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Review

Breast cancer genetics in young women: What do we know?

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ABSTRACT

Breast cancer (BC) in young women, generally defined in oncology as women who are 40 years of age or younger, represents 2 out of 10 BC cases in developing countries. Several research studies, including genetic cancer panel tests, genome-wide association studies, expression analyses and polymorphisms reports, have found that young women with BC exhibit a higher genetic susceptibility and specific genomic signature compared to postmenopausal women with BC. Thus, international guidelines recommend genetic counseling for this age population. This review presents the current state of the art of genetics and genomics with regards to young women with BC.

1. Introduction

Cancer is a leading cause of morbidity and mortality worldwide, with 14 million new cases and more than 8 million cancer-related deaths in 2012 [1]. Breast cancer (BC) is the most common neoplasia in women, representing 25.2% of total cancer cases. In developing countries, BC is the primary cause of cancer-related death (324,000 deaths) and the second main cause in developed regions (198,000 deaths) [2].

BC predominantly occurs during the sixth decade of life [2]; however, between 6 and 10% [3] of cases present in women younger than 45 years of age in developed countries, and this rate is nearly double in less-developed countries (20%), as is the mortality rate (7% vs. 14%, respectively) [3–6].

BC in young women, defined in the oncology literature as cases in women under the age of 40, represents a challenge to public health due to the considerable number of years of life lost, difficult treatment and often late diagnosis [7–10]. The objective of this article is to review the current knowledge of genetics and genomics with regards to young women with BC.

2. Breast cancer tumor characteristics in young women

Recent studies have shown that breast tumors in young women have distinctive characteristics compared to those that occur in postmenopausal women. Specifically, breast tumors in young women have been described as more aggressive than those in older women [11–13]. In addition, early-onset malignant breast tumors have a high histological grade, high proliferation rate and are poorly differentiated. Ki67 expression is increased in these tumors, and the expression level appears to be inversely proportional to age, being significantly higher in patients aged less than 40 years [14,15].

Most malignant breast tumors in young women are classified as triple-negative or HER-2-positive cancers [10,12,15–18]. Independent of the stage of detection and histological grade, young age is considered to be an adverse prognostic factor in BC and presents a high risk of both local recurrence [19–21] and contralateral BC [22,23]. Additionally, there is a strong family history of BC and other types of cancer (24,25), as well as tumoral expression of p53 [15], suggesting a genetic component [24,25].

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3. Genetics

Epidemiological data from BC patients without age stratification analysis show that approximately 10–30% of BC cases are attributed to familial factors. Only a small percentage (5–10%) of BC cases have a strong inherited component, and are autosomal dominant, being caused by highly penetrant deleterious mutations. [26,27]. Current international guidelines state that patients should be referred for genetic counseling when they are younger than 50 years or if they present with triple-negative BC. The identification of genetic mutations in this group of patients can have a meaningful impact on treatment, and closer medical follow-up. Screening and prevention for other family members are also beneficial [28–31].

Compared to postmenopausal BC patients, genetic and genomic data for young women with BC are scarce.

3.1. Breast-cancer-predisposing gene mutations in young women

Predisposing mutations can be categorized according to the relative risk they add to suffering from a particular type of cancer. Highly penetrant mutations are associated with a cancer relative risk greater than 5, and intermediate-penetrant mutations confer relative cancer risk from 1.5 to 5. Low-penetrance *loci* have a relative risk of approximately 1.5. These latter types of mutations are usually polymorphisms, and the risk assessment can vary in different populations [32].

Mutations in highly penetrant genes are associated with hereditary cancer syndromes, and more than 200 genetic syndromes linked to cancer have been described. Cancer can be the only phenotypic manifestation in individuals with such mutations, or it can be one clinical sign of a more complex phenotype. For hereditary BC associated syndromes, there are common characteristics of clinical presentation of BC and family aggregation that can lead to a suspicion of a highly penetrant mutation: high incidence of cancer within the family, the occurrence of the same type of cancer within the family, early-onset-age of presentation (< 50 years), bilaterally and multifocality.

3.1.1. High penetrance genes

3.1.1.1. BRCA1/2. The DNA repair associated *BRCA1* gene product is a nuclear phosphoprotein that participates in the DNA damage response, cell cycle progression, centrosome number, and transcriptional regulation [33,34].

Genetic variants leading to the premature termination of the BRCA1 protein are associated with increased risk of cancer. More than 500 missense variants of unknown significance (VUS) have been described in *BRCA1* [35,36].

The lifetime risks of breast and ovarian cancer are as high as 80% and 40%, respectively, among women carrying *BRCA1* mutations, with a higher frequency of cancer risk at younger ages [37].

The *BRCA2* gene encodes a protein that repairs double-stranded breaks during homologous recombination. The majority of *BRCA2* mutations are frameshifts, but there are a number of missense mutations with unclear pathogenicity. *BRCA2*-related tumors often express estrogen and progesterone receptors and tend to have similar features to those of sporadic BCs, unlike *BRCA1*-related cancers [33].

Malone *et al.* found that BC patients younger than 35 years old without a family history of BC had a 9.4% chance of carrying a germline mutation in *BRCA1/2*. This same study reported that 12% of women aged less than 45 years old with a family history of breast carcinoma had germline mutations in *BRCA1/2* [38].

The prevalence of *BRCA1/2* mutations varies between populations: from 0.2–0.3% in the general population, 3% in women with BC, 6% in women with BC onset before the age of 40, 10% in women with ovarian cancer, and 20% in high-risk families [33]. Among Ashkenazi Jewish women, the prevalence of *BRCA* mutations is 2% in unselected populations, 10% in high-risk families and BC patients of any age, and up to 21%-30% in women diagnosed with BC before the age of 40 [39,40].

For young patients aged from 30 to 34 years with ER-negative high-grade tumors, the chance of having a *BRCA1* mutation is close to 30%, while patients with *BRCA2* mutations have phenotypes similar to those of patients with sporadic BCs [41,42].

VUS are a significant limitation of *BRCA1* and *BRCA2* genetic testing, and represent a challenge for genetic counseling because their clinical meaning is unknown, making medical recommendations more complicated. Researchers use multiple analyses to reclassify these variants, including *in silico* analyses, *in vitro* functional analyses and both clinical and population reports [43]. Additional studies may lead to a VUS being reclassified as either deleterious or not, making it necessary to establish a policy for re-contacting patients for genetic counseling to provide updated results. Collaborative efforts to collate data on VUS are essential for improving *BRCA* cancer risk assessments.

3.1.1.2. TP53. The tumor protein p53 (*TP53*) gene encodes a peptide that responds to cellular stress to regulate the expression of target genes, inducing cell cycle arrest, apoptosis, senescence, DNA repair, and changes in cell metabolism [44]. Mutations in *TP53* are highly penetrant and cause the Li-Fraumeni syndrome, which is associated with a variety of human cancers, such as sarcoma and hematological malignancies; however, early-onset BC is the most common tumor in women with germline mutations in this gene [45,46].

The lifetime risk of any cancer for carriers of mutations in *TP53* is greater than 90% and up to 50% for BC in women [47]. The reported frequency of *TP53* mutations in women diagnosed with BC before 35 years of age ranges from < 1% to 7% [45,47,48–51]; this rate can reach up to 30% in patients diagnosed before the age of 30 [52].

3.1.1.3. PTEN. The phosphatase and tensin homolog (*PTEN*) gene encodes a protein that suppresses the PI3 K/Akt/mTOR pathway and regulates cell survival, proliferation, and metabolism [53,54]. Germline heterozygous pathogenic variants in *PTEN* are very uncommon and lead to clinical manifestations that are collectively labeled *PTEN* Hamartoma Tumor Syndrome (PHTS) [55], which includes the underdiagnosed Cowden syndrome (CS) and three other rare genetic syndromes [56]. BC is the most frequent malignancy in women diagnosed with CS, with a lifetime risk of 85%, and an age of diagnosis between 38 and 46 years. These patients subsequently present with tumors of the thyroid and endometrium [55,57]. BC and recurrence in women younger than 40 who carry *PTEN* mutations have been reported in the literature [58].

3.1.1.4. STK11. The tumor suppressor gene *STK11* which encodes a serine/threonine kinase, participates in cell proliferation, metabolism, and p53-dependent apoptosis. This gene also protects the genome from oxidative damage and is involved in the regulation of vascular endothelial growth factor (VEGF) and Wnt signal transduction [59]. Pathogenic mutations in *STK11* cause the autosomal dominant Peutz-Jeghers syndrome (PJS), which predisposes patients to digestive cancers, pancreatic cancer, and BC, with a cumulative incidence of 45% [60]. Malignancies appear at an average age of 41.5 years, with a higher risk in females (22-fold) than in males and a 20% risk of any cancer by the age of 40 compared to the general population [61–63]. A study by Hearle *et al.* found that the risk of BC by the age of 40 is 31% in women with PJS [64].

3.1.1.5. CDH1. The cadherin 1 (*CDH1*) gene encodes E-cadherin, an adhesion molecule expressed in the junctions of epithelial cells. The loss of function of this gene has been associated with increased cell proliferation, invasion, and metastasis [65]. *CDH1* germline mutations have been linked to the autosomal dominant hereditary diffuse gastric carcinoma (HDGC). Approximately 30% of families with germline mutations in *CDH1* and HDGC present cases of invasive lobular BC (ILC) [66–68]. However, the presence of hereditary ILC without a family history of diffuse gastric tumors has been described for some families with pathogenic *CDH1* mutations [69]. Moreover, female