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Risk Assessment, Genetic Counseling, and Clinical Care for Hereditary Breast Cancer

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ABSTRACT

During the last 30 years, key advances in the field of cancer genetics have improved identification of high-risk families in which cancer risk can be linked to mutations in cancer susceptible genes. Identification of individuals with heritable cancer risk may influence short- and long-term medical management issues. Heightened screening and risk reducing options can offer lifesaving interventions for the woman and family members who are at risk.

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Approximately one of every eight women (13%) in the United States will develop breast cancer in her lifetime; of these 80% are diagnosed when they are older than age 50 (Howlader et al., 2013). Compared to women without a family history, the risk of breast cancer is twofold for women with one affected first-degree relative, threefold for women with two affected first-degree relatives, and nearly fourfold for women with three or more affected first-degree relatives. Risk to relatives is also affected by the age of breast cancer diagnosis with earlier ages of onset being more suggestive of inherited or genetic risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Pharaoh, Day, Duffy, Easton, & Ponder, 1997).

Family history of breast cancer is one of the most well recognized risk factors for the disease, although only 5% to 10% of all breast cancer is considered hereditary (Claus, Schildkraut, Thompson, & Risch, 1996; Pharaoh et al., 2002; Whittemore, Gong, & Itnyre, 1997). Generally hereditary breast cancer is indicative of the presence of a mutation in a highly penetrant gene such as *BRCA1*, *BRCA2,* or *TP53,* which have profound effects on breast cancer risk. However, genetic risk for breast cancer is heterogeneous, and not all risk that runs in families can be attributed to mutations in these high-risk genes. Other genes increase risk more moderately, and in some cases multiple genes inherited together may create a genetic profile of risk. Genetic testing opportunities have largely focused on testing for rare genes with very significant impact on risk, and testing for these genes will continue to be critically important. This review provides clinicians with guidance about hereditary conditions including breast cancer, obtaining and interpreting relevant personal and family histories, performing risk assessments, identifying genetic testing candidates, and helping patients understand how these assessments may influence their long-term medical management, as well as provide their families with critical and potentially lifesaving information.

Major Inherited Cancer Syndromes Including Breast Cancer

Most of the major inherited cancer susceptibility syndromes involving breast cancer are inherited by an autosomal dominant mechanism and are due to germline (inherited) mutations in tumor suppressor genes. Such genes are important in maintaining genomic stability by promoting precise DNA repair as cells replicate and divide.

Accurate and thorough collection of family history remains the cornerstone of cancer risk assessment and identification of high-risk families.

This concept was first studied in patients with retinoblastoma and Wilm's tumor, demonstrating that deficiencies in this process may lead to a diagnosis of cancer (Cavenee et al., 1983; Pritchard-Jones, 1997). Genetic conditions inherited in an autosomal dominant fashion require only one gene in the gene pair be nonfunctional to manifest increased cancer risk. Those who carry a disruptive gene mutation have a 50% chance to pass it along to each child, regardless of gender – males and females are equally at risk for inheriting a gene mutation although cancer risks for men and women may vary. Autosomal dominant genes do not skip a generation – a person who did not inherit a mutated copy of a dominant cancer susceptibility gene from a parent cannot then pass it along to the next generation.

Penetrance, or the chance that an inherited gene mutation will lead to a cancer diagnosis, may vary in families due to the existence of other risk modifying genes that interact with a high-risk cancer susceptibility gene like *BRCA1* or *2*. In addition penetrance may be affected by the coexistence of other endogenous or lifestyle risk factors. Further research into modifiers of major cancer risk genes will allow individuals who carry these mutations to be offered more tailored risk estimates on which to base their decisions. Personalized risk estimates that incorporate the impact of risk modifier genes are not yet available, so counseling about cancer risks are based on the best estimates available from large collaborative studies.

Due to inherited mutations in the *BRCA1* and *BRCA2* genes, hereditary breast ovarian cancer syndrome (HBOC) is perhaps the best characterized of the hereditary cancer syndromes. Inherited mutations in *BRCA1/2* dramatically increase risk for a variety of cancers as outlined in Table 1. Since 1996 clinical genetic testing for mutations in *BRCA1/2* has been exclusively commercially available in the United States through Myriad Genetics, and in 2013 reinterpretation of patent law allowed other commercial labs to offer this testing.

Mutations in the *BRCA1/2* genes are found in every ethnic and racial group. About one in 500 individuals carry an inherited mutation in either gene, but those who are of Ashkenazi or Eastern European Jewish ancestry have a significantly higher or one in 40 chance of carrying a mutation in either gene (Tonin et al., 1996). Knowledge about Jewish ancestry can have a profound effect on the prior probability of a *BRCA1/2* mutation and is therefore an important component of breast cancer risk assessment.

Breast cancer is a major component of Li-Fraumeni syndrome (LFS), a condition associated inherited mutations in the gene *TP5*3 that predisposes individuals to a strikingly high lifetime risk for a wide variety of cancers. Although the *TP53* gene is one of most commonly somatically mutated genes in human cancer, inherited germline mutations in *TP53* are rare. This condition was initially characterized by Li and Fraumeni in families with pediatric soft-tissue sarcomas, early-onset breast cancer, adrenocortical carcinoma, and brain tumors. These tumors remain highly characteristic of LFS. The classic clinical criteria for the diagnosis of LFS are an individual diagnosed with sarcoma younger than age 45, and a first-degree relative with any cancer younger than age 45, and a first- or second-degree relative with any cancer younger than age 45 or sarcoma at any age (Li et al., 1988). Families meeting the classic familial criteria for LFS have the highest chance of having a detectable germline mutation found in *TP53*, but the clinical presentation has been recognized more recently to be quite variable. Additional clinical diagnostic and testing criteria have been developed to broaden chances of identifying this syndrome (Birch et al., 1994; Chompret et al., 2001; Tinat et al., 2009) and are summarized in Table 2 along with criteria for genetic testing.

Breast cancers associated with LFS can manifest extraordinarily early, occasionally presenting in teenagers and adults in their early twenties, although the median age of onset is age 33. Breast cancer accounts for 50% of all female cancers in those with LFS, and women have an overall lifetime cancer risk approaching 90% (Olivier et al., 2003). Individuals with LFS commonly develop multiple primary malignancies, with the risk of a second cancer approaching 57% at 30 years beyond the initial diagnosis, and the risk of a third primary cancer of 38% at 10 years beyond the second diagnosis (Cohen, Curtis, Inskip, & Fraumeni, 2005; Malkin et al., 1992). A significant number of individuals (7%–20%) are the first ones in their family to have LFS as a result of a de novo, or new mutation arising in the formation of the egg or sperm that participated in fertilization (Gonzalez et al., 2009). Therefore, the typical autosomal dominant pattern may not be present.