Hereditary Risk of Breast and Ovarian Carcinoma: The Role of the Oncologist

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ABSTRACT
The American Society of Clinical Oncology has affirmed the role of clinical oncologists in identifying and managing patients with familial cancer risk. Inherited mutations in the genes BRCA1 and BRCA2 are responsible for the majority of hereditary breast and ovarian cancers, and these mutations also increase the risk of second cancers in women already diagnosed with breast malignancy. Understanding the likelihood of breast and ovarian cancer associated with mutations in BRCA1 and BRCA2 begins with consideration of the biological basis of hereditary cancer risk. Identifying patients with hereditary risk requires documentation of appropriate family history, and recent studies have characterized criteria for identifying women most likely to have inherited mutations in these genes. Options for women with inherited mutations in BRCA1 and BRCA2 include surveillance, chemoprevention and prophylactic surgery, which must be considered separately for the management of the risk of breast cancer and of ovarian cancer. Knowledge of the hallmarks of hereditary risk, options for medical intervention, possible results of BRCA1 and BRCA2 laboratory analysis and the psychological concerns of patients about hereditary risk evaluation enables oncologists and other health care providers to effectively counsel and manage women with hereditary risk of breast and ovarian cancer.

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INTRODUCTION
Consider a test result that indicates an increased risk, but not a certainty, of breast carcinoma. Assume that the amount of increased risk is not known, and it is unclear which intervention most effectively reduces the risk of subsequent invasive carcinoma. Furthermore, assume that the result itself is subject to a great deal of inter-laboratory variation. Could this test result, by itself, be used as the basis for management decisions?

The above description of ductal carcinoma-in-situ (DCIS) of the breast illustrates how oncologists are frequently called upon to make clinical decisions based on identification of individuals with an increased risk of invasive carcinoma. It is believed that only a minority of incompletely treated or untreated intraductal carcinomas progress to invasive carcinoma [1, 2], and the diagnosis itself is subjective and often unreliable [3]. Despite these limitations, DCIS constitutes a well-established medical call to action for over 36,000 women each year.

DCIS, dysplasia, atypical hyperplasia and related “pre-cancerous” lesions are morphological entities defined and diagnosed by their microscopic appearance. The use of cellular morphology to identify cancer risk, despite its subjectivity, is well established and certainly familiar to physicians. In contrast, the identification of the genetic underpinnings of cancer is a recent development that for many physicians involves concepts far more abstract than microscopy. The characterization of the genetic changes that accompany the development of malignancy, however, may soon provide sensitive and reliable diagnostic tools to permit effective intervention for patients at increased risk of malignancy.

It is now possible to identify most women who have inherited changes in critical genes that increase dramatically the likelihood of developing carcinoma of the breast and ovary. The likelihood of breast carcinoma in a woman with such inherited genetic changes is far greater in general than for women diagnosed with DCIS and other “pre-cancerous” microscopic lesions. Identification of women with hereditary risk of breast and ovarian carcinoma thus presents an opportunity to intervene appropriately to address this risk.

Women have been subject to an extensive (and sometimes confusing) discussion of hereditary breast and ovarian...
carcinoma risk in the popular press. A woman’s most common questions may include whether her family history indicates an increased risk to herself of these cancers, whether medical management can effectively address these risks, and whether she should consider being tested for mutations in the genes responsible for most hereditary breast and ovarian carcinoma. This article is designed to help answer these questions.

WHAT CAUSES HEREDITARY BREAST AND OVARIAN CARCINOMA?

Most carcinomas arise from “somatic” mutations that are acquired after birth, such as through exposure to carcinogenic agents, or from mistakes made by cells during the process of cell division. In a minority of individuals, damage to critical growth-controlling genes is inherited. Such inherited mutations are called “germline” because they are present in an ovum or sperm, in contrast to mutations in somatic cells that occur later in life. When a mutation is inherited through the germline, it is present in every cell in the adult. Hereditary carcinoma syndromes result because every cell has a “head start” toward carcinoma, and the likelihood that at least one (and sometimes more than one) cell will sustain additional genetic damage and progress to malignancy is greatly increased (Fig. 1).

Approximately 7% of breast carcinomas and 10% of ovarian carcinomas result from alterations in genes that are passed down from either the mother or father [4]. The majority (approximately 84%) of hereditary breast carcinomas result from inherited mutations in two genes, BRCA1 and BRCA2 [5]. Although often referred to as the “breast carcinoma genes,” BRCA1 and BRCA2 are also responsible for most inherited risk of ovarian carcinoma. The reason that inherited mutations in BRCA1 and BRCA2 are associated primarily with tumors of the ovary and breast is not known but is presumably related to the effect of estrogen on the epithelial cells of these tissues.

The proteins encoded by BRCA1 and BRCA2 function—probably together [6]—to repair double-stranded breaks in DNA [7, 8]. By repairing damage in other genes, the BRCA1 and BRCA2 proteins prevent the accumulation of mutations and thus suppress the development of carcinoma. Both proteins may have other functions as well, such as activating the production of other proteins [9, 10] thought to be responsible for suppressing tumor development.

A woman inherits a mutation in BRCA1 and BRCA2 from one of her parents; de novo germline mutations (which usually occur during spermatogenesis) are thought to be rare in these genes. By definition, such mutations cannot be acquired after birth. Accordingly, tests for mutations in BRCA1 and BRCA2 are normally performed only once in a person’s lifetime.

WHAT ARE THE RISKS OF BREAST AND OVARIAN CARCINOMA ASSOCIATED WITH INHERITED MUTATIONS IN BRCA1 AND BRCA2?

Individuals who carry a mutation in BRCA1 or BRCA2 have one normal copy of each gene in addition to one mutated copy. Each offspring of a man or woman who carries a mutation has an equal chance of inheriting the normal copy as the mutated copy. Offspring who inherit the mutated gene are at a greatly increased risk of breast and ovarian cancer, whereas offspring who inherit the normal copy from their parent are not at increased risk even if their parent developed breast or ovarian cancer. Thus, mutations in BRCA1 and BRCA2 confer cancer risk as an autosomal dominant trait, with offspring having exactly a 50% chance of being at greatly increased risk of cancer or of being at the general population risk.

The majority of women who inherit mutations in BRCA1 and BRCA2 will develop breast and/or ovarian carcinoma. In fact, the risk of breast cancer before age 50 for a woman with a mutation in BRCA1 or BRCA2 is much greater than the risk...
of lung carcinoma in an individual who smokes four packs of cigarettes a day for 30 years. The range of cancer risks associated with mutations in these genes has been characterized through numerous studies. The risks of breast and ovarian carcinoma associated with mutations in these genes, which will be discussed separately, are summarized in Table 1.

**BRCA1 and BRCA2 Mutations and the Risk of Breast Carcinoma**

Mutations in BRCA1 and BRCA2 are associated with an 87% risk of breast carcinoma by age 70 in women selected for a strong family history of breast carcinoma [11]. In contrast, three specific mutations studied in women analyzed without regard to family history have been associated with a 56% risk of breast carcinoma by age 70 [12], suggesting that some mutations may vary in their conferred risk of cancer. For the most part, though, risk estimates are aggregate calculations for abnormalities throughout the genes rather than for individual gene mutations.

Mutations in BRCA1 and BRCA2 particularly increase the risk of early-onset breast carcinoma. Whereas a woman’s likelihood of developing breast carcinoma before age 50 is normally only 2%, the risk is 33%-50% for a woman with a mutation in BRCA1 or BRCA2 [12, 13].

**BRCA1 and BRCA2 Mutations and the Risk of Ovarian Carcinoma**

The risks of ovarian carcinoma conferred by mutations in BRCA1 appear to be higher than for BRCA2. Mutations in BRCA1 are associated with a risk of ovarian carcinoma estimated between 28% [14] and 44% [11, 13] by age 70 (compared with the general population risk of 1.8%). The risk of ovarian carcinoma by age 70 for most BRCA2 mutations is currently estimated to be 27% [5], which represents a 15-fold increase over that of the general population. Most ovarian carcinomas associated with mutations in BRCA2 appear to occur after age 50 [5].

**Mutations and Risk of Second Cancers in Women Diagnosed with Breast Carcinoma**

In women with breast cancer, mutations in BRCA1 have been associated with a 25% risk of contralateral breast cancer within five years of the initial diagnosis [15], or a 64% risk of contralateral breast cancer by age 70 [11]. It is assumed that mutations in BRCA2 are associated with comparable risks. In addition, women with breast carcinoma who carry mutations in either BRCA1 or BRCA2 have a 10-fold increase in the risk of subsequent ovarian carcinoma compared with women without mutations, including other women with early-onset breast cancer [16]. Conversely, women with mutations who develop ovarian cancer are at increased risk of breast cancer, although in most instances where women develop both diseases the ovarian cancer follows rather than precedes the breast cancer. Unfortunately, most women with mutations who develop ovarian cancer will not survive long enough for the risk of breast cancer to become a factor in medical management.

**BRCA1 and BRCA2 Mutations and the Risk of Other Malignancies**

Some studies have reported that mutations in BRCA2 are associated with a 6% risk of male breast cancer by age 70 [17], as well as an increased (but undefined) risk of pancreatic cancer [17, 18]. The relative risk of colorectal and prostate cancer may also be elevated by mutations in these genes [11, 17], but the age of onset of these cancers is believed to be equivalent to those in the general population, and therefore normal screening guidelines for these tumors have been recommended for mutation carriers [19].
**How Should an Individual Be Evaluated for Hereditary Breast-Ovarian Cancer Syndrome?**

The American Society of Clinical Oncology (ASCO) has recommended that hereditary cancer predisposition should be offered only when: A) the individual being tested has a strong family history of cancer or very early age of onset of disease; B) the results can be interpreted correctly, and C) the test results will influence medical management [20]. In practice, the first evaluation that usually takes place is whether an individual’s family or personal history of cancer indicates the likelihood of a germline mutation in BRCA1 or BRCA2. (Implications of genetic testing for medical management will be discussed below.)

Most physicians recognize that the presence of multiple first-degree relatives with breast cancer indicates the likelihood of a hereditary syndrome in a woman. As noted in a recent review by an expert in the field [21], however, “families with an obvious cancer syndrome are likely to represent only a small fraction of individuals with inherited predisposition to cancer.” The identification of hereditary cancer in a family has only recently been clarified by studies that correlate family history with the presence of mutations in BRCA1 and BRCA2 [16, 22-24]. What has emerged from these studies can be used to evaluate a patient’s personal and family history for the possibility of hereditary breast-ovarian cancer syndrome.

An example of what to look for in a woman’s family history is illustrated in Figure 2. In each family, a woman was diagnosed with breast carcinoma at age 42. The mother and maternal grandmother of woman “A” were both diagnosed with breast carcinoma after the ages of 60 and 70, respectively. The other woman (“B”) has no first-degree relatives with breast carcinoma, but her father’s sister was diagnosed with breast carcinoma at age 45. From modeled probabilities, patient B is actually twice as likely as patient A to carry a mutation in BRCA1 or BRCA2. This is because a woman diagnosed with breast carcinoma before age 50 has been shown to have a 25% chance of carrying a mutation if she has at least one first- or second-degree relative with breast carcinoma diagnosed at a similarly young age [16]. In contrast, women with breast cancer before age 45 with a “first-degree family history” that is not early-onset have a lower chance of harboring a mutation [25].

Other “red flags” of mutations in BRCA1 and BRCA2 include ovarian carcinoma and early-onset breast carcinoma diagnosed in the same individual, bilateral breast carcinoma (especially if one or both tumors were diagnosed before age 50), and male breast cancer at any age. In addition, individuals of Ashkenazi Jewish descent with a personal history of early-onset breast cancer or ovarian cancer at any age have a higher incidence of mutations in BRCA1 and BRCA2 [26, 27]. Indeed, mutations in BRCA1 and BRCA2 have been identified in nearly half of Ashkenazi Jewish women with ovarian cancer, including 23% of Ashkenazi ovarian cancer patients with no family history whatsoever of breast or ovarian cancer [28].

There are three common misconceptions about evaluating family history for the possibility of hereditary breast-ovarian cancer syndrome. The first is that “only a woman with multiple first-degree relatives with breast cancer is likely to have hereditary breast cancer syndrome.” The number of relatives in a family with breast cancer has been found to be a function mainly of family size [23]. Conversely, as discussed above, multiple relatives with breast cancer diagnosed over age 60 are less likely to indicate a hereditary mutation in BRCA1 or BRCA2 than a smaller number of relatives with breast cancer diagnosed before age 50. A second misconception is that “ovarian cancer in the family history is not related to hereditary breast cancer.” Several studies have demonstrated that ovarian carcinoma in a woman’s personal or family history is a significant indicator of the presence of a mutation in BRCA1.

Figure 2. A family history of early-onset breast cancer is more likely to indicate hereditary risk than breast cancer at a later age. In each of these families, a woman was diagnosed with breast carcinoma at age 42. The mother and maternal grandmother of woman “A” were both diagnosed with breast carcinoma at the ages of 61 and 71, respectively (purple circles). Although woman “B” has no first-degree relatives with breast carcinoma, her father’s sister was diagnosed with breast carcinoma at age 45. In conjunction with her own breast cancer at age 42, a second-degree relative with breast cancer under age 50 indicates that woman “B” has a 25% chance of carrying mutation in BRCA1 or BRCA2.
or BRCA2 [16, 23]. A third and remarkably common misconception is that “cancer on the father’s side of the family does not count.” In fact, in accordance with basic genetic principles, half of all women with hereditary breast-ovarian cancer risk inherited the susceptibility mutation from their father, very few of whom develop male breast cancer. The clinical significance of a mutation is the same whether it was inherited from one’s father or mother. In many families where the transmission of mutations is paternal, there may not be any affected first-degree relatives (since the mother is not a carrier), but rather aunts, cousins, or a grandparent on the father’s side with a history of breast or ovarian cancer.

Table 2 is an example of a published set of modeled probabilities that can be used to predict the presence of a BRCA1 or BRCA2 mutation based on a woman’s family history [16]. Women diagnosed with breast cancer before age 50 or ovarian cancer at any age should be asked about other relatives on the father’s or mother’s side of the family with breast cancer diagnosed before age 50 or ovarian cancer at any age. The presence of such a family history should prompt further evaluation [16].

Only epithelial malignancies of breast and ovary have been associated with mutations in BRCA1 and BRCA2. In addition, there is little evidence suggesting that DCIS in a personal or family history indicates hereditary risk. “Borderline” tumors of the ovary, however, have been associated with hereditary breast-ovarian cancer syndrome and thus should be noted in a woman’s family or personal history.

Finally, it should be noted that a minority of hereditary breast and ovarian cancer syndromes are associated with other genes than BRCA1 and BRCA2. The oncologist should therefore be familiar with such hereditary syndromes as Li-Fraumeni, in which breast carcinoma occurs in conjunction with other carcinomas, sarcoma and leukemia; Cowden’s syndrome, in which breast cancer is associated with thyroid and other cancers as well as mucosal lesions and facial trichilemmomas; and hereditary nonpolyposis colon cancer, in which ovarian carcinoma clusters with carcinomas of the colon and endometrium.

### WHAT INTERVENTIONS ARE AVAILABLE FOR WOMEN WITH HEREDITARY BREAST-OVARIAN CANCER SYNDROME?

As discussed above, ASCO recommended that genetic testing for cancer risk be offered only when the results will influence the medical management of the patient or family member. Many women with a strong family history of breast cancer already undergo increased surveillance for that disease, and identification of a germline mutation in BRCA1 or BRCA2 might not affect their cancer surveillance practices. In accordance with the ASCO guidelines, genetic testing should be offered to such women only if a positive test would lead to additional steps not otherwise taken (for example, to address the risk of ovarian cancer), or if a negative test would obviate the need for screening or other intervention that might have been considered appropriate based on her family history [29]. Management options generally available to cancer-prone individuals include heightened surveillance, prophylactic surgery, and, in some cases, chemoprevention.

The availability and efficacy of interventions for breast and ovarian cancer are considered separately below.

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These probabilities are based on analysis of women diagnosed with breast cancer before age 50 with at least one first or second degree relative with ovarian cancer or breast cancer before 50 years.

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Interventions That Address the Increased Risk of Breast Cancer

The high survival rate of women diagnosed with early-stage breast cancer warrants heightened surveillance for women who carry mutations in BRCA1 and BRCA2, commencing at an early age in recognition of the earlier age of onset of hereditary breast cancer. A national task force (the Cancer Genetics Studies Consortium) organized by the National Human Genome Research Institute has specifically recommended that women with mutations in BRCA1 and BRCA2 undergo annual or semiannual clinical breast examinations as well as annual mammography, to commence before age 35 [19].

In conjunction with increased surveillance, it may be possible to reduce breast cancer risk by selective estrogen receptor modulators. Tamoxifen, for instance, was recently demonstrated to reduce the risk of breast cancer by 45% in women with an elevated risk of the disease [30]. Significantly for young women with hereditary risk, side effects of tamoxifen (such as endometrial carcinoma and thromboembolic events) were not observed in any of the participants under age 50. The Gail model was used for defining high risk in women under age 50, which very likely included women with mutations in BRCA1 and BRCA2 [31]. Analysis of these genes is being performed for a subgroup of the study participants and is expected to be completed by late 1999.

Prophylactic simple mastectomy is chosen by only a minority of women with cancer-predisposing mutations [32]. This procedure does not eliminate the possibility of breast cancer, but has been shown in high-risk women to reduce the risk by more than 90% [33]. Prophylactic mastectomy may be chosen by women whose mammographic assessment is compromised (for example, by extensive fibrocystic change), or by women whose experience and perception of breast cancer has been influenced by relatives or close friends who suffered or died from early-stage disease.

In women with hereditary cancer syndromes who are newly diagnosed with breast cancer, the surgical management of the tumor may be altered to address the increased risk of a second breast cancer. It should be noted, however, that the evidence to date suggests that the prognosis of breast cancer in BRCA1-BRCA2 mutation carriers is similar to that of women with sporadic breast cancer [15, 34, 35].

Interventions That Address the Increased Risk of Ovarian Cancer

The increased risk of ovarian cancer is often unrecognized as a consequence of an inherited mutation in BRCA1 and BRCA2, especially for women already diagnosed with breast cancer. Unlike breast cancer, which usually can be detected at an early stage by widely employed screening methods, ovarian cancer usually is not diagnosed until it is advanced and relatively incurable. In fact, screening for ovarian cancer is difficult and often ineffective. Circulating antigen CA-125 is elevated in only half of patients with stage I ovarian cancers and elevated in many non-neoplastic conditions, and there is little data to suggest that regular measurement of CA-125 levels facilitates detection of ovarian cancer at an early stage. Similarly, transvaginal ultrasound lacks specificity, although color Doppler imaging may be able to distinguish benign from malignant processes by detecting the increased blood flow of tumor-related angiogenesis. Even though such screening tests at present are not considered effective for screening a population at large, their use may be justified for women with hereditary risk who wish to maintain fertility [36].

Oral contraceptive use may reduce the risk of ovarian cancer in women with pathogenic mutations in BRCA1 and BRCA2. A recent retrospective, multicenter, case-control study of 207 women with hereditary ovarian cancer (using their sisters as controls) found that the use of oral contraceptives for six or more years was associated with a 60% reduction in the risk of ovarian cancer [37]. Adjusting for parity, the presence or absence of a tubal ligation and ages at the delivery of a first or last child did not influence the protective effect of oral contraceptive use. While oral contraceptive use has been associated in some studies with a small increase in the risk of breast cancer, the authors observed no difference in the history of oral contraceptive use between women who had had breast cancer and those who had not [38], and other evidence also challenges whether the risk of breast cancer is increased by the use of oral contraceptives [39].

An NIH consensus development panel on ovarian cancer concluded that “the risk of ovarian cancer from families with hereditary ovarian cancer syndromes is sufficiently high to recommend prophylactic oophorectomy in these women at 35 years of age or after child-bearing is completed [40].” Most women with BRCA1 and BRCA2 mutations who develop ovarian carcinoma do so after age 45 [5, 16, 41], supporting deferral of this procedure until age 35 as recommended by this panel.

The most important concern regarding prophylactic oophorectomy is the possibility of subsequent peritoneal carcinomatosis, which has been documented in 2%-11% of women who have undergone this procedure [42, 43]. Most studies of this phenomenon were conducted before direct genetic testing for BRCA1 and BRCA2 was available, and consequently there is little data regarding the risks of peritoneal carcinoma following prophylactic oophorectomy for carriers of mutations in BRCA1 and BRCA2. An analysis of 12 families in which at least two women had ovarian cancer
demonstrated that prophylactic oophorectomy reduced the risk of ovarian-peritoneal cancer by 50%, but because of the small number of participants, these findings lacked statistical significance [44]. Thus, in contrast to the NIH consensus panel, the Cancer Genetics Studies Consortium stated that “there is insufficient evidence to recommend for or against prophylactic oophorectomy as a measure for reducing ovarian cancer risk [19].” This is an area of ongoing and much-needed investigation.

Another issue of particular concern to women with mutations in BRCA1 or BRCA2 who are considering prophylactic oophorectomy is whether hormone replacement therapy contributes to the risk of breast cancer. While the use of postmenopausal hormone replacement therapy for greater than five years has been associated with a 1.46 relative risk of breast cancer [45], hormone replacement therapy does not appear to increase the rate of breast cancer in women who have first-degree relatives with breast cancer [46]. Because of the deleterious side effects of premature menopause [47] and the lack of data regarding a contribution of hormone replacement therapy to breast cancer risk in mutation carriers, some have defended the use of estrogen following prophylactic oophorectomy even in high-risk women [36].

**WHAT ARE THE POSSIBLE RESULTS OF BRCA1 AND BRCA2 ANALYSIS?**

**Positive for a Deleterious Mutation**

Laboratory analysis of BRCA1 and BRCA2 can determine whether there is a defect in the gene which interferes with the production or function of the protein. A mutation in either gene that interrupts the production of the full-sized protein or that is known to interfere in other ways with the function of the protein is assumed to contribute to cancer risk even if it has not been seen before. The discovery of such a mutation has implications not only for the individual who was tested but also for family members, who must decide for themselves if they wish to learn whether or not they also inherited the cancer-susceptibility mutation.

**Negative for a Deleterious Mutation**

Since mutations in BRCA1 and BRCA2 transmit cancer risk as an autosomal dominant disorder, each child of a mutation carrier has an equal chance of being at population risk (by not inheriting the mutation) as of being at increased risk. Thus, if a mutation has been characterized in a family, a woman whose test indicates that she did not inherit the mutation has no elevated risk of breast or ovarian cancer despite her family history and can therefore avoid unnecessary interventions that might have previously been considered appropriate [29]. It is important to emphasize that the risk of breast and ovarian cancer in such individuals is not zero but that of the general population.

A negative test in a woman who has breast cancer has implications regarding her risk of subsequent ovarian or contralateral breast cancer but does not entirely rule out the possibility of hereditary breast-ovarian cancer syndrome. This is because the patient may carry an unusual genetic alteration in BRCA1 or BRCA2 that cannot be detected by a clinical laboratory test [48, 49] or may carry a mutation in a different gene less commonly associated with hereditary cancer risk. Accordingly, a negative test result in a woman with breast (or ovarian) cancer may not mean that her relatives are at population risk.

A negative test in a woman who does not have cancer must also be interpreted cautiously. The higher the prior probability of a mutation based on her family history (Table 2), the more likely a negative test result indicates the test, or she may be at increased cancer risk due to non-hereditary factors. Thus, unless a mutation has previously been identified in her family, a negative test in a woman who herself does not have cancer reduces the likelihood of hereditary breast-ovarian cancer syndrome but does not indicate that her cancer risk is that of the general population.

**Genetic Abnormality of Uncertain Clinical Significance**

In a high-risk population where 40% carried deleterious mutations in BRCA1 or BRCA2, another 15% were shown to have inherited abnormalities whose effect on the protein was not yet established [16]. For several such genetic variants, there is evidence that suggests either an association with hereditary cancer or a lack of such an association. In other instances, there may be little known about the clinical implications of the variant. In such situations, other family members may be tested for the variant to determine whether it “tracks” with cancer, and this may provide clarification of its significance.

**WHAT ARE THE IMPLICATIONS OF IDENTIFYING HEREDITARY CANCER RISK FOR ACCESS TO HEALTH INSURANCE?**

The phrase “genetic discrimination” has been used to apply to “discrimination directed against an individual or family based solely on an apparent or perceived genetic variation from the ‘normal’ human genotype [50].” As such, the
term specifically applies not to individuals with a genetic illness but only to those who are asymptomatic. When tests for hereditary cancer syndromes were introduced earlier this decade, there was widely voiced concern that individuals found to be at increased risk of cancer would be subject to increases in health insurance premiums or even loss of health insurance. Interestingly, this has been a concern raised specifically for tests of cancer risk that were genetic in nature; few women undergoing breast biopsies, for instance, have been urged to pay for histopathology studies out-of-pocket in order to avoid an insurance company’s finding out about a premalignant or malignant diagnosis.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA), which went into effect July of 1997, offers specific protections for those who have undergone genetic testing. This federal law applies to all group insurance plans and guarantees access to health insurance coverage regardless of health status and preexisting conditions, specifically including genetic predisposition to cancer and other illnesses. Under HIPAA, insurers cannot make eligibility conditional based on the individual’s genetic information and cannot use genetic information alone to demonstrate a pre-existing condition without a specific diagnosis of the condition. However, this law does not provide privacy protections for any medical tests, including genetic tests, and does not prohibit group health plans from increasing rates for everyone in the plan [51]. Additional federal legislation to address these issues has been drafted but as of this writing has not been enacted.

At present, there appears to be little documentation of discrimination in health insurance or employment in healthy individuals following genetic testing for breast or ovarian cancer risk. For this reason, some experts have concluded that “the perceptions of discrimination far exceed the reality [52].” Nonetheless, concerns about “genetic discrimination” should be recognized and addressed by individuals counseling women who are considering genetic testing for hereditary cancer risk.

**How Should Women Be Counseled About Their Hereditary Risk of Breast and Ovarian Cancer Risk?**

Unlike most other diagnostic tests related to cancer, the identification of hereditary susceptibility to malignancy may have profound implications for relatives of the individual being tested. For this reason, and because of the complex medical and psychosocial issues that may accompany identification of hereditary cancer risk, women being assessed for hereditary breast-ovarian cancer syndrome should be offered an unhurried and thorough discussion of the relevant issues. For women who choose to undergo genetic testing, such discussion should occur both before and after the test is performed. In addition, counseling may be appropriate for some women who choose to decline genetic testing. For example, in BRCA1/2-linked families, persons with high levels of cancer-related stress who declined genetic testing were shown to be at risk for depression [53].

Counseling should include a discussion of the basic principles of hereditary cancer susceptibility as well as an assessment of the woman’s own risks of cancer, how testing would contribute to the characterization of those risks, and how medical management would be affected by a positive and a negative test result.

The goals of appropriate counseling should at all times be beneficence (benefit to the patient), avoidance of malfeasance (harm to the patient), and respect for patient autonomy. The best individual to decide the appropriateness of genetic testing for hereditary cancer risk is the well-informed patient. The review and signing of the informed consent is not, therefore, a substitute for the counseling process, but rather documentation that appropriate discussion with the patient has taken place. Because this process may be time-consuming, many physicians utilize the professional skills of specially trained genetic counselors, nurses, or other health care professionals to counsel their patients. The use of qualified health care professionals other than geneticists and genetic counselors to provide counseling for hereditary breast-ovarian cancer risk is, in fact, considered appropriate [20, 54].

Appropriate counseling should include a discussion of the basic principles of hereditary cancer susceptibility as well as an assessment of the woman’s own risks of cancer, how testing would contribute to the characterization of those risks, and how medical management would be affected by a positive and a negative test result. The possibility that a test.
might not provide conclusive information should also be presented, as well as the sensitivity and specificity of the test being considered. The implications for family members should be discussed, and the patient encouraged to consider which relatives she would inform of the results (including her offspring) and when. Finally, as with any medical test that has the potential to disclose a significant medical condition, the implications of genetic testing for health insurance, life insurance and employment should be discussed, along with the benefits and limitations of such legal protections that apply to the individual.

**Conclusion: What is the Role of the Oncologist in Assessing and Managing Hereditary Risk?**

In hereditary breast-ovarian cancer syndrome, women inherit susceptibility to both breast and ovarian cancer as an autosomal dominant disorder. The ability to analyze **BRCA1** and **BRCA2** provides oncologists with an opportunity, when appropriate, to identify women who have inherited this increased risk. A significant proportion of breast cancer patients diagnosed before age 50 developed their malignancy because of detectable mutations in **BRCA1** or **BRCA2**. The increased risk of a contralateral breast cancer, as well as a subsequent carcinoma of the ovary, may warrant a specialized management strategy for these women. In addition, the identification of a mutation in **BRCA1** or **BRCA2** in a patient with or without cancer has implications for her relatives. The ability to diagnose hereditary susceptibility to breast and ovarian cancer through genetic testing may provide opportunities for enhanced medical management of “at-risk” women. An oncologist should be able to assess a patient’s personal and family history for the possibility of hereditary breast-ovarian cancer syndrome, understand the benefits and limitations of genetic tests for this condition, and accurately answer a patient’s questions about the hereditary syndrome of breast and ovarian cancer. Fortunately, oncologists possess the training and experience to identify women with increased cancer risk and manage them appropriately. The use of genes rather than slides to identify such women, and the added implications of genetic tests for other relatives, may simply represent an extension of skills already possessed and utilized by oncologists who care for women with cancer.

**References**


Hereditary Risk of Breast and Ovarian Carcinoma


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