Testing for Hereditary Risk of Ovarian Cancer

Thomas S. Frank, MD

Tests to identify specific hereditary ovarian cancer syndromes are reviewed.

Background: Approximately one out of every 10 ovarian cancers is caused by inherited mutations in identified genes. The characterization of hereditary ovarian cancer as an autosomal dominant disorder of specific gene mutations is more specific and useful than descriptive clinical syndromes such as "Lynch II," "site-specific ovarian cancer," or "breast-ovarian cancer."

Methods: The author reviewed recent studies of the biology, epidemiology, and medical management of hereditary ovarian cancer risk.

Results: Most hereditary ovarian cancer is attributable to two genes, BRCA1 and BRCA2, with other genes accounting for a smaller fraction. Women who inherit a mutation in any of these genes are far more likely than the general population to develop an epithelial malignancy of the ovary. Appropriate evaluation of family history can identify women most likely to have hereditary cancer risk, and genetic testing can definitively identify women with germline mutations that place them and their family at increased risk of ovarian cancer.

Conclusions: Hereditary risk assessment, including genetic testing, can enhance medical management when used appropriately and should be accompanied by patient education and counseling.

Introduction

Until relatively recently, hereditary risk of cancer was assumed to be multifactorial. The hypothesis that some hereditary cancer risk could be attributable to single genes and inherited as an autosomal dominant disorder was disputed for several years until such genes were actually characterized. The discovery of specific cancer-risk genes provides a basis for the identification of patients who have increased cancer risk due to inherited genetic mutations. Among the genes that have recently been characterized are those responsible for the vast majority of hereditary ovarian cancers. The family of genes responsible for hereditary nonpolyposis colon cancer (including the "Lynch II" syndrome) have been implicated in a few such families, but the majority of hereditary ovarian cancers results from inherited mutations in two genes, BRCA1 and BRCA2. Although often referred to as the "breast cancer genes," BRCA1 and BRCA2 are together responsible for most instances of inherited risk of ovarian cancer.

Most physicians appreciate that a strong family history of ovarian cancer indicates the likelihood of a hereditary syndrome. Many may not realize, however, that hereditary risk of ovarian cancer may be indicated primarily by a personal or family history of premenopausal breast cancer. Furthermore, even women who have a strong family history of ovarian cancer may not be at any increased risk of cancer themselves. This is because hereditary cancer risk due to a mutation in a specific gene such as BRCA1 or BRCA2 is transmitted as an autosomal dominant disorder. This means that each daughter of a mutation carrier is just as likely to inherit the normal copy of the gene as the mutated copy. Therefore, a woman with a strong family history of breast and/or ovarian cancer caused by a mutation in BRCA1 or BRCA2 is just as likely to be at the general population risk of cancer as she is to be at increased risk. In the appropriate circumstances, analysis of the BRCA1 and BRCA2 genes allows health care professionals to distinguish those women with a strong family history who are not actually themselves at increased risk from those who are.

This review summarizes the role of gene mutations in hereditary ovarian cancer, the features of family history that indicate the possibility of hereditary risk, the use of genetic tests in medical management, and the importance of patient education and counseling in the testing process.

Genetic Basis of Hereditary Ovarian Cancer

All cancer is genetic. That statement of fact refers to the recent characterization of cancer as the result of the accumulation of mutations in important genes within a single cell. Most of the genes involved in malignancy regulate cell division and differentiation. The majority of cancers arise from acquired mutations in these genes that occur throughout an individual’s lifetime, such as through exposure to carcinogenic agents or from mistakes made by cells during the process of cell division. In a minority of individuals, however, mutations in these genes are inherited and thus are present in every cell in the body. The result is a hereditary cancer syndrome because every cell has a "head start" toward cancer, increasing the likelihood that at least one (and sometimes more) will sustain additional mutations and will progress to malignancy. A few hereditary cancer syndromes, most notably the Li-Fraumeni syndrome, are associated with a plethora of cancers that arise in a variety of tissues. Most hereditary cancer syndromes, however, are associated with specific cancers, such as ovary and breast, or colon and endometrium. The basis for this tissue specificity is not yet known.

Genes Responsible for Hereditary Ovarian Cancer

Inherited mutations in the genes BRCA1 and BRCA2 are responsible for most hereditary ovarian cancers, as well as most hereditary breast cancers. This means that the majority of hereditary ovarian cancer occurs in the setting of familial breast cancer. Occasionally, families with mutations in BRCA1 and BRCA2 exhibit clustering of site-specific ovarian cancer, but this is the exception. In one recent study, one of five families with familial site-specific ovarian cancer was shown to have a mutation in BRCA1 and none in BRCA2. Using full-sequence analysis of BRCA1 and BRCA2, however, our laboratory has identified mutations in approximately 40% of women with a family history specific for ovarian cancer. While some familial clusters of site-specific ovarian cancer may represent unusual chance events, it is possible that a rare hereditary site-specific ovarian cancer syndrome will be genetically characterized in the future.

The proteins encoded by BRCA1 and BRCA2 are responsible for repairing double-stranded breaks in DNA such as those caused by radiation. By repairing damage in other genes, the protein products of BRCA1 and BRCA2 prevent the accumulation of mutations and thus suppress the development of cancer. A mutated copy of BRCA1 or...
BRCA2 inherited from either mother or father confers a greatly increased risk of ovarian cancer. Mutations in these genes have also been identified in 5% to 10% of presumed sporadic ovarian carcinomas\(^{13,14}\) in which the mutation is present in the cancer but not in the woman's germline. This is in contrast to breast cancer, where mutations in these genes occur exclusively in the hereditary form. The majority of ovarian tumors reported in women with mutations in \textit{BRCA1} and \textit{BRCA2} are invasive papillary serous carcinomas,\(^{4,15}\) although other histologic subtypes have also been observed.

A minority (probably fewer than 10%) of hereditary ovarian cancers result from germline mutations in the family of genes responsible for hereditary nonpolyposis colorectal cancer (HNPPCC), formerly known as the “Lynch II” syndrome. At least five genes are responsible for HNPPCC. Mutations in these genes are primarily responsible for familial clusters of early-onset colorectal and endometrial carcinoma, with ovarian carcinoma also reported in a minority of families. It appears that some HNPPCC families exhibit more clustering of gynecologic malignancies than others.

### Identifying Women With Hereditary Risk of Ovarian Cancer

A directed family history is the most important initial screening evaluation of hereditary ovarian cancer risk. An accurate evaluation of a personal and family history of cancer is the responsibility of every physician who cares for women, and an informative initial family history screen can and should be performed in a routine office setting. Even a few specific questions about family history can provide important information, but many physicians do not routinely obtain the necessary information for accurate assessment of hereditary cancer risk.\(^{16}\) In particular, asking about the father's side of a woman's family is frequently overlooked in recording a family history. In accord with Mendelian genetic principles, half of women with hereditary risk of ovarian cancer inherit the predisposing mutation from their fathers, but this side is often neglected in a family history taken to assess breast or ovarian cancer risk.\(^{16}\) The significance of a mutation inherited from a woman's father is the same as when inherited from her mother.

If a patient is unable to recall her family history in the office setting, a take-home questionnaire may facilitate the documentation of a family history, often with the help and recall of other family members. An example of such a questionnaire is illustrated in the Figure. The information provided on this form can be used in conjunction with the criteria discussed below to assess women for hereditary ovarian cancer risk. If a woman’s family history indicates the possibility of a hereditary cancer syndrome, it may be worthwhile to have a genetic counselor or other genetics professional develop a thorough and accurate cancer pedigree. The process of developing a formal pedigree is reviewed elsewhere.\(^{17}\)

#### Family History Questionnaire for Hereditary Cancer Risk

- **Your Name:**
- **Your Physician:**
- Date completed: __/__/___ (Family history information should be updated annually)
- Please check (✓) each box for anyone in your family who has had cancer.

<table>
<thead>
<tr>
<th>Breast cancer before age 50</th>
<th>Ovarian cancer at any age</th>
<th>Other cancers, especially endometrial and colorectal (age detected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yourself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
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<tr>
<td>Father</td>
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<td>Sister(s)</td>
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<td>Brother(s)</td>
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<td>Daughter(s)</td>
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<td>Son(s)</td>
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<td>Grandmother</td>
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<td>Grandfather</td>
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<td>Aunt(s)</td>
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<td>Uncle(s)</td>
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<tr>
<td>Cousin(s)</td>
<td></td>
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<tr>
<td>Others (Specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Check the box if you have in your family:
- [ ] Any female with both breast and ovarian cancer?
- [ ] Any female with bilateral breast cancer diagnosed under age 50?
- [ ] Is your family of Ashkenazi Jewish descent?

Sample of a patient questionnaire used to document a family history in assessing women for hereditary ovarian cancer risk.

The majority of women with hereditary ovarian cancer risk have a family history of early-onset breast cancer (ie, diagnosed at less than 50 years of age). Therefore, an assessment of a woman's risk for hereditary ovarian cancer should include questions about any relatives on either the mother's or father's side of the family who have had breast cancer diagnosed before 50 years of age. Fortunately, it has been shown that a family history of breast cancer as reported by a patient is generally reliable.\(^{18}\) Multiple relatives diagnosed with ovarian carcinoma also certainly indicate the possibility of hereditary risk, but such family histories appear to be the exception rather than the rule.\(^{1}\) This may be due in part to underreporting of ovarian cancer in a family history. A family history regarding ovarian cancer as provided by a patient is only 70% accurate,\(^{18}\) with many individuals reporting “gynecologic cancer” or “stomach cancer” if the tumor presented at a late stage.

A recent study found that mutations in \textit{BRCA1} and \textit{BRCA2} were found in a substantial proportion of families where even two first- or second-degree relatives (on the same side of the family) had breast cancer under 50 years of age.\(^{19}\) This study, as well as others,\(^{20}\) demonstrated that breast cancer diagnosed before age 50, even in a limited number of women in a family, is a more important indicator of hereditary cancer risk than a family history of breast cancer diagnosed at an advanced age. The observed correlation between family history and mutations in these genes was used to create a table of modeled probabilities to allow physicians to identify women who have a high likelihood of a mutation in \textit{BRCA1} or \textit{BRCA2}. As shown in the Table, a personal or family history that includes ovarian cancer (at any age) in addition to premenopausal breast cancer is especially likely to indicate a mutation in \textit{BRCA1} or \textit{BRCA2}.

### Modeled Probabilities of Women With Breast Cancer Under 50 Years of Age

<table>
<thead>
<tr>
<th>Modeled Probability (%)</th>
<th>Breast Cancer Before Age 50</th>
<th>Ovarian Cancer at Any Age</th>
<th>Other Cancers, Especially Endometrial and Colorectal (Age Detected)</th>
</tr>
</thead>
</table>
It is important to note, however, that when a family history suggests the possibility of a mutation in BRCA1 or BRCA2, an individual woman's own cancer risk can be assessed only through clinical genetic testing. This is because each woman in the family has only a 50-50 chance of inheriting the cancer susceptibility mutation from her parent. Genetic testing is in effect the "tissue diagnosis" of hereditary cancer risk. Where possible, a mutation should first be identified in an individual with cancer, after which other family members can be tested only for that specific mutation (which is clinically definitive and far less expensive than performing full sequence analysis on each woman in the family).

The value of genetic testing compared to family history assessment alone is particularly true for women of Ashkenazi Jewish ancestry, in whom ovarian or premenopausal breast cancer is associated with mutations in BRCA1 and BRCA2 even in the absence of a strong family history. For example, a recent study identified germline BRCA1 and BRCA2 mutations in 48% of Ashkenazi Jewish women with ovarian cancer, including 23% of women with no family history whatsoever of breast or ovarian cancer. The authors concluded that consideration of genetic testing was warranted in all Ashkenazi women with ovarian cancer regardless of family history.

The features of a family history that predict the possibility of HNPCC are not as well defined as for mutations in BRCA1 and BRCA2. The "Amsterdam criteria" of hereditary colorectal cancer risk stipulate that (1) at least three family members in two or more successive generations must have colorectal cancer, one of whom is a first-degree relative of the other two, (2) cancer must be diagnosed before the age of 50 in at least one family member, and (3) familial adenomatous polyposis must have been ruled out. These criteria were designed for research and not clinical purposes, and failure to meet these criteria does not exclude the possibility of HNPCC. The Amsterdam criteria do not take into account the contribution of a family history of gynecologic malignancy to the probability of a hereditary cancer risk syndrome. In fact, the possibility of this syndrome is raised in a patient with a personal or family history of colorectal cancer diagnosed before 50 years of age in conjunction with ovarian cancer diagnosed at any age or endometrial cancer diagnosed before age 50. Less restrictive clinical criteria of HNPCC have been proposed and the Amsterdam criteria are being revised, but it is unlikely that any simple clinical algorithm will be able to reliably identify individuals with HNPCC. Thus, as for hereditary breast-ovarian cancer, genetic testing rather than clinical assessment alone is usually necessary to diagnosis HNPCC in an individual.

### Genetic Tests of Hereditary Cancer Risk

The characterization of the genes responsible for hereditary ovarian cancer, as well as the identification of family features that indicate the presence of mutations in these genes, provides an opportunity for direct identification of women at an increased risk of ovarian carcinoma. An important point worth repeating is that even in families at high risk (due to BRCA1 or BRCA2 mutations or HNPCC), each individual woman has only a 1 in 2 chance of being at increased risk herself. Despite a strong family history, a woman who did not inherit the predisposing mutation in her family has the cancer risk of a woman in the general population (ie, not elevated) and would not benefit from measures appropriate for her high-risk relatives. Only direct gene analysis can distinguish individuals in a family who have inherited mutations from those who have not.

Most clinically available tests for mutations in BRCA1 and BRCA2 either use gene sequencing to analyze for unknown mutations or probes for specific mutations (such as those characterized in a relative, or three specific mutations most commonly reported in women of Ashkenazi Jewish ancestry). Clinically available tests for identifying HNPCC often use techniques for identifying mutations (such as single-strand conformation polymorphism [SSCP] or conformation-sensitive gel electrophoresis [CSGE]) that are less expensive than sequencing but may be less sensitive. Regardless of the method used, if the results of such tests are to be used for medical management decisions or reported to the patient, the tests should be performed in a laboratory that has been certified for clinical testing by the Clinical Laboratory Improvement Amendments (CLIA) or a comparable agency. An up-to-date directory of clinical laboratories performing tests for the genes responsible for hereditary ovarian cancer can be obtained online from the Helix service (www.hslib.washington.edu/helix). While genetic tests of cancer risk are generally available to the medical community, many physicians refer patients who are suspected to have hereditary risk to cancer risk specialists such as oncologists or geneticists who provide the genetic counseling necessary for informed decision making regarding genetic testing. As already noted, once a mutation has been identified in the family, the cancer risks of relatives of that individual can be assessed by analysis for that specific mutation, which is less expensive than full gene analysis.

### Hereditary Risks of Ovarian Cancer

The risks of ovarian carcinoma conferred by mutations in BRCA1 and BRCA2 appear to be higher than for those in the HNPCC genes. Mutations in BRCA1 are associated with a risk of ovarian carcinoma estimated between 29% and 44% by 70 years of age (compared with the general population risk of 1.8%). It appears that individual mutations may differ substantially in ovarian cancer risk, however, and in some families, mutations in BRCA1 confer a risk of ovarian cancer as high as 65% by age 70.

These figures represent the most widely used estimates of ovarian cancer risk for women with a family history of ovarian cancer and/or early-onset breast cancer. A study of women in the general population who were not selected for family history calculated an ovarian cancer risk of 12% and 22% for two specific BRCA1 mutations, but this was based solely on self-administered family history questionnaires. Because of the limited accuracy of a recalled family history of ovarian cancer as provided by a patient, this study likely underestimated the incidence of ovarian cancer in women with mutations in these genes.

The risks of ovarian carcinoma conferred by mutations in BRCA2 appear to be somewhat lower than for BRCA1. The risk of ovarian carcinoma by age 70 for most BRCA2 mutations is currently estimated to be 27%. Most ovarian carcinomas associated with mutations in BRCA2 appear to occur after age 50.

Mutations in BRCA1 and BRCA2 also confer an increased risk of ovarian cancer in women already diagnosed with breast cancer. Our recent study demonstrated that in women with breast cancer, the risk of subsequent ovarian cancer was increased 10-fold in women with mutations in either BRCA1 or BRCA2 compared to women without mutations.

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**Table: Carrying a Mutation in BRCA1 or BRCA2***

<table>
<thead>
<tr>
<th>Any Relative Age &lt;50</th>
<th>Any Relative Ovarian Cancer</th>
<th>Any Relative BRCA1 or Ovarian Cancer</th>
<th>Modeled Probability of Mutation in BRCA1 (%)</th>
<th>Modeled Probability of Mutation in BRCA2 (%)</th>
</tr>
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<tbody>
<tr>
<td>-</td>
<td>-</td>
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<td>16.1</td>
<td>14.5</td>
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<td>41.5</td>
<td>9.5</td>
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<td>4.7</td>
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<td>22.9</td>
<td>12.5</td>
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<td>65.0</td>
<td>5.7</td>
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<td>22.9</td>
<td>22.9</td>
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<td>50.9</td>
<td>7.9</td>
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<td>-</td>
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<td>-</td>
<td>65.0</td>
<td>5.7</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>19.9</td>
<td>5.7</td>
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<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>86.7</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*These probabilities are calculated for a woman who has breast cancer diagnosed before 50 years of age. The probability of a mutation in an unaffected first-degree relative (sister or daughter) of such a woman is equal to one-half of the probability of the woman with breast cancer.

The risk of ovarian cancer associated with mutations in the HNPCC genes is approximately 9%,33 which is substantially elevated above the general population risk of 1.8%,34 but far lower than for mutations in BRCA1 and BRCA2.

Management of Women With Hereditary Ovarian Cancer Risk

Unlike breast cancer, which usually can be detected early by physical examination or mammography, ovarian cancer is difficult to detect in stage I or II. Circulating antigen CA-125 is elevated in only half of patients with stage I ovarian cancers and is also elevated in many nonneoplastic conditions. There is little data to suggest that screening high-risk women for elevated levels of CA-125 can detect ovarian cancer at an early stage. Similarly, transvaginal ultrasound lacks specificity as well as sensitivity. 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.26

It may be possible to employ medications to reduce the risk of ovarian cancer ("chemoprevention"). The use of oral contraceptives has recently been shown to reduce the risk of ovarian cancer in women with mutations in BRCA1 and BRCA2.35 This 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 66% reduction in the risk of ovarian cancer. 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. Oral-contraceptive use has been associated in some studies with a small increase in the risk of breast cancer, raising the possibility that oral contraceptives may increase the risk of breast cancer in women with BRCA1 and BRCA2 mutations. In this study, however, the authors observed no difference in the history of oral-contraceptive use between women who had breast cancer and those who had not,35 and other studies indicate that in fact the use of oral contraceptives contributes little to the risk of breast cancer.36 The contribution of oral contraceptives to breast cancer risk in women with mutations in BRCA1 and BRCA2, however, remains to be elucidated.

Along with consideration of surveillance and chemoprevention, prophylactic removal of the ovaries is an option to be discussed with women at increased risk of ovarian cancer. A National Institutes of Health Consensus Development Panel 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 age 35 years of age or after child-bearing is completed."37 Most women with BRCA1 and BRCA2 mutations who develop ovarian carcinoma do so after age 45,9,18 supporting deferral of this procedure until age 35 as recommended by this panel.

An important concern regarding prophylactic oophorectomy is the possibility of subsequent peritoneal carcinomatosis, which has been documented in 2% to 11% of women who have undergone this procedure.38,39 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.40 In some instances, the development of peritoneal carcinomatosis following oophorectomy has been shown to be the result of microscopic ovarian carcinoma that was not diagnosed at the time of the initial procedure.41 Emphasizing this possibility is a report of clinically unsuspected invasive carcinoma in 2 of 10 "prophylactically" removed ovaries from high-risk women, including 1 of the 7 women with a known mutation in BRCA1.12 It is thus particularly important that a pathologist evaluating the ovaries of such women be alerted to serially section and examine the ovaries in their entirety.

An issue of particular concern to women with mutations in BRCA1 or BRCA2 who are considering prophylactic oophorectomy is whether hormone replacement therapy contributes to their risk of breast cancer. While the use of postmenopausal hormone replacement therapy for longer than five years has been associated with a 1.46 relative risk of breast cancer,42 hormone replacement therapy does not appear to increase the rate of breast cancer in women who have first-degree relatives with breast cancer.44 Furthermore, in most instances, the amount of exogenous estrogen administered following oophorectomy is lower than would have been produced by the ovaries themselves because of the deleterious side effects of premature menopause45 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.46

Discussing Hereditary Risk of Ovarian Cancer With Patients

Unlike most other diagnostic tests related to cancer, the identification of hereditary susceptibility to malignancy could have implications for relatives of the individual being tested. For this reason, and also because of the medical and psychosocial issues that may accompany identification of hereditary cancer risk, the relevant issues should be discussed thoroughly with women assessed for hereditary breast-ovarian cancer. For those 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.46

Discussion should include the following: an assessment of a woman's family history and whether it indicates the likelihood of hereditary ovarian cancer risk; how testing could contribute to the characterization of those risks; and how medical management would be affected by a positive or negative test result. The possibility that a test might not provide conclusive information should also be discussed, as well as implications for family members. The patient should be encouraged to consider which relatives she would inform of the results (including her offspring) and when. 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 available legal protections that apply to the individual. Fortunately, adverse consequences of hereditary cancer risk assessment on health insurance are uncommon, with few, if any, documented reports of "genetic discrimination" at this time.

Because such a discussion with a patient 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. Counseling regarding hereditary breast-ovarian cancer risk that is provided by qualified health care professionals other than geneticists and genetic counselors may in fact be appropriate.47,48

Conclusions

Health care professionals have been taught in the past that all women with a strong family history of breast or ovarian cancer are at an increased risk of cancer. It is now apparent, however, that hereditary susceptibility to ovarian cancer is usually inherited as a single-gene autosomal dominant disorder, meaning that a woman with a strong family history may or may not be at increased risk. Recent studies have characterized criteria for identifying women most likely to have inherited mutations in the genes responsible for hereditary ovarian cancer risk, and several options are available for the medical management of such women. Health care providers can effectively counsel and manage women with hereditary risk of breast and ovarian cancer by being aware of the hallmarks of hereditary ovarian cancer risk, the options for medical intervention, the availability of genetic tests, and the concerns of patients about hereditary risk.

References


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