High-, Moderate-, and Low-Penetrance Genes Involved in the Pathogenesis of a Hereditary Predisposition to Breast Cancer

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Breast cancer is the most common malignancy in women in the United States and the second leading cause of cancer-related death. The American Cancer Society estimates that in 2013, there will be approximately 232,000 new cases of breast cancer (of which 2,000 will be in males) and 40,000 related deaths.¹

A family history of breast or ovarian cancer, bilateral breast cancer, and early age of onset suggest a hereditary predisposition. However, a predisposing gene is identified in less than 30% of cases with suggestive features.² The vast majority of these cases are due to highly penetrant, but rare, genes. In recent years, additional rare, moderate-penetrance genes and common, low-penetrance alleles also have been identified. Despite this, in many cases of suspected familial breast cancer, no predisposing gene is identified. This review will discuss the known genetic causes of breast cancer and the issues associated with characterizing and understanding hereditary predispositions to breast cancer.

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High-Penetrance Genes

The first major gene associated with hereditary breast cancer was **BRCA1**, which was identified in 1990 via linkage analysis of families with suggestive pedigrees. In 1994, **BRCA2** was mapped to chromosome 13. A mutation in either **BRCA1** or **BRCA2** confers an increased risk for breast and other cancers. Clinically, this is referred to as the hereditary breast-ovarian cancer (HBOC) syndrome, although there are patients with this same clinical picture who are found to be negative for mutations in both **BRCA1** and **BRCA2**. Research into HBOC has focused on determining the associated risk for breast and other cancers, identifying specific clinical and histopathologic features, and developing therapeutic and prevention strategies.

Tumors due to mutations in **BRCA1** tend to be of the basal-like phenotype, with a higher histologic grade; they commonly are negative for the estrogen receptor (ER), progesterone receptor (PR), and Her2/neu, the so-called “triple-negative” tumor. **BRCA2**-related tumors more closely resemble sporadic tumors.

**BRCA1** and **BRCA2** mutations are inherited in an autosomal dominant fashion but act recessively on the cellular level as tumor-suppressor genes involved in double-stranded DNA (dsDNA) break repair. Female carriers of mutations in **BRCA1** or **BRCA2** have a lifetime risk for breast cancer of 50% to 85%, which is greater than 10 times the average population risk. Male carriers of **BRCA1** have an increased risk for breast cancer, although to a lesser degree than carriers of **BRCA2**, who have a 7% lifetime risk. Additional features of the syndromes are detailed in Table 1, most notably an increased risk for ovarian cancer, with an estimated lifetime risk of 54% for **BRCA1** carriers and 23% for **BRCA2** carriers. Bi-allelic **BRCA2** greatly increases the risk for childhood cancers with the clinical picture of Fanconi anemia type D. There is no corresponding effect noted for **BRCA1**, and, thus, it is thought to be embryonically lethal.

Mutations in **BRCA1** and **BRCA2** are estimated to explain only 15% of familial breast cancers. There are subpopulations with higher cancer frequencies due to founder mutations, most prominently the Ashkenazi Jewish population, in which 3 major mutations (**BRCA1** 185delAG, **BRCA1** 5382insC, and **BRCA2** 6174delT) alone account for approximately 10% of hereditary

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**Table 1. Breast Cancer High-Penetrance Genes and Their Associated Syndromes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Breast Cancer Incidence</th>
<th>Other Associated Cancers</th>
<th>Non-malignant Syndrome Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>Hereditary breast-ovarian cancer syndrome</td>
<td>82% lifetime risk</td>
<td>Ovarian and fallopian tube cancer, prostate cancer, pancreas and biliary cancer, melanoma</td>
<td></td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
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<tr>
<td><strong>PTEN</strong></td>
<td>PTEN hamartoma tumor syndrome, Cowden syndrome</td>
<td>85% lifetime risk</td>
<td>Non-medullary thyroid cancer, endometrial cancer, GU tumors, especially renal cell carcinoma</td>
<td>Pathognomonic skin changes, macrocephaly, benign breast and thyroid disease, uterine fibroids, Lhermitte-Duclos disease, fibromas, lipomas, intestinal hamartomas, mental retardation</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Li-Fraumeni syndrome</td>
<td>25% by age 74</td>
<td>Sarcoma, brain tumor, adrenocortical carcinoma, leukemia, bronchoalveolar cancer; multiple other cancers are seen but more rarely</td>
<td></td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>Hereditary diffuse gastric cancer</td>
<td>39% lifetime risk of lobular breast cancer</td>
<td>Gastric cancer (diffuse subtype), colorectal cancer</td>
<td></td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Peutz-Jeghers syndrome</td>
<td>32% by age 60</td>
<td>GI cancers (esophagus, stomach, small bowel, colon), pancreatic cancer, sex-cord stromal tumors</td>
<td>GI hamartomatous polyposis, hyperpigmented macules, hyperestrogenism</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; GU, genitourinary

* There are additional patients with this clinical phenotype, but they do not have an identified mutation in either **BRCA1** or **BRCA2**.
cases.7 With sequencing and haplotype analysis, additional population subgroups also have demonstrated founder mutations.12 Additional rare but highly penetrant genes include PTEN,13 TP53,10-17 CDH1,14 and STK11,19,20 each connoting a distinct clinical syndrome, as described in Table 1. Collectively with BRCA1 and BRCA2, it is estimated that the known high-penetrance genes account for no more than 25% of cases based on prior studies and mathematical modeling.11,21

It is crucial to recognize individuals with a hereditary cancer syndrome because this greatly affects their clinical management. The National Comprehensive Cancer Network guidelines recommend that women with mutations in BRCA1, BRCA2, or one of the other high-penetrance genes should perform monthly breast self-examinations starting at age 18.22 From age 25 (or 10 years before the youngest case in the family, whichever is earlier), clinical breast exam, mammogram, and breast magnetic resonance imaging (MRI) should be performed annually. Prophylactic salpingo-oophorectomy is recommended for women with mutations in BRCA1/2 by age 35 to 40, or earlier if child bearing is complete or there is indication based on the family history.23 This reduces the risk for ovarian cancer (although there is a residual risk for primary peritoneal cancer), and reduces breast cancer risk if it is performed before menopause.23,24 Prophylactic mastectomy, with discussion of a nipple-sparing approach, also may be considered due to the high lifetime risk for both primary and contralateral breast cancers.25,26 Tamoxifen has been shown to reduce the risk for ER-positive breast cancer in women with increased risk based on the Gail model, but it has not been well studied in BRCA mutation carriers. Biologic characteristics and limited clinical data suggest that tamoxifen may reduce the risk for breast cancer in women with a BRCA2 mutation who have not undergone prophylactic oophorectomy before menopause.27-29 As for sporadic tumors, medical treatment of hereditary breast cancer historically has been dictated by histology, immunohistochemistry, and stage. Early clinical data suggest that BRCA-associated tumors are exquisitely sensitive to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors, agents that inhibit the DNA damage-repair mechanism PARP, but these currently are only available in the setting of clinical trials.30

**Moderate-Penetrance Genes**

Linkage studies have failed to demonstrate additional reproducible loci for highly penetrant genes that predispose individuals to breast cancer,11 prompting new directions for efforts to elucidate hereditary causes for this disease. Specifically, genes proposed to increase the risk for breast cancer based on their known cellular functions have been screened for mutations in families with pedigrees suggestive of a predisposition to breast cancer. Positive studies have found CHEK2,31 BRIP1 (BACH),32 ATM,33 and PALB234 to be associated with breast cancer; each confers about a 2-fold increase in risk for breast cancer. As described in Table 2, these genes play a role in DNA repair, interacting with either BRCA1 or BRCA2. CHEK2 *1100delC, the most common mutation, is seen in 1% of the population overall but in higher numbers in breast cancer patients.31 There is no additional increase in risk for carriers of a mutation in BRCA1 or BRCA2 with CHEK2, possibly due to an overlapping effect on DNA repair.31 Additional genes involved in DNA damage repair, including RAD51C and genes in the MRN DNA repair pathway (MRE11, RAD50, NBN [NBS1]) also have been investigated. However, when high-risk families were screened, no mutations were clearly associated with cancer.35-37 It still is possible that somatic mutations within tumors, or founder effects in unique populations, are present and contribute to cancer development and progression.36,38,39

Studies performed in the United Kingdom in BRCA mutation-negative women with a personal or family history have estimated that these moderate-penetrance genes account for 2.3% of familial breast cancer cases. Some of these studies are underpowered to comment on an earlier age of onset or other associated syndrome features.2 Because these genes confer a lower lifetime risk for breast cancer than the highly penetrant genes described earlier, clinical management, including screening and preventive interventions, of women with mutations in moderate-penetrance genes is less clearly defined. Clinical management should incorporate risk assessment tools, such as the Gail and Tyrer-Cuzick models,40 which emphasize a woman’s personal and family history of cancer and precancerous lesions, along with established breast cancer risk factors, to determine risk. For women with a calculated lifetime risk for breast cancer of at least 20% by virtue of a family history, annual breast MRI is recommended in addition to standard mammography.41,42 Additionally, all women with a higher than average risk for breast cancer should have a clinical breast examination performed every 6 months.

**Low-Penetrance Alleles**

As laboratory techniques and sequencing capabilities have advanced, genome-wide studies have been performed to identify single-nucleotide polymorphisms (SNPs) that may contribute to breast cancer risk in a polygenic fashion. These studies require thousands of cases and controls to have sufficient power to appreciate a change in risk because individual alleles may be relatively common and even found in a majority of the population.2 An extremely stringent P-value (P<0.0001 or better) is required to minimize false-positives.3

A small number of polymorphisms associated with breast cancer risk have been noted in known breast cancer-associated genes. For example, a Pro919Ser polymorphism in BRIP1 is associated with an odds ratio of 1.39 (P=0.002) in premenopausal women but was
Table 2. Breast Cancer Moderate-Penetrance Genes and Associated Breast Cancer Risks

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Breast Cancer Risk</th>
<th>Bi-allelic Phenotype</th>
</tr>
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</table>
| CHEK2      | Protein kinase involved in cell cycle regulation at G2; rapidly phosphorylated in response to DNA damage; activated CHEK2 stabilizes p53 and interacts with BRCA1 | **Female:** RR, 1.70; 95% CI, 1.3–2.2  
**Male:** RR, 10.3; 95% CI, 3.5–30.0 | None known—presumed to be embryonic lethal                                      |
| BRI1P (BACH1) | Interacts with the BRCA1 C-Terminus (BRCT) domain of BRCA1               | **All women:** RR, 2.0; 95% CI, 1.2–3.2  
**Women younger than 50 y:** RR, 3.5; 95% CI, 1.9–5.7 | Fanconi anemia, type J—no significant increase in childhood cancers              |
| ATM        | Protein kinase involved in monitoring and repair of dsDNA and regulation of BRCA1 and CHEK2 | RR, 2.37; 95% CI, 1.5–3.8 | Ataxia-telangiectasia—autosomal recessive inheritance                                 |
| PALB2      | Associates with BRCA2. Involved in nuclear localization and stability        | **All women:** RR, 2.3; 95% CI, 1.4–3.9  
**Women older than 50 y:** RR, 3.0; 95% CI, 1.4–5.5 | Fanconi anemia type N—higher incidence of childhood cancers                    |

CI, confidence interval; RR, relative risk

not associated with an increased risk for breast cancer in the overall population. Often, low-penetrance SNPs are located in noncoding regions of the genome (eg, 2q35, 8q24), making it more difficult to identify an associated gene. The mutation mechanism may be activation of growth-promoting genes rather than inactivation of DNA repair. On average, each allele only mildly increases risk and is additive per allele rather than multiplicative, with a 1.07- to 1.26-fold increase in risk for heterozygotes and a 1.65-fold increase for homozygotes.

The majority of studies thus far have focused on one or a few variants at a time. However, a recent large meta-analysis assessed the examined variants to date, excluding those in highly penetrant genes. This analysis excluded the first report of a variant, as well as small studies (<500 samples) and studies involving groups not deemed to be in Harvey-Weinberg equilibrium. Strong associations were seen for 10 variants across 6 genes—ATM, CASP8 (cysteine-aspartic acid protease family with a role in apoptosis), CHEK2, CTLA4 (encodes an inhibitory signal to T cells, affecting carcinogenesis via anti-tumor immunity), NBN, and TP53—and moderate associations were seen for 4 variants across 4 genes—ATM, CYP19A1, TERT, and XRCC3. Odds ratios greater than 2 were seen for truncating mutations in ATM and NBN and for 3 rare variants in CHEK2. However, the remainder had a more minor calculated effect. Additional studies have not yet been published regarding the clinical application, frequency, or relative risk of these variants. Thus, evaluation for low-penetrance alleles is not part of standard clinical evaluation for breast cancer, and management of individuals found to carry these variants should be based on their estimated risk as calculated by validated risk assessment models, such as the Tyrer-Cuzick and Gail models.

**Mutation Testing in Those With Suspected Hereditary Predisposition to Breast Cancer**

Individuals with a family and personal history suspicious for a familial syndrome should be referred to a genetic counselor for a comprehensive evaluation. Testing for mutations in cancer-associated genes is individually based, and requires a high index of suspicion for a particular gene based on the clinical situation. In general, when a family history is suggestive, it is best to test an individual with a cancer diagnosis because this increases the probability of a positive test result. Standard clinical BRCA1 and BRCA2 testing has been performed using polymerase chain reaction amplification and Sanger sequencing. For the Ashkenazi Jewish population, testing can be targeted to the 3 major founder mutations. In 2007, testing for large rearrangements was added for secondary analysis after research studies published the relatively frequent finding of missed large insertions and deletions. If a mutation is identified in one family member, targeted testing can be done for other members of the family to assess risk. With testing, possible outcomes are a true positive, a true negative (ie, an individual in a family with a known mutation tests negative for that mutation), uninformative (ie, a negative test in a family where a mutation has yet to be identified), or a variant of unknown significance (VUS). By definition, a VUS is a detected genetic change without good description of any correlating clinical risk.
In patients who test negative for mutations in *BRCA1* and *BRCA2* but in whom the family history is suggestive of an inherited predisposition, there are emerging options for additional evaluation. For example, the BROCA assay, developed by researchers at the University of Washington, is a 21-gene assay that includes the 10 previously mentioned high- and moderate-penetrance genes, the panel of genes known to predispose to colon cancer, and promising low-penetrance genes. With next-generation sequencing, multiple genes can be tested for mutations at a fraction of the cost of sequencing genes individually,\(^4^5\) and this may be useful in detecting mutation changes not identified by conventional sequencing, such as large rearrangements.\(^4^6\) This is especially helpful in patients with a more rare cause for their hereditary predisposition to cancer or women with a less obvious history, including those with fewer female relatives, paternal inheritance of the gene, and few other relatives who have inherited the predisposing gene.\(^4^5\)

However, with more detailed genetic analysis, an increased amount of indeterminate information often is obtained. Thus, next-generation sequencing testing will require careful analysis and interpretation of VUS. As costs for genomic assays have decreased, the number of commercially available assays billed as personal genomic testing (PGT) has increased substantially, but our ability to interpret the results of these assays remains limited. A major concern with this new avenue of medical risk assessment is that patients and physicians often feel underinformed regarding the interpretation of results. In a survey of more than 10,000 physicians, 98% felt that PGT results may influence drug therapy, but only 10% believed they were adequately informed about how to interpret the results.\(^4^7\) In a survey of individuals who elected PGT testing, 10% discussed their results with the company genetic counselor and only 27% chose to share results with their physician, increasing risk that the test would be associated with inadequate counseling and interpretation.\(^4^8\) Limited data suggest that in the appropriate clinical setting, PGT can be effective in modulating clinical behavior.\(^4^7\)

**Conclusion**

A hereditary predisposition to breast cancer significantly influences screening, treatment, and surveillance recommendations. However, despite decades of medical research, less than 30% of cases with a suggestive personal and/or family history of hereditary breast cancer have an identified causative gene mutation. The vast majority of these cases are due to a mutation in one of the highly penetrant breast cancer genes (*BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11*), and current guidelines provide concrete direction for the management of these patients. A minority of cases is due to mutations in moderate-penetrance genes (*CHEK2, ATM, BRIP1, and PALB2*). A small number of low-penetrance alleles have been identified using advanced genetic testing methods. Although these may contribute to risk in a polygenic fashion, this is likely to be relevant to a minority of cases, and identification of these low-penetrance alleles is not part of routine practice patterns. In such patients, standard models are used to predict an individual’s lifetime risk by clinical history rather than genomic information. At this point, mutation testing requires a high index of suspicion for a specific contributing etiology, but next-generation sequencing may improve the identification of such genes and the clinical management of breast cancer.

**References**


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