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Seminars in
RADIATION
ONCOLOGY

Breast Cancer Risk Assessment: Moving Beyond BRCA 1 and 2

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The National Cancer Institute estimates that 12.3% of all women (about 1 in 8) would be diagnosed with breast cancer throughout their lifetime. In 2015, a projected 231,840 new cases are expected in the United States, accompanied by 40,290 deaths. Presently, breast cancer is responsible for 6.8% of all cancer deaths, and roughly 30% of all cancers in women. Since the discovery of the *BRCA* gene in 1994, efforts have been made to develop effective screening methods for breast cancer detection. Although the *BRCA* gene certainly opened the door to breast cancer genetics, a wide variety of new genes have recently been linked to breast cancer risk, and the tools to screen for genes beyond just BRCA1 and BRCA2 are available. However, the indications for both screening and prevention of inherited predispositions beyond BRCA1 and BRCA2 are not entirely clear, and as a result, much of the ongoing work is aimed at determining the role of broader genetic screening in women deemed at sufficiently high risk for breast cancer based on family history. On this topic, we provide a brief overview of the genes associated with breast cancer risk as well as the technological platforms available to patients. We conclude by discussing recommendations of expert groups and what they practically mean for patients.
Semin Radiat Oncol 26:3-8

Introduction

Breast cancer is the most common cancer in women worldwide, and in the United States alone, it is estimated that there would be more than 230,000 patients with invasive disease in 2015 with more than 40,000 deaths expected in 2015.[1] The discovery that BRCA mutations are associated with an increased risk of breast cancer (as well as ovarian and other cancers) was a seminal event in cancer genetics. For the first time, genomic linkage analysis revealed the presence of deleterious mutations on chromosome 17q21 associated with breast and ovarian cancers in high-risk families.[2] These gene mutations were discovered to be located on the *BRCA1* gene. A subsequent discovery of families with high risk who were not found to have a *BRCA1* mutation identified *BRCA2* located on chromosome 13q12-13.[3] Yet, although mutations in BRCA account for between 12% and 31% of breast cancer risk among high-risk families,[4,5] it is now recognized that other breast cancer susceptibility genes also exist.

Evidence-based testing guidelines, counseling, and risk-reducing interventions have been established for hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*) as well as other less common high-penetrance autosomal dominantly inherited breast cancer conditions, including Li-Fraumeni syndrome (*TP53*), hereditary diffuse gastric cancer (*CDH1*), Cowden's syndrome (PTEN), and Peutz-Jeghers syndrome (*STK11*).[6] However, next-generation technology has enabled massively parallel sequencing at low cost, which has fostered the advent of multiplex genetic testing and the identification of other less penetrant genes carrying a predisposition to breast and other cancers.

Genes Associated With High Familial Penetrance

TP53

Mutations involving p53 are inherited in an autosomal dominant fashion. The result is a familial predisposition to a

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http://dx.doi.org/10.1016/j.semradonc.2015.09.004
1053-4296/

diverse array of cancers, including breast cancer. Indeed, the estimated risk of breast cancer in women with this condition is roughly 49% by 60 years, and in several studies, up to one-third of those women diagnosed with breast cancers were diagnosed before 30 years.[7,8]

STK11

Mutations in the serine-threonine kinase STK11 result in Peutz-Jeghers syndrome, which is associated with the development of hamartomas around the lips, hands, and genitals, polyps throughout the gastrointestinal tract, and multiple malignancies, including those of the uterus, breast, and ovary.[9] In addition, these patients have been consistently seen to have an elevated risk of breast cancer, with 1 individual patient meta-analysis (based on 210 individuals from 6 publications) estimating the relative risk as 15-fold higher compared with the general population.[10]

PTEN

Mutations in the PTEN tumor suppressor gene result in Cowden syndrome, which is also inherited in autosomal dominant fashion. It is characterized by the development of multiple hamartomas on the skin and mucous membranes and an increased risk for developing malignancies of the breast, thyroid, and endometrium. In a study, the estimated lifetime risk of developing breast cancer for these patients was over 85%.[11]

Genes Associated With Moderate Familial Penetrance

CHEK2

The CHEK2 gene is a member of the Fanconi Anemia (FA)-BRCA pathway and is involved in both checkpoint function and in BRCA1- and p53-mediated repair. Mutations in CHEK2, including 1100delC, have recently been associated with a 3- to 5-fold increase of breast cancer.[12] In a large meta-analysis of 26,000 cases compared to as many controls, for example, the aggregated odds ratio of breast cancer in general, early-onset breast cancer, and familial breast cancer was 2.7, 2.6, and 4.8, respectively. The corresponding cumulative risk of breast cancer by 70 years among CHEK✻1100delC heterozygotes was 37%.[12] In another study, Meijers-Heijboer et al evaluated 718 families with a family history of breast cancer who tested negative for a BRCA mutation and reported that it was present in 5%, including 13.5% of families with male breast cancer.[13]

PALB2

PALB2 is another gene in the FA-BRCA pathway. It encodes a protein that intimately binds to BRCA2, stabilizing it and allowing it to perform its reparative functions. This interaction is essential for BRCA2 tumor suppression and damage control activity. Germline PALB2 mutations appear to confer the risk of young onset breast cancer, although further studies are necessary to confirm these findings. The risk of breast cancer was evaluated by Antoniou et al,[14] who studied 362 members of 154 families with a PALB2 mutation (deleterious truncating, splice, or deletion mutations). In their study, women with a PALB2 mutation who were less than 40, 40-60, and more than 60 years had an increased risk of breast cancer ranging from 8-9, 6-8, and 5-fold higher, respectively. Of interest, despite the functional relationship between PALB2 and BRCA2, these investigators found that patients with a PALB2 mutation did not have a statistically significant increased risk of ovarian cancer.

ATM

Mutations in the ATM gene result in ataxia-telangiectasia, an autosomal recessive neurodegenerative disease that causes cerebellar dysfunction and a weakened immune response. The ATM protein is an important cell cycle checkpoint kinase within the FA-BRCA pathway and, among its roles, it phosphorylates BRCA1. Studies have shown that heterozygous mutation carriers have an elevated risk of breast cancer. In a study by Renwick et al[15] 443 individuals from hereditary breast cancer families were screened for an ATM mutation along with 521 normal patients who served as controls. A total of 12 mutations were identified among the cases, only 2 of which appeared in controls. These data indicated that the risk of breast cancer associated with an ATM mutation was approximately 2.37 (95% CI: 1.51-3.78).

Moderately Penetrant Genes Not As Well Characterized

There are also a number of hereditary breast cancer genes that are not characterized very well at this time. Researchers are not certain of the risk they carry for breast and other cancers, and investigations are under way.

BRIP1

BRIP1 interacts with BRCA1 and functions in BRCA1-dependent DNA repair, in addition to particular checkpoint functions. In a study, Seal et al[16] identified significantly more common truncating mutations of *BRIP1* among individuals with familial breast cancer who tested negative for a BRCA1/2 mutation (9 of 1212) than in controls who did not have a history of breast cancer in their families (2 of 2081, $P = 0.0030$). Mutations in this gene may impart a 2.0 relative risk of breast cancer (95% CI: 1.2-3.2, $P = 0.012$). However, further characterization of this risk and other possible cancer risks is warranted.

NBN

The NBN protein is a member of the MRE11A/RAD50 double-strand break-repair complex that consists of 5 proteins. As part of this complex the NBN product is believed to be involved in DNA damage–induced checkpoint activation and DNA double-strand break repair, suggesting that it may function