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Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer

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ABSTRACT

Since the initial discovery that pathogenic germline alterations in *BRCA 1/2* increase susceptibility to breast and ovarian cancer, many additional genes have now been discovered that also increase breast cancer risk. Given that several more genes have now been implicated in hereditary breast cancer syndromes, there is increased clinical use of multigene panel testing to evaluate patients with a suspected genetic predisposition to breast cancer. While this is most certainly a cost-effective approach, broader testing strategies have resulted in a higher likelihood of identifying moderate-penetrance genes, for which management guidelines regarding breast cancer risk reduction have not been firmly established. In addition, the testing of more genes has led to increased detection of variants of uncertain significance. We review the current knowledge regarding both high- and moderate-risk hereditary breast cancer syndromes, as well as additional genes implicated in hereditary breast cancer for which there is limited data. Furthermore, strategies for cancer risk reduction in mutation carriers as well as therapeutic implications for those patients who harbor pathogenic germline alterations are discussed.

1. Introduction

1.1. History of BRCA1 and BRCA2 gene mapping and discovery

In 1990, Mary-Claire King and colleagues reported genetic linkage studies in families with early-onset breast cancer which implicated a relatively narrow region in chromosome 17q [1]. The previous year, Narod and colleagues had identified linkage in the same region in families with breast and ovarian cancer [2]. These seminal reports spurred a competitive race between several international collaborations to isolate the *BRCA1* gene, which was finally cloned in 1994 [3] and mutations were identified in tumors belonging to the linked kindreds [4]. *BRCA1*, and *BRCA2* isolated in 1995 [5], are essential to the process of repairing double strand breaks in DNA via homologous recombination [6]. In this form of repair, the DNA is restored to its original sequence; however, when this process is deficient, other forms of less conservative DNA repair take place. One such mechanism is non-homologous end joining, which simply joins two ends of broken DNA without using a template sequencing, often resulting in the introduction of mutations [7]. Interestingly, whereas somatic de novo mutations were identified in sporadic ovarian cancers [8] they were relatively rare in breast cancers, suggesting that *BRCA1* differed from classic tumor suppressors such as *WT1* or *TP53* in its spectrum of somatic changes. Finding germline mutations in families affected with breast and ovarian cancer set the stage for the integration of genetic counseling and predisposition testing into clinical care for cancer risk management of high-risk patients and families [9].

1.2. Early efforts to incorporate genetic counseling and testing into the clinic

The discovery of the breast cancer susceptibility genes *BRCA1* and *BRCA2* made predictive genetic testing possible. Academic centers initially took the lead in offering integrated risk evaluations, including counseling before and after genetic testing and personalized risk management plans tailored to patients' age, health status, reproductive plans, and cultural background. Since then, genetic risk assessment for breast cancer risk has been integrated into clinical care in a number of different clinical settings (primary care, obstetrics and gynecology, oncology, and screening mammography) and the emergence of patient advocacy groups and increasing interest about genetic medicine on the part of patients and their providers has significantly increased referrals for genetic risk evaluation.

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2. Hereditary breast cancer syndromes

Most women who present with breast cancer do not have an inherited predisposition to developing the disease. However, up to 20% of patients with a family history of breast cancer may harbor a germline mutation associated with increased cancer risk [10]. Inherited susceptibility to developing breast cancer most commonly results from mutations in *BRCA1* or *BRCA2;* however, additional genes have been implicated in genetic predisposition to breast cancer. Below, these syndromes are classified into high-risk and moderate-risk of developing breast cancer (Table 1).

2.1. High-risk syndromes

2.1.1. BRCA1- and BRCA2-associated hereditary breast cancer

Approximately 40% of hereditary breast and ovarian cancer (HBOC) cases are associated with pathogenic germline alterations in *BRCA1* or *BRCA2*, which are inherited in an autosomal dominant fashion. Families that harbor these pathogenic mutations are often characterized by multiple females affected by breast cancer at an early age (premenopausal). While tumors associated with germline alterations in *BRCA1* or *BRCA2* are more likely to be triple negative [11], other histologic subtypes can be seen. Estimates of lifetime risk of developing breast cancer for patients with *BRCA1* and *BRCA2* mutations varies across studies; however, pooled results suggest cumulative risk of developing breast cancer by age 70 in *BRCA1* mutations carriers is approximately 65% compared to 45% in *BRCA2* mutation carriers [12]. In addition to a higher lifetime risk of developing breast cancer with a *BRCA1* mutation, these patients also tend to have earlier onset of disease, particularly before age of 50 [13–15]. *BRCA1* and *BRCA2* germline mutations are also found at higher frequency among certain ethnic groups. For example, approximately 1 in 40 individuals of Ashkenazi Jewish decent unselected for personal or family history of malignancy carry one of three founder mutations: 187delAG or 5385insC in BRCA1 or 6174delT in BRCA2 [16]. Founder mutations in *BRCA1* and *BRCA2* have also been reported in the Netherlands, Sweden, Hungary, Iceland, Italy, France, South Africa, Pakistan, Asia, French Canadians, Hispanics, and African Americans [12,17–21]. Men with *BRCA2* mutations have an approximately 7%–8% lifetime risk of developing breast cancer (a risk comparable to women who are at lower than average risk) versus 1% lifetime risk for those with *BRCA1* mutations [22,23].

2.1.2. Li-Fraumeni syndrome

Li-Fraumeni Syndrome (LFS) is associated with germline alterations in the tumor-suppressor gene *TP53* and is inherited in an autosomal dominant fashion. Individuals with this syndrome are at very high risk of developing multiple malignancies in childhood or early adulthood, including but not limited to: breast cancer, sarcomas, brain cancer, leukemias, lung cancers, and adrenocortical cancers [24,25]. For females, the risk of developing breast cancer by the age of 60 is approximately 50% and the median age at diagnosis is under 35 years [25–28]. Breast cancer arising in women with a germline *TP53* mutation is more likely to have amplification of the human epidermal growth factor receptor 2 (HER2) [29]. In general, mastectomy is usually recommended for surgical management of breast cancers in patients with LFS, as radiation exposure can markedly increase the risk for developing a secondary radiation-associated malignancy.

2.1.3. Peutz-Jeghers syndrome

Peutz-Jeghers Syndrome (PJS) results from germline alterations in the *STK11* gene and is inherited in an autosomal dominant fashion. Patients with PJS often present with intestinal obstructions as a result of small bowel polyps; however, they also have very elevated risks of gastrointestinal cancers [30], and women are at increased risk for breast and ovarian cancer. Lifetime risk for breast cancer is approximately 55% and median age at diagnosis is in the late 30s [30,31]. Mucocutaneous pigmentation and or gastrointestinal hamartomatous polyps are noted in 95% of individuals with PJS [30].

2.1.4. PTEN hamartoma tumor syndrome (Cowden syndrome)

PTEN hamartoma tumor syndrome (PTHS) results from germline alterations in the tumor-suppressor gene *PTEN*. For patients with this condition, the lifetime risk of developing breast cancer is approximately 85% [32]. Most women are diagnosed with premenopausal breast cancer [33] and these patients also have increased risk of benign breast diseases such as fibroadenomas [34]. Women with this syndrome also have an increased risk for endometrial cancer. Men and women with a PTEN gene mutation also have an increased risk for thyroid cancer (particularly follicular type), renal cancer, and colon cancer. Additional non-cancer manifestations include autism spectrum disorder, macrocephaly, hamartomas, trichilemmomas, and plantar keratosis.

2.1.5. Hereditary diffuse gastric cancer syndrome

This syndrome is characterized by genetic susceptibility to diffuse gastric cancer, associated with germline cadherin-1 (*CDH1*) mutations [35,36]; however, *CDH1* mutations are also associated with increased risk of lobular breast cancer in women,

Table 1
Summary of high- and moderate-penetrance genes implicated in genetic predisposition to breast cancer.

Germline alteration	Lifetime breast cancer risk	Most common associated breast cancer pathology	Other associated malignancies
BRCA1	65% (by age 70)	Triple Negative	Ovarian, fallopian tube, primary peritoneal, pancreas, prostate
BRCA2	45% (by age 70)	Triple-negative or estrogen receptor–positive	Ovarian, melanoma, fallopian tube, primary peritoneal, pancreas, prostate. stomach, gallbladder/biliary
TP53	50% (by age 60)	Her2-amplified	Sarcoma, CNS malignancies, adrenocortical carcinoma, gastrointestinal, radiation-associated cancers
STK11	30%–50% (lifetime)	N/A	Colorectal, stomach, small bowel, pancreas, ovarian, cervical, Sertoli cell testicular
PTEN	85% (lifetime)	N/A	Thyroid, endometrial, colorectal, renal
CDH1	60% (lifetime)	Invasive lobular carcinoma	Stomach (diffuse)
MSH1, MSH2, MLH1, PMS2, EPCAM	Unknown	N/A	Colorectal, endometrial, ovary, stomach, small bowel, hepatobiliary, CNS
CHEK2	20%–25% (lifetime)	Estrogen receptor–positive	Colorectal (1100delC mutation), stomach, prostate, kidney, thyroid, sarcoma
PALB2	33% (by age 70 without family history), 58% (by age 70 with family history)	N/A	Pancreas
ATM	20% (lifetime)	N/A	Pancreas