Risk of Breast and Ovarian Cancer in Women With Strong Family Histories

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Assessing the risk of breast and ovarian cancer starts with obtaining a complete and accurate family history. This can reveal evidence of inherited cancer risk. The highest risk of cancer is associated with germ-line abnormalities.

Introduction

Approximately 30% of individuals with breast cancer have some family history of cancer (generally breast and/or ovarian cancer).[1,2] However, the majority of women who present with a family history of cancer will not have a history that is suggestive of an autosomal dominantly inherited disorder (cancer in multiple generations). It is estimated that only 5% to 10% of breast and ovarian cancers are associated with a strong family history of cancer and are, therefore, likely to be attributed to inheritance of a mutation in a known cancer-causing gene.[3] Current information suggests that these genes may be grouped into high-, moderate-, and low-risk genes.[4] Genes that confer the greatest lifetime cancer risk can be thought of as high-risk genes.

In this article, we will focus on BRCA1, BRCA2, and TP53 (aka p53) as high-risk genes.[3] Moderate-risk genes are inherited in an autosomal dominant fashion with lower penetrance and therefore less cancer risk. Low-risk genes can be associated with the smallest cancer risk. These genes and their risk for cancer are less well understood, and the associated cancer risks are controversial. Likely, cancer attributable to low-risk genes develops later in life and is linked to significant environmental exposure.[5,6]

The commercial availability of genetic testing for cancer risk introduces a new dimension in the assessment of breast and ovarian cancer risk. Genetic testing for cancer risk is a complex process. Appropriate individuals for testing should have the highest likelihood, within a family, of carrying a cancer-causing gene mutation. Before undergoing genetic testing, individuals must understand the risks, benefits, and limitations of genetic testing. This includes understanding the psychological and ethical issues that surround genetic testing.

The first steps in this process are gathering an accurate family history and recognizing the features of hereditary breast and ovarian cancer. It is also important to understand the options that are available for individuals who are at high risk of cancer (those with a family history or found to be gene mutation carriers).

High-risk cancer screening is available; however, these screening recommendations are based on expert opinions and are largely unproven. Options for cancer prevention include prophylactic surgery (oophorectomies, mastectomy) and chemoprevention. The ability to counsel and provide an accurate assessment of risk and appropriate screening recommendations for these individuals is critical for the provider. We present guidelines for risk assessment in individuals with a family history of breast and ovarian cancer and review the management issues involved in caring for this group of women.

Gathering the History

Even in this era of microchip technology, an accurate family history continues to be the most informative tool for assessing cancer risk. Despite its importance in assessing risk, obtaining a family history is rapidly becoming a lost skill. Significant deficits exist in the documentation of family history in the primary care setting. This may stem from a diminution of the time that is available for physician and patient interactions, as well as a lack of emphasis during physician training. In one
cross-sectional study, a family history was obtained in only 50% of new patient visits and was updated in 22% of established patient visits.[7]

The first step in obtaining an accurate cancer family history involves gathering information to generate a pedigree that spans at least three generations. The history should include all types of cancer in both the paternal and maternal lineage, since breast and ovarian cancer risks can be transmitted through the father. For each affected relative, it is important to try to ascertain the site of the primary tumor, laterality of disease, age at diagnosis, treatment, and age at death. Eliciting information about unaffected family members is key to interpreting the family history and should include cause of and age at death. If the total number of female relatives is small, significant expression of an inherited gene may not be apparent. Gathering information about the presence of other chronic diseases in the family, such as osteoporosis and coronary artery disease, is important since this information may influence management recommendations (eg, recommendations for hormone replacement therapy).

Studies have shown that family history information that identifies breast or colon cancer as a primary cancer site in first-degree relatives may be accurate in 89% to 91% of cases.[8] However, the accuracy rate for such information decreases in the case of second- and third-degree relatives. Often, the diagnosis of premalignant conditions may be confused with cancer, and sites of recurrence can be misidentified as second primary tumors. Hence, procuring pathology reports or medical records to verify a family history of cancer is strongly recommended. Ascertaining ancestry is an integral component of the process. The existence of specific mutations (eg, BRCA1/BRCA2) in certain populations makes ethnicity-based testing an important option to consider.

Current advances in technology may incorporate new tools such as computer programs to record genetic information,[9] but physicians will continue to play an important role in the interpretation of this information and the definition of risk. Future developments in genetic research will only serve to increase the importance of an accurate family history. All physicians should develop methods to capture family history at the time of an initial patient visit and then periodically update this information.

**Features of Hereditary Breast and Ovarian Cancer**

Certain features of an individual's personal or family history may lead the clinician to suspect an inherited predisposition to breast and/or ovarian cancer. A personal history of early breast cancer (onset at age < 50 years) or bilateral breast cancer may be a clue to a genetic predisposition. Additionally, breast and ovarian cancer in the same individual may herald the presence of hereditary malignancies. As we will discuss later, a history of ovarian cancer or early breast cancer plus Ashkenazi Jewish ancestry carries a significant risk of an inherited form of the diseases.

Inherited factors may play a role when the above personal history coexists with early-onset breast cancer, bilateral breast cancer, male breast cancer, or ovarian cancer in more than one generation. The presence of other cancers in the family, such as cancers occurring at early ages (eg, colon cancer at age < 50 years) or cancers without the usual risk factors (such as lung cancer in a nonsmoker) may be clues to an inherited form of cancer. See [Table 1](#) for a list of other cancers that can be associated with hereditary breast or ovarian cancer.

Families vary in size, and it is important to take into account the number of individuals within a family, as well as the number of women at risk. For example, a small family with few women over age 40 diagnosed with one early breast cancer and ovarian cancer can be significant, whereas a very large family with several women over age 60 affected with breast cancer may be less likely to carry a genetic alteration in BRCA1/2.

Breast and ovarian cancer are features of several hereditary syndromes. Families with clear autosomal dominant patterns of inheritance are in the minority (5% to 10% of all individuals with either breast or ovarian cancer).[3] More than 70% percent of such families will be found to carry mutations in BRCA1 or BRCA2.[3] Individuals with BRCA mutations have high lifetime cancer risks and will be discussed below as high-risk genes. Other syndromes, such as Cowden's disease,
hereditary nonpolyposis colorectal cancer (HNPCC), Muir-Torre syndrome, and Peutz-Jeghers syndrome also display autosomal dominant patterns of inheritance. However, these carry a lower penetrance and, therefore, a lesser lifetime risk of cancer. These syndromes have a moderate lifetime cancer risk, and the genes associated with the syndromes have often been termed moderate-risk genes.

Low-risk genes carry the lowest risk of cancer (relative risks of 2.0 to 7.0) but are likely to be more prevalent than either high- or moderate-risk genes. Therefore, they contribute more to the overall development of cancer. To date, low-risk genes have not been associated with ovarian cancer, and consequently, only low-risk genes associated with the risk of breast cancer will be discussed in this article. See Table 2 for a list of high-, moderate-, and low-risk genes, their associated syndromes, and lifetime risk of breast and/or ovarian cancer.

High-Risk Genes

The greatest lifetime risk of breast and ovarian cancer is conferred by mutations in either BRCA1 or BRCA2. Since their identification, we have learned much about these two genes over the years. First identified in 1994,[10] BRCA1 is a large gene located on chromosome 17. The gene codes for a protein, 1,836 amino acids in length. More than 500 mutations have been detected in this gene. BRCA2, identified in 1995, is approximately twice as large as BRCA1 and is located along chromosome 13.[11] Over 300 mutations in this gene have been detected. The exact functions of BRCA1/2 are unclear; however, evidence suggests that these genes are involved in DNA repair.[12]

Mutations in BRCA1/2 account for a small percentage of all breast or ovarian cancer cases. However, they account for the majority (70%) of hereditary breast and ovarian cancers, with “other” genes held responsible for the remaining 30%.[3,13] Much research has been carried out to quantitate the contribution of hereditary breast and/or ovarian cancer to specific populations.[14] Several studies have examined groups of young women with breast cancer.[15-18] In aggregate, these studies suggest that the contribution of BRCA1 to early-onset breast cancer (diagnosed before age 45) is less than 10%. In all of these studies, a woman with early breast cancer was more likely to carry a mutation if she had a family history of breast cancer.

Founder mutations are genetic abnormalities that are commonly seen in a specific population. They are found when a population has been reduced to small numbers because of war, famine, or geographic isolation, and then expands. The most clinically important examples of this phenomenon are the three founder mutations (two in BRCA1 and one in BRCA2) that exist in the Ashkenazi Jewish population.[19,20] Studies of Jewish women suggest that approximately 30% of Jewish women diagnosed with breast cancer prior to age 45, and 30% to 60% of Jewish women diagnosed with ovarian cancer will harbor one of the three common mutations.[21-23] These three mutations account for more than 90% of all BRCA mutations in the Jewish population.

Women with mutations in BRCA1 or BRCA2 have a 56% to 87% probability of developing breast cancer by age 70.[24,25] The risk of a second primary cancer (often defined as breast cancer in the contralateral breast or separate quadrant of the ipsilateral breast) is thought to be between 40% and 60%.[26]

Ovarian cancer risk differs between these two genes. BRCA1 is associated with a 15% to 44% lifetime risk of ovarian cancer, while BRCA2 has a 10% to 27% lifetime risk.[26,27] There is a risk of prostate and colon cancer for carriers of BRCA1 mutations, with relative risks of 3.3 and 4.0, respectively.[25] Men with mutations in BRCA2 have a 6% lifetime risk of male breast cancer.[26] Individuals with BRCA2 mutations appear to be at risk for other types of cancer as well.

Cancers with an estimated relative risk greater than 2.0 include gastric, gallbladder, pancreatic, and prostate carcinoma, as well as melanoma.[26] The probability of finding a mutation in BRCA1/2 based on a specific family history is discussed later. Further information regarding BRCA1/2 can be found in the Breast Cancer Linkage Consortium website (www.medfac.leidenuniv.nl/lab-devilee/bclichome.htm).

Li-Fraumeni syndrome is a cancer family syndrome associated with multiple types of cancer
(soft-tissue sarcomas, breast carcinoma, brain tumors, leukemia, and adrenal cortical carcinoma), with cancer often presenting at very early ages. Germ-line mutations in TP53, a tumor-suppressor gene, have been identified in these families.[28] Breast cancer is a significant component of this syndrome, with the majority of patients being affected before age 45, and with a high incidence of bilateral metachronous tumors.[29] The lifetime risk of cancer may be higher than 50%; however, there are no published studies that quantify breast cancer risk with this syndrome.

Moderate- and Low-Risk Genes

Compared to BRCA1 and BRCA2, the role of moderate- and low-risk genes in the causation of breast and ovarian cancer is less well defined. As we have discussed above, moderate-risk genes have lower penetrance than BRCA1/2 (conferring a lower lifetime cancer risk). Low-risk genes include those genes associated with chromosome fragility, carcinogen metabolism, and regulation of steroid hormone levels. Little information is available regarding ovarian cancer and low-risk genes, and therefore, our discussion will focus only on breast cancer risk.

Low-risk genes will be far less penetrant than moderate- and high-risk genes, but may actually account for more cases of breast cancer because alterations in these genes are likely to be more prevalent. Clinically, the tumors attributable to low-risk genes are likely to present at a later age, and the usual pattern of cancer in every generation may not be seen.[4] See Table 2 for lifetime cancer risks associated with the genes discussed below.

Moderate-Risk Genes: Syndromes associated with moderate risk of breast and/or ovarian cancer likely account for a very small proportion of hereditary breast and ovarian cancer. Cowden’s disease is a rare disorder that is inherited as an autosomal dominant trait. Individuals often have pathognomonic facial trichilemmomas, oral mucosal papillomas, and fibroadenomas of multiple organs (breast and uterine being the most common). Breast cancer has been described in a large number of female patients with this syndrome.[30] A lifetime risk estimate of 30% to 50% for breast cancer has been quoted for patients with this syndrome.[31] Germ-line mutations of PTEN have been associated with Cowden’s disease kindreds.[32] Individuals with either Cowden’s disease or germ-line mutations of PTEN may also be at risk of nonmedullary thyroid carcinoma.

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by mucocutaneous hyperpigmentation, hamartomatous polyps, and malignancy. Germ-line mutations in STK11, a gene coding for a serine/threonine kinase, have been found in families with Peutz-Jeghers syndrome.[33] The incidence of breast cancer associated with this syndrome is not well characterized. Women in these families tend to develop early and bilateral breast cancer.[34]

Hereditary nonpolyposis colorectal cancer is an autosomal dominantly inherited syndrome associated with an increased risk of ovarian cancer, as well as other cancers. Germ-line mutations in the family of DNA mismatch repair genes (MSH2, MLH1, MSH6, PMS1, and PMS2) can be found in HNPCC families. Members of HNPCC kindreds have a high lifetime risk for both colonic and extracolonic cancers. An analysis of the Finnish HNPCC Registry data revealed a lifetime risk of 9% for ovarian cancer among putative gene carriers.[35] Although molecular evidence suggests that breast cancer may be associated with the HNPCC syndrome,[36] the frequency and lifetime risk are unknown.

A syndrome similar to HNPCC, Muir-Torre syndrome is defined by a detected association between malignancy (colonic and extracolonic) and sebaceous skin tumors (sebaceous gland tumors and keratoacanthomas). The spectrum of malignancies seen in these patients is similar to HNPCC, and germ-line mutations of MSH2 and MLH1 have been identified in individuals with Muir-Torre syndrome.[37] Both benign and malignant breast tumors are seen in patients with Muir-Torre syndrome; however, a clear lifetime risk of breast cancer is not known.[38]

Low-Risk Genes: Ataxia telangiectasia (AT) is an autosomal recessive disease associated with mutations in the ATM gene, an elevated lifetime risk of leukemia and lymphomas, and sensitivity to radiation-induced damage. The role of the ATM gene in breast cancer risk is controversial. Studies[39] have demonstrated an elevated risk of breast cancer for AT heterozygotes. However, subsequent studies have provided conflicting data.[40] Increased utilization of mammographic
screening by individuals who have one or more abnormal copy of the ATM gene may be associated with an increased risk of breast cancers. However, no studies to date have been able to demonstrate this.

Polymorphisms are genetic abnormalities that are frequently seen in the general population. They have little or no significant impact on the structure or function of the gene. Specific polymorphisms in genes that code for a number of enzymes involved in carcinogen metabolism have been associated with increased risk of breast cancer. The studies in this field often reveal conflicting results. In Table 2, we have attempted to outline cancer risk from the best-studied genes (CYP1A1, CYP17, GSTM1, and NAT2).[41-48]

Hormone exposure is believed to be a significant risk factor for the development of breast cancer. Catechol-O-methyltransferase (COMT) catalyzes the O-methylation of catechol estrogens, which causes inactivation. Low-activity alleles of COMT were reported to be associated with increased breast cancer risk in postmenopausal women with a high body mass index (odds ratio [OR] = 3.58).[49-50] Additional studies have not been able to support these findings.

The HRAS1 proto-oncogene has function in mitogenic signal transduction. It is tightly linked to a microsatellite locus downstream. The microsatellite region is highly polymorphic and certain mutant alleles are associated with an increased risk of breast (OR = 2.29) and other cancers.[51]

The current level of information on low-risk genes is inadequate to move testing into the clinical setting. Genetic polymorphisms, however, are more prevalent than high-risk genes and may ultimately account for a higher population-attributable risk.[6]

**Assessing Personal Risk of Breast or Ovarian Cancer**

It is well known that women often overestimate their personal risk of breast cancer.[52-53] For women who have breast and ovarian cancers in their families, providing an accurate assessment of lifetime cancer risk can reduce cancer-related anxiety. This is often an important function of cancer-risk assessment clinics. Today, every woman has a 12.2% lifetime risk of breast cancer and a 1.5% lifetime risk of ovarian cancer.[54-55] Although the exact cause of either malignancy remains unknown, risk factors for these diseases do exist.

The two most important risk factors for either breast or ovarian cancer are age and family history. Having one first- or second-degree relative with ovarian cancer increases the lifetime risk of ovarian cancer to between 5% and 7%.[56] To date, there are no more accurate estimates for the lifetime risk of ovarian cancer based on family history or other risk factors.

Having a first- or second-degree relative with breast cancer can significantly increase a woman’s lifetime risk of breast cancer.[57] Several models exist for the assessment of lifetime risk of breast cancer: The Gail and Claus models are the most commonly utilized examples.[58,59]

**The Gail Model**

The Gail Model combines a variety of hormonal and other risk factors (onset of menarche, age at first live birth, number and outcome of breast biopsies) with a very limited family history (number of first-degree relatives with breast cancer).

The Gail Model has been validated and proven to accurately predict risk of breast cancer.[60] This model is quite limited in evaluating potential hereditary breast cancer. The family history is limited to first-degree relatives, thus excluding paternal transmission of cancer. Additionally, no information about other types of cancer, age of cancer diagnoses, or ethnicity (other than white, black, Asian, and Hispanic) is obtained. Calculation of 5-year and lifetime breast cancer risks according to the Gail Model can be performed by accessing the National Cancer Institute’s website (www.nci.nih.gov) and searching for information on breast cancer risk.

**The Claus Model**
The Claus model provides more helpful information for women who have a family history of breast cancer.[59] Using the first- and second-degree family history and age at diagnosis, a lifetime risk of breast cancer can be derived. Thus, a woman with a mother and sister diagnosed with breast cancer, both at age 45, would have a 35% lifetime risk of developing breast cancer (see Table 3). This model is most effective when there are only one or two relatives with cancer. Thus, it may underestimate risk when there is a high likelihood of a BRCA1/2 mutation. Additionally, this model does not take into account cases of ovarian cancer and may underestimate cancer risk where there is paternal transmission of cancer.

Assessing the Probability of BRCA1/2 Mutations

The clinical availability of genetic testing of cancer risk means that we now have ways to more clearly quantitate cancer risk for individuals with a strong family history of cancer. If there is a known genetic alteration within a family, then specific individuals may undergo genetic testing and find that they are either at the general population risk of cancer (no mutation identified) or at a greatly increased risk of cancer (mutation-positive). It becomes important to identify which families are the best candidates for genetic testing. The first step in this process is to gather a complete family history, as outlined above.

Quantifying the probability of finding a mutation in the two most common breast cancer genes, BRCA1 and BRCA2, is difficult. For other hereditary cancer syndromes, criteria have been established to assist in identifying individuals who are most likely to have inherited cancer. Clinical criteria exist for identifying Li-Fraumeni syndrome families, and Amsterdam or Bethesda criteria are used for identifying families that are likely to have HNPCC.[29,61,62] To date, however, there have been no generally accepted criteria for either hereditary breast cancer, hereditary ovarian cancer, or hereditary breast/ovarian cancer.

**Criteria for Identifying High-Risk Families:** Several research studies have utilized criteria for identifying high-risk families. These criteria, while using the features of hereditary breast and ovarian cancer as discussed in Table 1, have not been consistent from study to study. In general, these criteria have included cancer in first- or second-degree relatives.

The more widely accepted criteria for identifying high-risk families have been established by Myriad Genetics Laboratory (Salt Lake City, Utah) for use in their beta testing of BRCA1/2 sequencing. In this study, women were eligible if they were diagnosed with either early breast cancer (diagnosed at age < 50 years) or ovarian cancer and had at least one first- or second-degree relative with either early breast or ovarian cancer. Using these uniform criteria, mutations in BRCA1 or BRCA2 were found in 39% of women.[63]

Hereditary breast and ovarian cancers are most likely a heterogeneous set of disorders, and thus, it has been difficult to develop a set of criteria that will identify families that are most likely to carry a BRCA1/2 mutation. The first study to estimate the probability of finding a mutation in BRCA1/2 based on family history was by Couch et al.[64] This study was based on families that presented to high-risk clinics for evaluation. Recent information suggests that the presence of ovarian cancer within a family may be more predictive of a BRCA1 mutation than the number of breast cancer cases in a family.

**Risk Estimation Models:** Two models for risk estimation—the Myriad and BRCAPRO models[65,66]—have become popular.[63] Using data from 235 women with breast cancer before age 50 or ovarian cancer (at any age) and at least one first- or second-degree relative with either early breast cancer or ovarian cancer, Frank et al were able to develop modeled probabilities of carrying a mutation in BRCA1/2.63 This Myriad model utilizes extended family history information, age at breast cancer diagnosis, and presence of ovarian cancer in the family. As an expansion of this model, mutation prevalence data were made available by Myriad Genetic Laboratories (www.myriad.com/med/brac/mutptables.html). This information, which is regularly updated, represents individuals who have undergone clinical genetic testing for mutations in BRCA1 and BRCA2 by Myriad Genetic Laboratories. The tables found on this website can be used to estimate the likelihood of finding a mutation in BRCA1/2 based on extended family history, age of breast cancer
diagnosis, and ethnicity (ie, Ashkenazi ancestry or not). Table 4 represents a summary of the data on their website.

The second popular model is a computer program called BRCAPRO, developed by investigators at Duke University.[65,66] This model utilizes first- and second-degree family history, presence of breast cancer (male or female) and/or ovarian cancer, age at diagnosis of cancer, ethnicity, and size of the family to estimate the probability of finding a mutation in BRCA1/2. This model is being widely used clinically. A multisite validation study has shown BRCAPRO to be an accurate tool for determining the probability of BRCA1/2 mutations (personal communication, D. Berry, 2000). The BRCAPRO computer program is required when using this model. Further information can be found at www.jhsph.edu/biostats/brcapro.html.

Genetic Testing and Counseling

When deciding to undergo genetic testing, one needs to consider the likelihood of finding a specific germ-line mutation (positive result), as well as the appropriateness of genetic testing for the individual and family; eg, will it change medical management for the individual or other family members? No established guidelines exist for undergoing genetic testing for BRCA1/2. The American Society of Clinical Oncology recommends that a 10% prior probability of BRCA mutation be used as a guideline for offering genetic testing.[67]

As genetic testing for breast and ovarian cancer susceptibility genes has moved from the research laboratory into the clinical setting, interest in this field has increased rapidly. In surveys, 70% to 90% of women with a family history of breast and ovarian cancer expressed interest in undergoing genetic testing. Among first-degree relatives of cancer patients, interest in testing is associated with cancer worry and mood disturbance.[68] There is also a tendency among these individuals to overestimate the benefits and underplay the risks of genetic testing.[69] Women who desire genetic testing are more likely to have a heightened perception of personal risk for being a mutation carrier.

Genetic testing offers a unique method to accurately determine individual risk in families that have an inherited susceptibility to breast and ovarian cancer. Benefits of testing are not universally applicable to all individuals with a family history of cancer. Most women, regardless of their family history, present with the belief that, in terms of their cancer risk, a simple "yes or no" answer will be revealed by testing. The majority of women seek genetic testing as a means to quantify risk for their children and to end uncertainty.[68,70] More importantly, high-risk women might view genetic testing as part of their information-seeking process or as one of their coping strategies.

Thus, the first step in the process must be education. This involves providing information about the basic principles of inheritance and the concepts of inherited and sporadic cancer, along with a personalized assessment of risk and benefits, and limitations of testing as applicable to that individual. These discussions can be time consuming and often require a multidisciplinary approach that includes genetic counselors, medical geneticists, oncologists, and nurses.

Educating the Patient

Studies have shown that genetic counseling has a significant impact on the perception of risk by women who are referred to familial cancer clinics.[53] Combining education with a discussion of psychosocial issues and individual reactions to testing contributes greatly to the changing perception of the risks and benefits of genetic testing.[71]

Genetic testing for mutations that predispose to cancer is not as straightforward as testing for single-mutation diseases, such as sickle cell anemia or Huntington's disease. As a substantial proportion of breast and ovarian cancer is sporadic, more than one family member can be affected by chance. Thus, decisions of whom to test and the interpretation of results are complex and should be part of the discussion before embarking upon genetic testing.

The process of genetic testing should begin with the individual in the family who is most likely to be carrying a germ-line mutation in BRCA1/2. This is always a person with cancer (an affected
individual) and is usually the person who has developed cancer at an early age or has an unusual form of cancer (ie, bilateral or multiple primary cancers or rare cancers, such as adrenal cortical carcinoma or osteogenic sarcoma).

Interpretation of genetic test results can be complicated. For the first individuals tested in a family, three types of results are possible:

(1) A deleterious or functional mutation is identified, meaning that the identified mutation is known to interrupt the function of the gene and/or be associated with breast and ovarian cancer in other families. This is a positive result, and this individual has the risk of cancer outlined above and in Table 2. There is now a test to offer others in the family (testing for the specific identified mutation). This test will be either positive (a mutation is identified) or negative (no mutation is identified), and can be performed on both affected and unaffected individuals.

(2) No mutation may be identified. For the first person tested in a family, there are two possible interpretations of this result. If the person is not affected with cancer or has a cancer that is not usually associated with BRCA mutations (such as late-onset breast cancer), then there may still be a mutation in the family, but you have not tested the right person. This is considered a false-negative result. Alternatively, a mutation in BRCA1/2 may not exist in either the individual or the family. Cancer in the latter case may be associated with other genes (not yet identified or not tested for). In either case, recommendations for screening and medical management must be based on the family history.

(3) A mutation of uncertain significance may be identified. In this case, it may not be known whether this mutation is a normal variant of BRCA1/2 (genetic polymorphism) or truly a disease-causing mutation. This test result cannot be used to test others in the family, and recommendations for screening and medical management (discussed below) must be based on the family history.

Limitations of Genetic Testing

Individuals planning to undergo genetic testing must be aware of the limitations of testing. Testing may miss genetic abnormalities in BRCA1/2 that actually exist within a family. For example, this is true if there is a large deletion of the gene. A large deletion will not be picked up through DNA sequencing, because the presence of the normal copy of the gene makes the result appear normal.

As many as 30% of families with breast and ovarian cancer may actually have a germ-line mutation in BRCA1 or BRCA2 that is not identified by conventional genetic testing for these two genes.[13] If no mutation can be identified within a family, it may mean that other genes (not yet identified for which no genetic test is available)[14] are operating in that family. A positive test result (a mutation in BRCA1/2) can only provide an estimation of cancer risk, as not all individuals who test positive will actually develop cancer. Recommendations for the management of mutation carriers are largely based on expert opinion (see below). Prior to undergoing genetic testing, individuals must understand the uncertainty associated with both high-risk cancer screening and options for prevention.

Psychological Distress

The psychological issues involved with testing cannot be underestimated. Discussion of a family history of cancer and the possible implications of genetic tests for other family members, including children, can induce strong emotional responses that need to be dealt with in order to make a balanced decision regarding testing. As discussed earlier, women at high risk often have higher levels of anxiety and psychological distress at baseline. In one study of 60 patients, BRCA1 mutation carriers manifested greater levels of psychological distress 1 to 2 weeks after genetic test results were revealed[15] even when pretest and posttest counseling was provided.[72] When genetic testing is offered without counseling, it may have an even more negative impact on psychological functioning.

Other studies have shown no significant increase in depressive symptoms in BRCA1 mutation carriers.[73] Feelings of guilt may be an unexpected result of testing among both mutation carriers and noncarriers. Guilt among affected persons often stems from worry of transmitting the gene to
children. Among persons who test negative, "survivor guilt" may be observed. Although initially relieved that they do not have high levels of cancer risk, individuals will often feel guilty that they do not have the same risk of cancer as their siblings.

Insurance Discrimination

Fear of insurance discrimination is one of the most cited concerns by patients regarding genetic testing. To address this concern, the Health Insurance Portability and Accountability Act was passed in July 1997. This act prohibits group health insurance plans from using genetic testing results to determine eligibility for coverage or to increase premiums. On a local level, 28 states have enacted laws to prevent the use of presymptomatic genetic testing information by health insurers to discriminate against potential subscribers.

There are no well-documented cases that demonstrate health insurance denial or discrimination on the basis of genetic test results, but these laws have not been adequately tested in our legal system. The choice of the majority of consumers not to disclose genetic testing results to insurance companies or employers without written consent demonstrates the degree of concern with which they view disclosure of this information. Thus, even legal deterrents do not completely allay the fears that individuals have regarding the potential misuse of information obtained from genetic testing.

Effect on Other Family Members

Genetic testing applies to the entire family and not just the tested individual. Testing of one individual has implications for other family members. The mutation status of an untested family member can be revealed through the genetic testing of other relatives. For example, a daughter who tests positive for a mutation found in another maternal relative (aunt or cousin) will reveal the genetic status of her mother, as the mother will be an obligate carrier of that mutation. On occasion, the family member who is most appropriate for testing may refuse to participate, making genetic testing impossible to interpret for other family members. Reviewing the potential impact of genetic testing for the entire family prior to testing may often prevent future problems. Counseling should focus not only on the impact of testing for the immediate family, but on developing a plan for disclosure of results to other family members.

Informed Consent

Counseling is an integral part of the process of obtaining informed consent. The American Society of Clinical Oncology and the National Society of Genetic Counselors have both endorsed the importance of a thorough discussion of the risks, benefits, and limitations of genetic testing prior to signing a written consent form. Certified genetic counselors serving locations across the nation can be identified by accessing the website of the National Society of Genetic Counselors (www.nsgc.org).

Follow-up After Genetic Testing

Following disclosure of test results, counseling involves a discussion of the implications of the results both for the tested individual and other family members. For individuals who test negative when there is a mutation in other family members, it is important to reiterate that the general population risk of breast and ovarian cancer still exists. For persons testing negative without a mutation in the family, it must be stressed that testing does not exclude the possibility of hereditary cancer especially if there is a strong family history of cancer. For mutation carriers, the focus of discussion centers on high-risk cancer screening recommendations and available management options, which might include chemoprevention or prophylactic surgery (see below). Additional follow-up counseling should be offered either in person or by telephone. A letter detailing the pretest discussion, the test results, and follow-up recommendations is an excellent tool for reference (both for the individual and other family members).

The goal of genetic testing is to provide information that can be used to improve cancer screening and offer management options to women at high risk of breast and ovarian cancer. Several studies have shown that high levels of anxiety can pose a barrier to adhering to cancer screening
recommendations.[77] Education and counseling have the potential to empower women at high risk with an understanding of the complex issues that surround genetic testing and to encourage active participation in cancer screening and prevention strategies.

**Management of Hereditary Breast and Ovarian Cancer**

Women at increased risk of breast or ovarian cancer have several medical options to consider. Expanded cancer screening is frequently offered. Although screening will not prevent cancer, it can diagnose cancer at an earlier stage—ones associated with better survival. Prophylactic surgery and chemoprevention using selective estrogen-receptor modulators (SERMs) or oral contraceptives are modalities that have been associated with lowering the risk of breast and/or ovarian cancer. Additionally, issues of hormone replacement therapy must be considered in women at increased risk of breast cancer. We will briefly discuss these issues, as well as discuss the implications of a strong family history of breast and ovarian cancer in women with newly diagnosed breast cancer.

**Breast Cancer Screening in Women at High Risk**

Women who have a greater-than-average risk of either breast or ovarian cancer are candidates for increased cancer surveillance. Cancer screening recommendations are often tailored to the family history and to the individual’s personal risk of breast or ovarian cancer. The benefits of screening for women at high risk have not been proven in clinical trials. When making recommendations for increased cancer surveillance in either BRCA1/2 carriers or women at increased risk, it is important to discuss the limitations of screening, as well as the unproved nature of screening recommendations.

Screening mammography has been associated with improved survival for women over age 50.[78,79] Women between the ages of 40 and 49 also benefit from mammography, but that benefit is smaller.[80] More frequent breast cancer screening is recommended for women who are found to carry BRCA1/2 mutations.[81] Recommended screening includes monthly breast self-examination, twice-yearly clinical breast examination, and yearly mammography starting at age 25 (see Table 5). These recommendations are based on expert opinion.[81]

Emerging data suggest that early mammography for women at high risk may be beneficial and associated with an earlier stage at diagnosis.[82] Most women with a family history of breast and/or ovarian cancer will not undergo genetic testing, or if they do undergo testing, no mutations will be found in the family. Increased cancer surveillance seems prudent for these women, although screening recommendations often differ from center to center.[83]

It is generally recommended that women at higher-than-average risk of breast cancer perform monthly breast self-examination and undergo twice-yearly clinical breast examination. Yearly mammography is also recommended for women at greater-than-average risk. Mammography should be initiated 5 to 10 years prior to the youngest diagnosis of breast cancer in the family, but not before age 25. Women in high-risk families should be encouraged to have any lump evaluated promptly and thoroughly. Recent information supports the use of breast ultrasound for the evaluation of high-risk women.[84] See Table 5 for recommendations for high-risk women.

**Ovarian Cancer Screening in Women at High Risk**

High-risk screening for ovarian cancer is a controversial subject. No techniques have shown high sensitivity and specificity for detection of ovarian cancer.[85,86] Some studies suggest that screening women at increased risk is associated with higher cancer identification rates than in the general population.[87] Ovarian cancer screening is recommended for women who are found to carry mutations in BRCA1/2. These recommendations are supported by expert opinion.[81]

Additionally, increased surveillance is often recommended for women who have a first- or second-degree relative with ovarian cancer. Recommendations include annual pelvic examination, annual or semiannual CA-125 measurement, and transvaginal ultrasound. These recommendations rely on the fact that some studies have demonstrated improved screening efficacy when both
techniques are used.[88,89] Women should understand that CA-125 levels are higher for premenopausal women (compared with postmenopausal women) and can be elevated due to other benign and malignant conditions such as pregnancy, endometriosis, pelvic inflammatory disease, hepatitis, and colon cancer. Furthermore, false-positive tests may result in exploratory surgery.

**Chemoprevention in Women at High Risk**

**Chemoprevention for Breast Cancer:** Women at increased risk of breast cancer may be candidates for chemoprevention. Three trials of the SERM tamoxifen (Nolvadex) for the prevention of breast cancer have been conducted. The largest and most recently completed trial showed a 50% reduction in the development of invasive breast cancer among women taking tamoxifen for 5 years.[90] This trial, performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP), randomly assigned women at increased risk of breast cancer (based on age, hormonal factors, family history of cancer, or personal history of a breast biopsy) to either tamoxifen or placebo. Significant reductions in both invasive and noninvasive breast cancers were seen for all groups of women in the study. However, the reduction in invasive breast cancer was limited to estrogen receptor-positive tumors.

These results need to be interpreted with caution in high-risk individuals. Women with hereditary breast cancer tend to develop hormone receptor-negative breast cancer.[91,92] Therefore, there is concern that women with a strong family history of breast cancer may not achieve the same benefit from tamoxifen.

Two other clinical trials of tamoxifen in women at increased risk of breast cancer have been performed. Neither of these studies showed any benefit of tamoxifen for women at increased risk.[93,94] Although both of these studies were smaller and had different eligibility criteria, they were well designed and had longer follow-up periods than the NSABP P1 trial.[90,93,94] The Royal Marsden trial was performed in women with a family history of breast cancer.[93]

The SERM raloxifene (Evista) may turn out to be another alternative for women at risk of breast cancer. Two studies have shown reductions in the incidence of breast cancer in women taking this drug.[95,96] Again, caution is warranted, as these two trials used only postmenopausal women and were primarily performed to investigate the role of raloxifene in the treatment of osteoporosis.

**Chemoprevention for Ovarian Cancer:** Chemoprevention for ovarian cancer is available. Studies have shown that women who are at average or increased risk of ovarian cancer benefit from treatment with oral contraceptives.[97-99] A 60% reduction in the risk of ovarian cancer was seen for women with BRCA1/2 mutations who used oral contraceptives for more than 6 years.[99]

Long-term, uninterrupted use of oral contraceptives is associated with a slight increase in the incidence of breast cancer.[100] This risk may be greatest for women with a family history of breast cancer.[101] For women at increased risk of ovarian cancer or those who have a great likelihood of carrying a germ-line mutation in either BRCA1 or BRCA2, the benefits (reduction in ovarian cancer risk) need to be weighed against the slightly increased risk of breast cancer.

**Surgical Prophylaxis in Women at High Risk**

Women at the greatest risk of breast and/or ovarian cancer may consider the prophylactic removal of breast or ovarian tissue. Women who undergo prophylactic mastectomy can reduce their risk of breast cancer by 90%.[102] Satisfaction is generally high, and quality of life may be improved by prophylactic mastectomy for high-risk women.[103] Prophylactic oophorectomy has also recently been shown to reduce the risk of ovarian cancer by 90%.[104] Additionally, prophylactic oophorectomy in women who carry BRCA1/2 mutations has been shown to decrease the risk of breast cancer by at least 50%.[105]

For high-risk women and their caregivers, these are complex issues. While a prophylactic oophorectomy may reduce the risk of both breast and ovarian cancer, the consequences of a lifetime lack of estrogen must be considered. For women who undergo early prophylactic oophorectomy, some would advocate the use of hormone replacement therapy until age 50.[106] These women...
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should be closely monitored for changes in bone density and cholesterol.

Hormone Replacement Therapy in Women at High Risk

The use of hormone replacement therapy for women in high-risk families is also a complex issue. Women and their primary caregivers are often reluctant to initiate hormone replacement therapy in women with an elevated risk of breast cancer. It is known that women on prolonged hormone replacement therapy (> 4 years) have a slightly increased risk of breast cancer.[107] Risk also appears greater for women with a family history of breast cancer. However, survival is no different in the two groups.[108]

Two recent studies suggest that, for all women, the combination of estrogen and progestin may be associated with a greater risk of breast cancer, compared to estrogen alone.[109,110] For any woman, the risks and benefits of hormone replacement therapy need to be considered; it may be prudent to limit the amount of progesterone exposure, especially for women at increased risk of breast cancer. All women on hormone replacement therapy should have yearly mammograms and be encouraged to perform breast self-examination in conjunction with yearly or twice-yearly clinical breast examination.

Second Primary Breast Cancer in Women at High Risk

The surgical treatment of breast cancer has become less aggressive over time. Women often have the option of undergoing lumpectomy, axillary evaluation, and radiation therapy (breast-conserving therapy) or mastectomy as primary treatment for their breast cancer. For women with either a family history of breast cancer[111-113] or a BRCA mutation,[114] there is no increase in local recurrence with breast-conserving therapy. There is, however, an increased risk of developing a second primary breast cancer for both groups.[113-116]

Second primary breast cancers may be seen in a different quadrant of the same breast, or more commonly, in the contralateral breast. The studies cited above are not large, but they suggest that women with a family history of breast cancer or BRCA mutation can be safely treated for their primary breast cancer with breast-conserving therapy. Nevertheless, a woman should consider her risk of a second breast cancer and prophylactic surgery at the time of a first breast cancer diagnosis. Of course, this can be a difficult decision to make at the time of diagnosis, and there is no harm in delaying this decision until the completion of the primary breast cancer therapy.

Conclusions

Women with a strong family history of breast and ovarian cancer have several options to consider. Only a minority of individuals with a strong family history will be candidates for genetic testing for BRCA1/2, and mutations will be found in even fewer persons. Candidates for genetic testing need to understand the risks, benefits, and limitations of genetic testing prior to testing.

The risk of cancer for individuals with a strong family history of breast and/or ovarian cancer makes high-risk screening a prudent consideration. Benefits of screening for this population are not clear. Options for chemoprevention in high-risk individuals are also available. Prophylactic surgery (mastectomy or oophorectomy) although an irreversible and life-altering decision offers the greatest reduction in cancer risk.

We have much to learn in this rapidly developing field. Women who are at high risk may be candidates for clinical trials and/or research studies, and should be informed of these options when they are available.

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