Hereditary Breast and Ovarian Cancer: The BRCA1 and BRCA2 Genes
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Introduction
Breast cancer is the most frequently occurring cancer among women, with an estimated 178,480 new cases and 40,460 related deaths in 2007. Most female breast cancer is caused by a combination of factors, including environment, genes, and lifestyle. Among known risk factors are advanced age, high breast density, family history of breast cancer, older age at first childbirth, nulliparity, early age at menarche, late age at menopause, presence of benign breast disease, history of high-dose radiation to the chest, recent oral contraceptive use, post-menopause hormonal replacement therapy, obesity after menopause, decreased physical activity, and consumption of one or more alcoholic beverages per day. Approximately 5–10% of breast cancer cases are believed to be due to mutations in high-penetrance susceptibility alleles. Rarely, mutations in TP53 (Li-Fraumeni Syndrome), PTEN (Cowden Syndrome), ATM (Ataxia Telangiectasia Syndrome), and CHEK2, among others, appear to contribute to a hereditary predisposition to breast cancer. Approximately 2–3% of all breast cancer cases are directly attributable to mutations in two predisposing genes, BRCA1 and BRCA2.

Family history is the greatest risk factor for ovarian cancer. Approximately 10% of epithelial ovarian cancers are believed to be hereditary. Mutations in BRCA1 and BRCA2 are responsible for 90% of these cases. Most of the remaining 10% are thought to occur as part of the Hereditary Non-Polyposis Colon Cancer (HNPCC) syndrome.

BRCA1 and BRCA2
Hereditary breast and ovarian cancer syndromes caused by mutations in BRCA1 (on chromosome 17q21) and BRCA2 (on chromosome 13q12-13) are autosomal dominant in their transmission. It is important to understand that males can transmit BRCA mutations and related breast cancer predisposition to their female offspring, although they themselves have limited risks of contracting the disease. The prevalence of breast cancer in women with disease-causing mutations in BRCA1 and BRCA2 has not been established with certainty and likely varies among populations and pedigrees. Nevertheless, the cumulative lifetime breast cancer risk for female BRCA1 and BRCA2 carriers appears to exceed 80%. Susceptibility to ovarian cancer may be greater in carriers of BRCA1 mutations.
than in BRCA2 mutation carriers, with these risks estimated at 40–50% for BRCA1 carriers and 20–30% for BRCA2 carriers, respectively.\textsuperscript{5}

**Genetic Testing**

Myriad Genetics in Salt Lake City, Utah,\textsuperscript{7} has been able to obtain U.S. patent rights to the BRCA1 and BRCA2 genes, specific genetic variants, and related diagnostic testing, despite a legal prohibition against patenting natural phenomena that dates to litigation over Samuel Morse's patents on the telegraph.\textsuperscript{8} Although the "natural phenomenon doctrine" would appear to prohibit enforcement of patents that directly or indirectly claim ownership of genotype-phenotype correlations, Myriad has used the threat of patent infringement litigation to prevent many laboratories from testing for mutations in BRCA1 and BRCA2.\textsuperscript{9} As a result, Myriad is by far the largest provider of BRCA testing in the United States.

The U.S. Preventive Services Task Force (USPSTF) recommends referral for genetic counseling and evaluation for genetic testing for women with family histories that place them at increased risk for BRCA mutations.\textsuperscript{10} Several mathematical models have been used to assist in pretest counseling and select candidates for BRCA testing, although the efficacy of these models has been questioned.\textsuperscript{11} Included among the personal and family characteristics that are associated with an increased risk for deleterious BRCA mutations are:\textsuperscript{10}

- A relative with a known mutation in BRCA1 or BRCA2;
- Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger;
- A personal history of breast cancer diagnosed at an early age;
- A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis;
- Bilateral breast cancer in the patient or a first-degree relative;
- Two primary cases of breast cancer in the patient or one or more family members;
- A combination of both breast and ovarian cancer in the patient or among first- and second-degree relatives;
- A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis;
- A first- or second-degree relative with both breast and ovarian cancer at any age;
- A family history of breast cancer in a male relative (also a personal history of breast cancer for a male patient).

For women of Ashkenazi Jewish heritage:

- A first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer.
Every effort should be made to first test an affected individual within an apparent hereditary breast and ovarian cancer family to establish the presence or absence of a detectable mutation in the pedigree. Women with early onset disease are most likely to carry a BRCA mutation. Therefore, if possible a family member with early-onset breast or ovarian cancer should be tested initially to avoid the possibility of testing a coincidentally sporadic patient within a mutation-positive hereditary breast and ovarian cancer pedigree. If an affected individual is not tested before unaffected at-risk family members, the significance of a negative test result in an unaffected family member is unclear. Moreover, initially testing a family member most likely to carry a mutation allows for later testing of at-risk family members at significantly reduced cost if a family-specific mutation is identified.

Specific testing for ethnic founder mutations, such as the 187delAG*, 5385insC**, and 6174delT variants found in Ashkenazi Jews, should be initially ordered in appropriate risk-related individuals. Likewise, in pedigrees with a previously identified mutation, testing for this mutation is ordered for at-risk family members. In high-risk families that do not carry an applicable, high-frequency ethnic variant, and in other pedigrees that are at elevated risk for a BRCA mutation, direct sequencing of the BRCA1 and BRCA2 coding and junctional regions is the gold standard for mutation detection. Additional procedures can be used to identify genomic rearrangements that cannot be found by direct sequencing. These combined methods will detect mutations in 90% of pedigrees with demonstrated linkage to BRCA1 or BRCA2.6

BRCA1 or BRCA2 mutations may not be detected in families that appear to carry inherited breast cancer syndromes because their specific BRCA mutations are not detectable by current testing methods, they have phenocopy mutations in other known or unknown genes, or there exists chance clustering of breast cancer cases within the particular families.

Genetic variants of unknown significance can present diagnostic dilemmas. These are most often missense changes that are not ordinarily seen in the population. Testing multiple family members for the variant to assess segregation with disease can increase or decrease the likelihood that such a genetic change is cancer-causing. Linkage studies may also be useful in some families in whom BRCA mutations are not detected. In addition, the National Human Genome Research Institute has established a Breast Cancer Information Core to act as such an international repository of mutations and polymorphisms associated with the BRCA genes.12

In conclusion, BRCA surveillance is not recommended as routine screening in the general population. However, for identified individuals at increased risk for a hereditary breast and ovarian cancer syndrome, BRCA testing is an invaluable tool for subsequent risk reduction management.
*Also known as "185delAG."
**Also known as “5382insC.”

References


