Clinical Assessment of Breast Cancer Risk Based on Family History

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Key Words
Breast cancer, family history, risk assessment

Abstract
Family history is a key component of breast cancer risk assessment. Family history provides clues as to the likelihood of a hereditary breast cancer syndrome and the need for a cancer genetics referral and can be used in the setting of a breast cancer risk assessment model to estimate a woman’s risk. Appropriate breast cancer screening and risk reduction management plans rely on an accurate assessment of a patient’s family history. This article reviews the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction and provides insight into the application of the guidelines in clinical practice. (JNCCN 2010;8:1148–1155)

Breast cancer is the most common cancer among women in the United States with a lifetime risk of 1 in 8 (12%).1 Multiple risk factors for breast cancer have been identified and include gender, age, race, benign breast disease (atypical ductal hyperplasia [ADH], atypical lobular hyperplasia [ALH], lobular carcinoma in situ [LCIS]), age at menarche, parity, breast feeding, diethylstilbestrol (DES) exposure, early breast radiation, hormone replacement therapy, obesity, alcohol intake, family history, and genes. Based on all these factors, breast cancer risk assessment can be difficult, but is necessary to provide women with the most accurate estimate of their risk and the most appropriate risk management options. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) provide recommendations for the management of breast cancer risk based on many of these risk factors, but one of the most important risk factors is family history and/or genetics.

The NCCN Breast Cancer Risk Reduction Guidelines
The NCCN Guidelines for Breast Cancer Risk Reduction advise evaluating the family history of cancer to determine a woman’s breast cancer risk. The purpose of the guidelines is to identify women with a hereditary form of breast cancer, and to identify those without hereditary forms but who are still at increased risk based on a family history of breast cancer. Approximately 5% to 10% of breast cancers are hereditary or can be attributed to genetic mutations in tumor suppressor genes. Hereditary forms of breast cancer tend to occur at earlier ages than breast cancers in the general population, and are often associated with an increased risk of multiple primary breast cancers.

The most common hereditary breast cancer syndrome is hereditary breast and ovarian cancer, which is caused by mutations in the BRCA1 and BRCA2 genes. Mutations in these genes account for approximately 60% to 80% of all inherited breast cancers.2 Other hereditary cancer syndromes associated with an increased risk of breast cancer include Li-Fraumeni syndrome, caused by mutations in the p53 gene; Cowden disease, caused by mutations in the PTEN gene; and hereditary diffuse gastric cancer, caused by mutations in the CDH1 gene. The familial/genetic criteria outlined in the NCCN Guidelines is designed to determine which...
Application of the NCCN Guidelines in Clinical Practice

Obtaining a Family History
To use the guidelines appropriately, clinicians must ask patients about their family history of cancer. Ideally, a 3-generation pedigree should be obtained and should include the patient, children, siblings, nieces and nephews, parents, maternal and paternal aunts and uncles, maternal and paternal cousins, and maternal and paternal grandparents. For each family member, the pedigree should note family members’ vital status, their current age or age at death, cancer diagnoses, and age at cancer diagnoses. The presence or absence of Ashkenazi Jewish ancestry should also be noted, as the chance of carrying a $BRCA1$ or $BRCA2$ mutation increases from approximately 1 in 500 to 1 in 800 in the general population to 1 in 40 in the Ashkenazi Jewish population. An example of a 3-generation pedigree can be seen in Figure 1. When performing risk assessment for a patient, it is important to consider both the patient’s maternal and paternal family histories of cancer, because the genes that are associated with an increased risk of breast cancer can be inherited from the maternal and paternal lineage. However, the maternal and paternal family histories must be considered separately, because they are not genetically related to one another.

Unfortunately, not many clinicians have the time or staff to obtain a complete 3-generation pedigree for every patient. Thus, clinicians may wish to consider including a checklist on their intake form that either mirrors or closely mimics the familial/patients/families might benefit from further evaluation for these hereditary cancer syndromes. Table 1 summarizes the hereditary breast cancer syndromes included in the NCCN Guidelines. Identification of women affected by hereditary cancer syndromes is important because, in many cases, proven screening and risk reduction modalities are available. For example, a woman carrying a $BRCA1$ or $BRCA2$ mutation can be offered the following risk management options: semiannual breast cancer screening using both mammogram and breast MRI; chemoprevention in the form of tamoxifen, which may reduce breast cancer risk by up to 50%; prophylactic mastectomy, which reduces breast cancer risk by 90% to 95%; and prophylactic oophorectomy, which reduces breast cancer risk by 55% to 70% if performed premenopausally.

However, not all women with a family history of breast or other cancers will be affected by a known hereditary cancer syndrome. Nonetheless, these women still have an increased risk of breast cancer based on their family history. Multiple epidemiologic studies have shown that a family history of breast cancer is a reliable predictor of risk. Having one first-degree relative (mother, sister, or daughter) increases a woman’s risk for breast cancer twofold, and having 2 first-degree relatives increases the risk fivefold. A woman’s risk of breast cancer can also be increased if a second-degree (aunt, niece, or grandmother) or third-degree (cousin) relative has or had breast cancer. Overall, the risk for breast cancer is related to the number of affected relatives, their degree of relatedness, and their age at breast cancer diagnosis.

Table 1 Hereditary Breast Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Breast Cancer Risk</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>$BRCA1$</td>
<td>50%–85%</td>
<td>Increased risk of ovarian/fallopian tube/primary peritoneal cancer</td>
</tr>
<tr>
<td></td>
<td>$BRCA2$</td>
<td></td>
<td>Increased risk of pancreatic and possibly other cancers ($BRCA2$ only)</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>$p53$</td>
<td>Exact risk unknown, but up to a 90% lifetime risk for any cancer</td>
<td>Increased risk of cancers such as sarcomas, brain tumors, leukemias, and adrenocortical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>An excess of cancer diagnosed in people younger than 30 years</td>
</tr>
<tr>
<td>Cowden</td>
<td>$PTEN$</td>
<td>25%–50%</td>
<td>Increased risk of thyroid and endometrial cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Affected individuals often have macrocephaly, trichilemmomas, papillomatous papules, and hamartomatous polyps</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer</td>
<td>$CDH1$</td>
<td>Up to 40% (lobular only)</td>
<td>Increased risk of diffuse/signet ring/isolated cell-type gastric cancer</td>
</tr>
</tbody>
</table>
Clinicians should also remember that family history is dynamic and can change over time, so patients’ family history information will need to be updated regularly.

**Referral to a Cancer Genetics Professional**

When a woman meets one or more of the familial/genetic risk factors outlined in the NCCN Guidelines, a referral to a cancer genetics professional is recommended. The purpose of referral is so that the patient’s breast cancer risk can be accurately estimated by evaluating the likelihood of a hereditary breast cancer syndrome, and accounting for the patient’s family history of breast cancer using a series of risk assessment models. Patients should be advised that this may require obtaining further family history information, and may include genetic testing for her or her family members. Genetic testing recommendations will be made by the cancer genetics professional based on a complete assessment of the patient’s family history. Once genetic testing is complete, or if genetic testing is deemed unnecessary, the cancer genetics professional can then apply the relevant risk models to best assess the patient’s lifetime risk of breast cancer.

Cancer genetics professionals may include various health care providers, such as genetic counselors, nurses, physicians’ assistants, geneticists, and oncologists. The National Society of Genetic Counselors (NSGC; www.nsgc.org), the NCI (http://www.cancer.gov/search/geneticsservices/), and the National Center for Biotechnology Information (NCBI; www.genetests.org) have searchable databases to help identify cancer genetics professionals throughout the country and even the world. Each cancer genetics professional and associated clinic may have different requirements for accepting referrals and scheduling appointments, and therefore clinicians are advised to contact the clinic and become familiar with its process.

**Cancer Genetic Risk Assessment**

To better understand how to manage patients who have an increased risk of breast cancer based on family history, a basic understanding of the process of cancer genetic risk assessment and the possible results and recommendations of cancer genetic risk assessment is necessary. The foundation of breast cancer risk assessment is the construction of a 3-generation family history, which informs appropriate clinical genetic testing recommendations. Genetic testing recommendations specify not only which tests are indicated but also who in the family is the best candidate for genetic testing.
is most informative when an affected family member is tested first. Thus, patients who are referred for cancer genetic risk assessment may need to prepare themselves to discuss genetic testing with family members. However, in some circumstances an unaffected person in the family may be the first person to undergo genetic testing, such as when affected family members are deceased. In any case, the benefits, risks, limitations, testing process, and possible results of genetic testing should be discussed. The goal of this discussion is to allow the patient to make an informed decision regarding genetic testing and to understand how genetic testing may influence her breast cancer risk management.

Genetic Test Results

Patients who undergo genetic testing can receive 3 possible test results: positive, negative, or variant of uncertain significance (VUS).

A positive result means that a mutation that is known to be deleterious was identified and the patient is at increased risk for certain types of cancer. The increased cancer risks may include breast cancer and various other cancers, depending on which gene the mutation was identified. A positive result does not guarantee that a patient will develop breast or other cancers, nor does it predict at what age a cancer might develop. A positive result allows the patient and her physician to consider more aggressive screening or risk reduction options, which will be discussed in greater detail later in this article.

The next possible outcome is a negative result, which actually has 2 possible types: true-negative and inconclusive negative. A true-negative result can only occur when a positive result has previously been identified in a family member. A true-negative result is achieved when the patient undergoes testing for the mutation that was identified in her relative and she is found not to have the same mutation. In contrast, an inconclusive negative result occurs when a patient undergoes genetic testing and no deleterious mutations are identified. Inconclusive negative results require an individualized breast cancer risk management plan based on the patient’s personal and family history.

The last possible genetic test result is a VUS. With a VUS, the mutation’s effect on the gene function is unknown. A VUS could be a deleterious mutation that is associated with an increased risk of cancer, or it could be a harmless change in the gene that is not at all associated with an increased risk of cancer. A VUS also requires an individualized breast cancer risk management plan based on the patient’s personal and family history.

Breast Cancer Risk Assessment Models

The American Cancer Society recently recommended that breast MRI should be used as an adjunct to mammogram in patients whose lifetime breast cancer risk is greater than 20% to 25% based on models largely dependent on family history.3 This recommendation emphasizes the importance of family history in breast cancer risk assessment and clinical management. If genetic testing is deemed unnecessary, or once genetic testing is complete, and if an inconclusive negative result or a VUS is identified, breast cancer risk assessment models can be used to estimate a woman’s breast cancer risk and make appropriate recommendations about risk management. The Gail,15 Claus,16 and Tyrer-Cuzick17 models are some of the more commonly used models that estimate breast cancer risk. Table 2 summarizes the risk factors incorporated into each of these models, and their strengths and limitations. Notably, these models are different from models such as BRCAPRO or BOADICEA, which are more commonly used to estimate the likelihood of a BRCA1 or BRCA2 mutation. Additionally, these models are not appropriate for use in women with a known deleterious gene mutation associated with a hereditary breast cancer syndrome, because the models will likely underestimate the woman’s breast cancer risk.

The accuracy of any breast cancer risk assessment depends on the accuracy of the reported family history. In general, breast cancer is often accurately reported in families, whereas abdominal cancers, such as gynecologic cancers, are often misreported.18 The cancer genetics professional will work with the patient to try to obtain the most accurate family history possible, either through medical or death records, or asking follow-up questions regarding how the cancer was diagnosed or treated. Finally, the cancer genetics professional will choose the models that best account for the patient’s personal and family history risk factors for breast cancer.
Incorporating the Results of Cancer Genetic Risk Assessment into Clinical Management

Ideally, when a patient returns from a referral to a cancer genetics professional, she should have a summary of which genetic tests were performed, if any; the results of each genetic test; and her breast cancer risk based on the relevant breast cancer risk assessment models. The physician must then use this information to create an individualized breast cancer risk management plan. In general, clinical management of patients at potentially increased risk for breast cancer can be divided into 3 groups: 1) patients with known or highly suspected hereditary breast cancer syndromes; 2) patients unaffected by hereditary breast cancer syndromes with a 20% or greater lifetime breast cancer risk; and 3) patients unaffected by hereditary breast cancer syndromes with a less than 20% lifetime breast cancer risk. A flow chart outlining these categories and the relevant NCCN Guidelines can be seen in Figure 2.

Management of Patients with Known or Highly Suspected Hereditary Breast Cancer Syndromes

If a patient returns from a cancer genetic risk assessment with a known *BRCA1*, *BRCA2*, *p53*, *PTEN*, or *CDH1* gene mutation, she will require either high-risk breast screening or risk reduction therapy, depending on her personal preferences. High-risk breast screening typically includes breast self-awareness, semiannual or annual clinical breast examination, annual mammogram, and annual breast MRI beginning between 25 and 35 years of age, depending on the hereditary breast cancer syndrome or family history of breast cancer.19 Breast MRI has consistently been shown to be more sensitive than mammograms in the high-risk population; however, mammograms may be better than MRIs at detecting DCIS,3 and therefore both modalities are recommended. The appropriate timing of and interval between mammograms and breast MRI remain to be determined. However, some women will desire chemoprevention or prophylactic mastectomy to reduce their risk, and physicians should be prepared to discuss the benefits and limitations of screening versus risk reduction.

Unfortunately, family history of breast or other cancers cannot be used to predict breast cancer risk in these patients. Published risk ranges are available for each of the hereditary breast cancer syndromes.10

Patients with highly suspected hereditary breast cancer syndromes may also require breast cancer risk

### Table 2 Breast Cancer Risk Assessment Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Personal Risk Factors</th>
<th>Family History Risk Factors</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Gail      | Age, age at menarche, age at first live birth, number of breast biopsies, and presence of atypia | Breast cancer in first-degree relatives                                                    | Easily accessible online  
Well validated                                                                 | Family history limited to 2 first-degree relatives, which limits use in evaluating patients for breast MRI  
Age of breast cancer diagnosis not included  
Limited to women aged 35 years and older                                                                 |
| Claus     | None                                                                                  | Breast cancer diagnosis and age of diagnosis in first- and second-degree relatives           | Easily accessible through computer software and in published tables  
Incorporates more family history than Gail                                                                 | Does not account for personal risk factors                                                                 |
| Tyrer-Cuzick | Age at menarche, age at parity, age at menopause, presence of hyperplasia or atypical hyperplasia, lobular carcinoma in situ, ovarian cancer, height, weight, use of hormone replacement therapy, and BRCA genetic test results | Breast and ovarian cancer diagnosis and age of diagnosis in first-, second-, and third-degree relatives  
BRCA genetic test results | Incorporates many personal and family history risk factors, and BRCA test results  
Can only be performed with a computer program  
Requires extensive family history information |
management. Highly suspected hereditary breast cancer syndromes are those in which the family history is suggestive (e.g., multiple early-onset cases of breast and ovarian cancer or multiple cases of ovarian cancer only), but genetic testing has failed to identify a deleterious mutation. Families such as these are often managed as if they have a known hereditary breast cancer syndrome, because the family history is so compelling. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian outline the appropriate clinical management for individuals with known or highly suspected hereditary breast cancer syndromes (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Finally, although some physicians are comfortable managing patients with this very high risk of breast cancer, others choose to refer these patients to established high-risk screening and risk reduction clinics in their geographic area. The cancer genetics professional that tested the patient should be able to recommend appropriate high-risk clinics. Clinics may also be found through the clinic directories of the NCI (http://www.cancer.gov/search/geneticservices/) or the NCBI (www.genetests.org). Physicians should also be aware that patients with hereditary breast cancer syndromes are at increased risk for other cancers besides breast cancer, and may require high-risk screening or risk reduction for these other sites (Table 1).

**Management of Patients Unaffected by Hereditary Breast Cancer Syndromes With 20% or Greater Lifetime Breast Cancer Risk**

If a patient returns from cancer genetic risk assessment and is not found to be affected by a hereditary breast cancer syndrome but has a significant family history of breast cancer, her risk can be estimated using one of the risk assessment models described in Table 2. If the patient's lifetime breast cancer risk is calculated to be 20% or greater using one of these models, the benefits and risks of screening with breast MRI as an adjunct to mammogram should be discussed. This recommendation was first described by the American Cancer Society in 2006 and is based on evidence from nonrandomized screening trials and observational studies. Typically, breast screening in these women should begin 10 years earlier...
Management of Patients Unaffected by Hereditary Breast Cancer Syndromes With Less Than 20% Lifetime Breast Cancer Risk

In many cases, patients will be found to be unaffected by a hereditary breast cancer syndrome and will have a less than 20% lifetime risk of breast cancer based on their family history. Nonetheless, family history is still an important part of estimating breast cancer risk for these women. Most notably, family history may affect the calculation of a woman’s 5-year breast cancer risk, and thus her eligibility for chemoprevention. The NCCN Guidelines for Breast Cancer Screening and Diagnosis for women at increased risk and the NCCN Guidelines for Breast Cancer Risk Reduction can be used in these cases, depending on whether the woman is eligible for chemoprevention (available at www.NCCN.org).

Included in this category are women with a family history of a known hereditary breast cancer syndrome gene mutation who have tested negative for the familial mutation (i.e., “true-negatives”). True-negatives have the same cancer risk as the general population and do not require high-risk screening or risk reduction. Additionally, the risk assessment models should be performed with caution in these cases, because they will often overestimate a woman’s breast cancer risk. These women should follow the NCCN Guidelines for Breast Cancer Screening and Diagnosis for women at “normal” risk, unless they develop personal risk factors for breast cancer, such as ADH or LCIS.

Conclusions

Given the importance of family history in risk assessment, the NCCN Guidelines advise obtaining patients’ family histories and incorporating family history into risk management plans. Family history will inform appropriate cancer genetics referrals and can be used in the setting of breast cancer risk assessment models to estimate a woman’s 5-year and lifetime breast cancer risk. The addition of family history in risk assessment will ideally better identify women at increased risk and result in better patient care.

References

Breast Cancer Risk and Family History