveillance versus prophylactic surgery, showed that there was a minor increase in survival at age 70 years when RRM was done at 25 years of age: an 8% and 13% survival gain in *BRCA2* and *BRCA1*, respectively; and if RRM was done at age 40 years, the survival gain was 7% and 11% in *BRCA2* and *BRCA1*, respectively[37].

In North America, 64–78% of *BRCA* mutation carriers choose screening over RRM[38]; in fact, screening alone with MRI and mammogram increases the survival chance at 70 years by 4–6%[37], slightly less than prophylactic mastectomy.

On the other hand, risk-reducing salpingo-oophorectomy (RRSO) has been shown to have a positive effect on overall survival in *BRCA* mutation carriers and reduces the risk of ovarian cancer in 85–90% and the risk of breast cancer in 50% in a 6-year follow up[39,40]. Thus, the NCCN suggests performing RRSO at 35–40 years of age in *BRCA1* and *BRCA2* mutation carriers, if childbearing is completed. For the decision on the age at which to perform this surgery, it should be considered that in *BRCA2* mutations the risk of ovarian cancer by age 50 years is only 2–3%, but in *BRCA1* mutations the risk of ovarian cancer is 2–3% by 40 years of age, and up to 10–21% by 50 years[9]. The age of the youngest affected relative can offer some guidance on the age at which to recommend RRSO. For breast cancer risk reduction, RRSO should be performed before age 50 years[39].

In order to delay oophorectomy, bilateral salpingectomy has been proposed as a possible risk-reducing surgery for ovarian cancer, under the theory that ovarian cancer may originate in the fimbria of the fallopian tube[41]. Nevertheless, it is not included by the NCCN as a risk-reducing strategy; the effectiveness of this surgery is still under study.

The decision to perform a hysterectomy together with the RRSO should be analyzed and discussed with each patient, in order to avoid progestogens if HT is indicated, and also to avoid endometrial concerns if the patient should choose tamoxifen (TMX) for chemoprophylaxis (discussed later)[42].

The survival analysis cited earlier showed that the combination of RRM and RRSO at age 40 years was better than any single intervention, showing a gain in survival at age 70 years of 24% and 11% in *BRCA1* and *BRCA2* mutation carriers, respectively. This strategy is more acceptable for patients than combining RRSO at 40 years of age with RRM at 25 years of age without significant benefit in survival[37].

The concern that oophorectomy in premenopausal women is associated with risk of osteoporosis, cardiovascular disease, and neurological conditions and an increase in overall mortality plays a role in the decision of choosing RRSO[12]. Also, vasomotor symptoms and impaired sexual function have been specifically reported in *BRCA* premenopausal

mutation carriers who choose RRSO[43]. Nevertheless, a review of quality of life in these patients showed that women referred high levels of satisfaction with this surgery[43]. In fact, a study describes that 74% of women who tested positive for *BRCA* mutations chose RRSO, 17% being under 40 years of age[30].

Chemoprevention is also a strategy that may be offered to *BRCA* mutation carriers when they reject prophylactic surgeries.

In the case of breast cancer prevention with TMX, a study of a small number of mutated patients followed during 5.7 years showed a decrease of breast cancer risk by 62% in *BRCA2* mutation carriers ($n = 8$), but no reduction of risk in *BRCA1* mutation carriers ($n = 11$)[44]. Another study evaluated the reduction of contralateral breast cancer with TMX after 5–10 years of follow up, showing a 50% reduction of risk in both *BRCA1* and *BRCA2* mutation carriers ($n = 285$ cases and 715 controls), suggesting that TMX might have some effect in estrogen receptor-negative breast cancer as well[45]. There are no studies yet published with raloxifene or aromatase inhibitors as chemoprevention in this particular population.

Oral contraceptives (OC) have been proposed to be used in *BRCA* mutation carriers to reduce the risk of ovarian cancer, after a meta-analysis grouping 18 studies ($n = 1503$ carriers with ovarian cancer and 6315 healthy carriers) showed a 50% risk reduction; this, proportional to the years of use, and without an increase in breast cancer[46]. Similar results were found in another meta-analysis on women with high risk of breast and ovarian cancers, including *BRCA1/2* mutation carriers[47]. In both studies, a non-statistically significant increase of breast cancer was found in mutation carriers with newer OC formulations[46,47]. This contradicts previous findings that showed an increase in early onset breast cancer in *BRCA1* mutation carriers who used OC before age 30 years or for more than 5 years, but these were formulations existing before the year 1975, with higher doses of estrogen; there was no significant risk in *BRCA2* mutated women, though[48]. Nevertheless, a later case–control analysis found an increased breast cancer risk in *BRCA2*, but not *BRCA1*, mutation carriers who used OC during $\geq$5 years[49].

Chemoprevention could be indicated when the surgical risk-reduction strategies have been rejected, and always associated with the recommended screening techniques described.

Prescribing hormone therapy

Premenopausal patients who undergo RRSO may express an abrupt onset of vasomotor symptoms and sexual dysfunction. Menopause hormone therapy has shown to be effective in reducing hot flushes and improving sexual function in women in the reproductive stage of life, after RRSO was performed for high risk of hereditary ovarian cancer[50]. The Prevention and Observation of Surgical Endpoints (PROSE) study is a multinational and multicenter ongoing project examining outcomes in *BRCA* mutation carriers; in 2005, this study group reported that 60% of women with *BRCA* mutations who underwent RRSO used HT after surgery[51]. The concern for menopause hormone therapy in these patients is that this may counteract the achievement on breast cancer risk reduction, even in mastectomized patients since after RRM there still is a chance to develop cancer in the remaining tissue; also, women with a uterus would need an estrogen/progestogen combination, which could mean a higher breast cancer risk.

Few studies have analyzed the safety of prescribing HT in *BRCA* mutation carriers with no personal history of breast cancer and with intact breasts. The PROSE study published that there were no changes in the benefit of breast cancer reduction in women under HT in a follow-up of 3.6 years[51]. A case–control study published in 2008, evaluating 472 postmenopausal (natural and surgical) *BRCA1* mutation carriers, showed a significant decreased risk of breast cancer in HT users versus non-users (odds ratio 0.58, 95% confidence interval 0.35–0.96; $p = 0.03$) in a 4-year follow-up; even more, the use of combined HT did not increase the risk of cancer either[52].

On the whole, in these two studies analyzed, there was no increase in breast cancer risk when comparing estrogen-only therapy versus combined estrogen/progesterone[51,52].

A recent cohort study in 872 *BRCA1* mutation carriers showed that 40% of patients used HT after RRSO. During a 7.6-year follow-up, with use of any type of HT, there was no increase in breast cancer in these patients, when comparing HT users versus non-users. In this study, though, there was a significant difference between breast cancer risk when comparing estrogen-alone therapy versus estrogen plus progesterone, describing a higher risk in combined therapy users: 12% versus 22%, respectively[53].

Since evidence is limited in the high cancer risk patients with *BRCA* mutations, estrogen or estrogen/progestogen therapy, if indicated, needs to be informed on its benefits and risks, and discussed with the oncologists treating the patients, as well as the woman herself. The safest HT must be chosen and the duration of treatment must be considered in an individualized way.

Also, it is important to note that *BRCA* mutation carriers with prior history of breast cancer have an absolute contraindication for estrogen systemic therapy, and they should consider non-hormonal management of vasomotor symptoms.

Conclusions

There is a high risk of family early onset breast and ovarian cancers due to *BRCA1* and *BRCA2* gene mutations; a mutation in one copy of *BRCA1* or *BRCA2* on the germline is inherited in an autosomal dominant manner. When indicated, according to the NCCN criteria, full sequencing of *BRCA1* and *BRCA2* genes in the affected cancer individual is performed, and family members should be studied for the specific gene mutation found in the index case. When a mutation is confirmed, specific surveillance for breast and ovarian cancers is indicated to achieve early diagnosis and treatment.

The effectiveness of screening for breast cancer with mammography in combination with clinical breast

examination or ultrasound is low, due to specific limitations of screening in high-risk women, with more frequent interval cancers than in the normal-risk population. Breast resonance was introduced for early diagnosis after demonstrating better sensitivity. The NCCN guidelines display the age to begin surveillance, and the type and frequency of the screening method. On ovarian cancer surveillance, there is no proven specific or sensitive diagnosis method. Also, early diagnosis has not proven better survival. Hence, surgical or pharmacological risk-reducing strategies can be a choice.

There is insufficient evidence to prescribe chemoprevention in *BRCA1/2* mutation carriers: TMX for breast prevention and OC for ovarian cancer prevention. Moreover, TMX treatment can increase the appearance of ovarian tumors, and hormonal contraceptives could increase breast cancer, these patients being more susceptible to develop cancer.

On surgical reducing strategies, bilateral mastectomy achieves a minor increase in survival at age 70 years, slightly less than breast imaging surveillance. Otherwise, RRSO does have an effect in improving overall survival, and decreases the risk of both ovarian cancer and breast cancer. The NCCN recommendation is to perform RRSO for ovarian cancer risk at 35–40 years of age, when childbearing is completed, in *BRCA1* mutation carriers[28]; breast cancer reduction should be performed before age 50 years[39].

Nevertheless, preventive bilateral salpingo-oophorectomy in women of reproductive age or who are premenopausal has the implications of premature surgical menopause effects on quality of life and future general health concerns. Then, menopause hormone therapy might become a need in symptomatic women and heart, bone, and brain health prevention should become an issue to care about. The limited evidence of the few studies analyzing the safety of prescribing HT in these high cancer risk women makes it necessary for the HT to be reserved for symptomatic women and to discuss risks and benefits with the patient and the oncologists treating her.

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