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Hereditary breast cancer and genetic counseling in young women

Joan Brunet¹

¹Hospital Josep Trueta, Girona, Spain.

Corresponding author:

Joan Brunet, MD

Genetic Counseling Unit

Hospital Universitari de Girona Doctor Josep Trueta

Avenida França, S/N

17007-Girona. Spain

E-mail: jbrunet@ico.scs.es

Phone: +34 972 94 02 00

Fax: +34 972 94 02 70

Introduction

It is well established that a family history of breast cancer is associated with an increased risk of developing breast cancer. In fact, among those variables that have been shown to bear a relationship with breast cancer, the highest risk, after age, is the presence of a positive family history of breast cancer [1].

Among breast cancer patients, up to 5%-10% are considered directly related to the inheritance of mutations in *BRCA1* or *BRCA2* genes [2], which accounts for most hereditary breast cancers. Claus et al. [2] estimated the proportion of breast cancer attributable to inherited autosomal dominant genes to be approximately 33% in subjects aged 20-29 years. This estimated risk decreased with age at onset to approximately 1.5% of case subjects aged 70 years or more. Women carrying these mutations have a lifetime risk of breast cancer of 60%-80% [3]; therefore, detection of mutations in these two genes can be used as a molecular predictor for breast cancer.

At present, data suggest that a mutation in *BRCA1* accounts for the majority (80%-90%) of families containing multiple case subjects with breast and/or ovarian cancer, and approximately 45% of inherited breast cancers [4], whereas a mutation in *BRCA2* is thought to account for approximately 35% of inherited breast cancers [3].

Genetic screening

As a consequence of current trends in multidisciplinary therapy for breast cancer, *BRCA1* and *BRCA2* genes are not only useful as molecular markers for hereditary breast cancer risk screening, but have also become important indicators for prevention, treatment and prognosis of breast cancer.

Screening for *BRCA1* or *BRCA2* mutations is difficult. In a large proportion of patients with breast cancer who have a family history strongly pointing to hereditary disease, a *BRCA1* or *BRCA2* mutation cannot be demonstrated. This may be partly explained by germline mutations in less common genes other than *BRCA1* or *BRCA2*, such as in the

TP53 gene, which is associated with Li-Fraumeni syndrome; in the *PTEN* gene, which is associated with Cowden syndrome; in the *CHEK2* gene; or in the ataxia telangiectasia mutated gene [5]. Mutations in *BRCA1* or *BRCA2* may be missed in current screening procedures, even with complete sequencing [6]. It is currently possible to detect about 90% of all *BRCA1* or *BRCA2* mutations by using standard diagnostic procedures, and a mutation is detected in almost 25% of cases presenting with familial cancer.

Not all women are candidates for genetic testing. In order to maximize both the efficiency of testing and the public health impact of a genetic screening program, many centers offer screening to women when the prior probability of finding a mutation is 10% or greater [7]. Several mathematical models such as BRCAPRO (<http://astor.som.jhmi.edu/BayesMendel/brcapro.html>) and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) can be used to estimate the prior probability of carrying a mutation [8, 9]. These models consider age of onset and family history of cancer.

Although the decision to offer genetic testing to a breast cancer patient is usually based on family history, if the family history is not available, some women may qualify for testing based on age of onset or the breast tumor's pathologic features.

Certain tumor characteristics can also be used to predict the presence of a mutation. *BRCA1*-associated cancers are typically of high grade and 'triple negative' (i.e. negative for estrogen receptors [ER], progesterone receptors [PR] and human epidermal growth factor receptor-2 [HER2] expression) [10]. The majority of triple negative cancers (80% to 90%) also exhibit a basal phenotype (expression of cytokeratins and HER2). The proportion of basal phenotype *BRCA1*-associated cancers has been estimated at 88% [10].

The proportion of *BRCA1*-associated cancers that are ER-negative diminishes with increasing age of onset. Foulkes et al. [11] found that 81% of *BRCA1*-associated

breast cancers diagnosed before age 45 were ER-negative, compared to 62% of breast cancers diagnosed after age 65.

Genetic syndromes that carry a significant risk of breast cancer are responsible for a small but significant percentage of these cancers. However, the vast majority of breast tumors occur in women with no family history of the disease. Non-genetic risk factors include age, previous breast disease, breast tissue density, radiation exposure, and lifestyle factors such as weight, exercise, and alcohol consumption [12].

When a woman under the age of 40 years develops breast cancer, a hereditary predisposition may be suspected whether there is a family history or not. If there is a family history of two or more family members under 50 years of age with breast cancer, male breast cancer, or ovarian cancer, or a Li-Fraumeni or Cowden syndrome is suspected, the likelihood of a genetic predisposition is high. If there is no family history, the suspicion that the breast cancer is due to a heritable genetic mutation is based in tumor bilaterality, tumor phenotype (triple negative and basal phenotypes), and a simultaneous diagnosis of ovarian cancer. It is also important to discard a possible paternal transmission due to little information regarding inheritance patterns.

Studies comparing survival between *BRCA1* and *BRCA2*-associated and sporadic breast cancers have inconsistent results. The prognosis of the disease depends on whether the mutation has occurred in the *BRCA1* or *BRCA2* gene. If a mutation has occurred in *BRCA1*, some studies have attributed a similar prognosis when compared with sporadic breast cancer patients [13], while other studies have attributed a worse prognosis [14]. In *BRCA2* mutation carriers, the prognosis may also be better [15] or similar when compared with age-matched sporadic breast cancer patients [16].

Genetic counseling and management of women with hereditary breast cancer

A young woman with breast cancer will probably express her concern about whether her tumor is inherited because of the possibility of transmitting it to her offspring. The

patient will also be concerned about whether there will be additional risks throughout her life to develop other mutations or, if by virtue of being inherited, she has a worse prognosis. Furthermore, knowing if breast cancer is inherited is important in deciding the treatment of advanced disease.

The discovery of *BRCA1* and *BRCA2* mutations has raised a number of questions regarding the optimal management of women with hereditary breast carcinoma. The appropriateness of breast-conserving therapy for women with hereditary breast carcinoma is an area of ongoing discussion. Women with *BRCA*-associated breast carcinoma who undergo breast-conserving surgery appear to have a risk of metachronous ipsilateral breast carcinoma similar to that reported for young women without known mutations [17]. The indications for unilateral mastectomy in this group of women should therefore be the same as for women with nonhereditary carcinoma. However, a significant risk of contralateral breast carcinoma and possibly late metachronous ipsilateral breast carcinoma may prompt consideration of bilateral mastectomy as a preventive measure [17]. A study by Garcia-Etienne et al. [18] showed that the risk of ipsilateral breast tumor recurrence after breast-conserving surgery in *BRCA1/2* mutation carriers was increased compared with patients who had sporadic breast cancer. Likewise, the risk of contralateral breast cancer seemed to be increased in this group.

Neoadjuvant chemotherapy for breast cancer is often given prior to surgery to decrease the size of the tumor so that breast-conserving surgery can be performed, and to reduce the probability of lymph node involvement. Patients with *BRCA1/2* mutations show a better clinical response rate to neoadjuvant chemotherapy than patients without mutations in the *BRCA* gene.

The use of platinum-based neoadjuvant chemotherapy has been effective in a high proportion of patients with *BRCA1*-associated breast cancers [19]. Another study reported that *BRCA1/2* carriers showed a better clinical response rate to neoadjuvant

treatment than non-carriers [20]. There is also a study that has demonstrated the therapeutic efficacy of treatment in advanced breast cancer. In a phase II trial, the efficacy of the oral poly (ADP-ribose) polymerase inhibitor olaparib in *BRCA*-deficient advanced breast cancer was evidenced [21].

BRCA1/2 genes are transmitted in an autosomal dominant pattern. Because this can influence an individual's decision regarding reproduction, health care professionals should ensure patient education regarding the potential impact of *BRCA* inheritance on family planning. Preimplantation genetic diagnosis in women carrying *BRCA* mutations has been approved in some countries. Women at increased risk for hereditary cancer may consider this procedure as part of their reproductive decision making. Therefore, it is important to understand existing levels of awareness and attitudes toward this technology to provide optimal counseling and support [22].

Conclusions

The identification of a possible hereditary predisposition to breast cancer is important because the prevalence of familial breast cancer is sufficiently high to have a clinical impact. Importantly, genetic screening must be done at the time of diagnosis, not when adjuvant chemotherapy is being administered as has been done so far. This is because information regarding *BRCA1/2* mutation status is important for the young patient with breast cancer in order to undertake opportune prophylactic measures, such as bilateral mastectomy, evaluate consequences on reproduction, make timely treatment decisions in case a breast tumor develops, and provide adequate genetic counseling to the patient and family members. Hospitals that do not have access to Genetic Counseling Units should have contact with a referral center.

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