Breast and Ovarian Cancer

A resident asks....

Why should a primary care doctor know about breast or ovarian cancer genetics?

Key Points:
- Family history is an important tool in the assessment of breast and ovarian cancer risk
- Women are concerned about breast cancer and often over-estimate their risk. They may view themselves as candidates for genetic testing when their likelihood of a positive test is minimal.
- BRCA1/2 mutations are rare and there are few data to assess the outcome benefits of interventions to reduce risk
- Testing for BRCA1/2 is mentioned frequently in the medical and lay press. Your patient may ask you about the availability of gene testing for breast cancer

Learning Objectives for the Breast Cancer Module:
Participants will be able to:
- Evaluate family history information to identify women with an increased risk of breast and ovarian cancer
- Describe important features of autosomal dominant inheritance, including the potential for inheritance of risk through the paternal side
- Use current breast cancer risk assessment models and understand their limitations
- Evaluate management strategies for women with a high risk of breast or ovarian cancer

Web Resources for Genetics of Breast Cancer:
http://www.geneclinics.org
http://cancernet.nci.nih.gov/clinpdq/cancer_genetics/Cancer_genetics.html
CASE # 1

Your patient, a 36-year-old woman, recently attended her 15-year college reunion. She talked with her college roommate, who had been diagnosed with breast cancer. Her friend had genetic tests (done after her cancer diagnosis) that indicated she had a genetic predisposition to cancer. Your patient wants to know what she should do. Specifically, she asks if she should get the genetic test her friend got, to determine her own risk. She has checked the Internet and identified a company that offers this testing. She adds that her aunt had breast cancer at age 72.

Questions for Discussion:

1. What additional information would be helpful in determining this patient’s risk for breast cancer?
2. Assuming she has no additional family history of breast cancer, should BRCA1/2 testing be offered?
CASE # 1 - Discussion

1. What additional information would be helpful in determining this patient’s risk for breast cancer?

Family history represents the most useful tool for identifying women who may have an inherited predisposition to breast cancer. At the same time, the implications of a positive family history are variable - many women with a positive family history of breast cancer do not have a risk significantly above average.

Key elements in the family history are as follows (see Pinsky et al, 2001):

1. Unusual breast cancer history:
   - 2 or more relative with breast cancer
   - early onset of breast cancer (before age 50)
   - breast cancer in a male relative

2. Father’s side should be checked as well as mother’s side – breast cancer risk can be inherited from either side of the family

3. Ovarian cancer is also important - genetic risk typically involves both cancers

When is genetic risk present? There is no simple, well-defined threshold. In general, the more family history risk factors present, the greater the likelihood of genetic risk. One expert group (deBock et al, 1999) recommends genetics consultation if family history includes:

   2+ relatives with breast cancer, at least one affected < 50, or

   3+ relatives with breast cancer at any age

(These criteria assume that affected relatives are all in a single biological line (i.e., all on father’s side or mother’s side).

In addition, if both breast and ovarian cancer are present, or if male breast cancer is present, the likelihood of a genetic risk is higher for any given level of family history. (Males who carry BRCA1/2 mutations also have an increased risk of prostate cancer; however, prostate cancer is very common, so that a family history of prostate cancer is not highly predictive).
When evaluating family history, it is important to bear in mind that most women with a family history of breast cancer have a modestly increased risk, compared to the general population risk of 10% by age 80 (Feuer et al. 1993). Some have may NO increased risk compared to the average: for example, a US study estimated risk based on population-based data and found that breast cancer risk is in the average range for women whose mother or sister developed breast cancer at age 60 or older (the Claus model; see table below).

### Estimated risk of breast cancer according to family history (Claus et al. 1994)

<table>
<thead>
<tr>
<th>Breast Cancer in a Mother OR Sister, Affected at Age</th>
<th>Risk of Breast Cancer by Age 79</th>
<th>Breast Cancer In a Mother AND Sister, BOTH Affected at Age</th>
<th>Risk of Breast Cancer By Age 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>21%</td>
<td>20-29</td>
<td>48%</td>
</tr>
<tr>
<td>30-39</td>
<td>17%</td>
<td>30-39</td>
<td>44%</td>
</tr>
<tr>
<td>40-49</td>
<td>13%</td>
<td>40-49</td>
<td>35%</td>
</tr>
<tr>
<td>50-59</td>
<td>11%</td>
<td>50-59</td>
<td>25%</td>
</tr>
<tr>
<td>60-69</td>
<td>10%</td>
<td>60-69</td>
<td>16%</td>
</tr>
<tr>
<td>70-79</td>
<td>9%</td>
<td>70-79</td>
<td>11%</td>
</tr>
</tbody>
</table>

Ovarian cancer risk is also most readily predicted by family history. The table below provides estimates of the *relative risk (RR)* of ovarian cancer according to family history. A RR of 2 indicates a two-fold increased risk compared to women without a family history of ovarian cancer.

### Relative risk of ovarian cancer according to family history (Stratton et al., 1998)

<table>
<thead>
<tr>
<th>Family History of Ovarian Cancer</th>
<th>Relative risk of ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any 1st degree relative with ovarian cancer (mother, sister or daughter)</td>
<td>3.1 (95% CI 2.6-3.7)</td>
</tr>
<tr>
<td>Daughter with ovarian cancer</td>
<td>1.1 (95% CI 0.8-1.6)</td>
</tr>
<tr>
<td>Sister with ovarian cancer</td>
<td>3.8 (95% CI 2.0-5.1)</td>
</tr>
<tr>
<td>Mother with ovarian cancer</td>
<td>6.0 (95% CI 3.0-11.9)</td>
</tr>
<tr>
<td>More than one affected relative (1st or 2nd degree)</td>
<td>11.7 (95% CI 5.3-25.9)</td>
</tr>
<tr>
<td>2nd degree relative with ovarian cancer (Aunt or grandmother)</td>
<td>2.5 (95% CI 1.5-4.3)</td>
</tr>
</tbody>
</table>
Claus and Gail models for estimating breast cancer risk

Two empiric models for predicting breast cancer risk, the Claus model (Claus et al. 1994) and the Gail model (Gail et al. 1989) are available. Both have limitations, and the risk estimates derived from the two models may differ for an individual patient. Despite their limitations, they represent the best methods currently available for quantifying breast cancer risk.

Claus Model

The Claus model projects the probability of developing breast cancer for women with a family history of breast cancer; the Table on page 4 provides an example of risk estimates using this model. It is based on empiric data from the Cancer and Steroid Hormone Study (Claus et al., 1994). This model assumes that inherited risk is attributable to a rare autosomal dominant mutation with high penetrance (that is, almost all people who have the mutation get the disease). The risk estimate is based on a woman's current age; the number of first-degree and second-degree relatives with breast cancer (up to two); and their age of onset. The model provides cumulative risk estimates for several different family history configurations. It does not take other risk factors into account and thus may underestimate risk for women with behavioral factors, or reproductive histories that increase risk. It provides useful estimate for most women with a positive family history of breast cancer, but is not suitable for use with women who have three or more relatives with breast cancer.

Gail Model

The Gail model projects the probability of developing breast cancer (both invasive and non-invasive) based on some of the known non-genetic risk factors as well as limited family history information. It is based on the major predictors of risk identified in the Breast Cancer Detection Demonstration Project study (Gail et al, 1989). Risk factors utilized in the Gail model include current age, age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives (mother or sister) with breast cancer (categorized as 0, 1 or 2+). It does not consider second-degree relatives, paternal relatives, or importantly, the age of onset of breast cancer in the affected relative. It thus may overestimate risk in women whose mothers or sisters had breast cancer at an elderly age and underestimate risk for women who have second-degree relatives with early breast cancer. The Gail model has been validated as a predictor of breast cancer risk in women who adhere to...
regular mammography screening (Bondy et al. 1994; Speigelman et al. 1994). Validation studies indicate that the model overestimates risk in women who do not get screened regularly. The reasons for this discrepancy are not clear. It could reflect a selection bias in favor of higher risk among women who participated in the studies from which the Gail risk estimates were made; or it could reflect the increased detection in screened women of lesions that are unlikely to progress to clinical cancer (e.g., small, slow-growing cancers or DCIS).

The Gail model is the basis for the **Breast Cancer Risk Assessment Tool**, a computer program that is available from the National Cancer Institute by calling the **Cancer Information Service** (1-800-4-CANCER). This version of the Gail model estimates only the risk of invasive breast cancer. This same model was used to determine subject eligibility in the NSABP Tamoxifen Breast Cancer Prevention Trial.

**Identifying inherited risk - BRCA1/2 mutations**

The women at highest risk of both breast and ovarian cancer are those with an inherited autosomal dominant risk for breast/ovarian cancer – e.g., risk based on the presence of a BRCA1 or BRCA2 mutation. These mutations are rare: prevalence is estimated to be about 1/800. As noted above, examination of the details and pattern of the family history is the most useful approach for identifying women who are likely to carry such mutations (Biesecker et al. 1993; Ford et al. 1995). **CancerGene** software includes a tool for assessing the likelihood of a mutation, using family history data (http://www.swmed.edu/home_pages/cancergene/).

2. **Assuming she has no additional family history of breast cancer, should BRCA1/2 testing be offered?**

In addition to family history of breast cancer, a family history of ovarian cancer is relevant. Assuming there is no history of ovarian cancer and no further history of breast cancer (including none on her father’s side), the patient’s risk to have breast cancer based on her family history is similar to that of an average risk woman, according to the Claus model. Indeed, her risk would be in the average range even if her mother, rather than her aunt, had had breast cancer in her 70s.
(see Table page 4). It would be difficult to justify BRCA1/2 testing in this setting. Her likelihood of having a negative test result is very high, and could lead to a mistaken belief that her negative test result lowered her risk. In fact, her pre-test risk would not be changed by a negative test result, because she is not expected to be carrying a cancer-predisposing mutation.

Other risk factors, such as those assessed in the Breast Cancer Risk Assessment Tool, could provide additional information about her risk. Note, however, that her family history of an aunt with breast cancer (a second degree relative) would not be considered positive in the Gail model on which this tool is based. In the absence of family history, her Gail model risk would not be elevated unless she had a history of prior dysplasia on breast biopsy or lobular carcinoma in situ. Such history of breast disease would probably already have led to an appropriate follow-up plan for breast surveillance.

Common over-estimate of breast cancer risk

The patient may benefit most from a discussion of risk that allows her to recognize her average lifetime risk, and, given her age, her very low short-term risk. A review of recommended breast cancer prevention strategies may also be helpful (mammography, breast self-exam and clinician exam).

An important context for this case is that women commonly misunderstand their risk of breast cancer. Many over-estimate their lifetime risk to a significant degree (Alexander et al. 1996; Black, Nease & Tosteson 1995; Bunker, Houghton & Baum 1998; McCaul et al. 1998; Pilote & Hlatky 1995) and over-estimate the proportion of female deaths attributable to breast cancer as well (Black, Nease & Tosteson 1995; Gallup Survey 1995). In addition, women often see breast cancer as a risk of young women. In one survey, for example, women between 40 and 50 over-estimated their short-term risk of dying from breast cancer by 22-fold and their lifetime risk by 12-fold (Black, Nease & Tosteson 1995). Many women also have the mistaken belief that their risk diminishes as they get older (Dolan, Lee & McDermott 1997; Fulton, Rakowski & Jones 1995). Taken together, these misperceptions of risk can be a cause of undue anxiety among younger women and of failure to complete mammography screening among older women.
CASE # 2

A woman of Ashkenazi Jewish descent asks about the “breast cancer gene.” She has been reading in the papers that Jewish women may be more at risk. Her cousin and grandmother both had breast cancer, but they are on her father’s side, so she assumes their cancers do not affect her risk. Clarification of her family history reveals that her paternal grandmother had breast cancer at age 42. A first cousin (daughter of a paternal aunt) had breast cancer at age 45.

Questions for Discussion:

1. What counseling should be provided regarding her family history of breast cancer?
2. Assuming she has no additional family history, should BRCA1/2 testing be offered?
CASE #2 - Discussion

1. What counseling should be provided regarding her family history of breast cancer?

Her family history raises the possibility of an inherited breast cancer predisposition on her father’s side. The patient has articulated a common misunderstanding, that a family history of breast cancer is important only if it is present on the mother’s side. In fact, the cancer predisposition can be passed on by either the father or the mother (see Review of family history characteristics associated with BRCA1/2 mutations below). Two additional comments can be made about her family history. If a cancer-predisposing mutation is present, both her affected relatives (her grandmother and her cousin) probably carry it, based on their age of diagnosis. If this is the case, her cousin’s mother (her paternal aunt) is an unaffected mutation carrier – a phenomenon that has been described for both BRCA1 and BRCA2 mutations.\(^1\) If a mutation is present, her father has a 50% chance of carrying it, and as a result, the patient has a 25% chance of inheriting it.

Review of family history characteristics associated with BRCA1/2 mutations (autosomal dominant inheritance)

- The cancer predisposition is passed from one generation to the next (“vertical transmission”).
- Each child of a person with the inherited predisposition has a 50% chance of inheriting the predisposition.
- Males and females inherit the cancer predisposition with equal frequency.
- Male carriers will usually not be affected, that is, the cancer predisposition is largely sex-limited. However, they can still pass the predisposition on to their children as above. Men with BRCA2 mutations have a 60-fold increased risk of developing breast cancer increased (from 0.10% to 6%).
- Lifetime cancer risk may be very high in those who inherit the cancer predisposition but appears to be subject to modifying factors - e.g. lifetime risk of breast cancer associated with BRCA1 mutations has been estimated to range from 37%-85%.

\(^1\) As an alternative explanation, the grandmother and cousin could carry different mutations, with the cousin inheriting a mutation from her father. This situation has been observed in Ashkenazi Jewish families, where the
• Inherited risk for breast cancer is usually associated with inherited risk for ovarian cancer.

Other cancer risks may also occur, including an increased risk of prostate cancer in males.

The most important issues to address in counseling the patient about a potential inherited risk are her understanding of inherited cancer risk, her concerns and worries, and the options available to her to reduce risk (see the Discussion for Question # 2 below). People vary in the value they place on knowing about genetic risk. For some, the possibility of an inherited cancer predisposition provides a powerful motivation to be tested. Others feel less motivation to pursue such knowledge, and some find it threatening. The patient’s age may influence her decision. If she is 50 years old, already having regular mammograms, and uninterested in interventions such as prophylactic surgery, she may feel no urgency to pursue the question of inherited risk. If she is 38, knowledge about risk may change her screening decisions. It is important to address the patient’s assessment of her own personal risk and the impact of her learning that the family history on her father’s side is pertinent to her own risk.

Pursuing genetic testing involves a number of complex issues as outlined in question 2 below. Testing may or may not be informative, and should ideally start with an affected family member. A positive result would have implications both for herself and for her children. All of these issues may influence the patient’s thinking about cancer risk and interest in pursuing genetic testing. Discussion of inherited cancer risk might ideally occur over several visits, giving the patient time to absorb information. Other family members on the paternal side of the family might also benefit from genetic counseling at some point in the future, to discuss genetic testing options.

2. Assuming she has no additional family history, should BRCA1/2 testing be offered?

The phrasing of the question as “should the test be offered?” as opposed to “recommended” represents the two dynamics of the testing decision. 1) Is there a justification for the testing based on her estimated risk, and 2) how do the benefits and risks of testing coincide with the patient’s reasons for testing and management decisions she would make based on the results?

cumulative prevalence of BRCA1/2 mutations is about 2.5% due to 3 relatively common mutations (Roa et al.)
It is reasonable to offer testing to this patient; however the offer of testing is actually to the patient’s family, as testing should be offered first to an affected family member. In addition, the results of the test will affect more than just the patient. The likelihood of a BRCA1 or BRCA2 mutation in the family is approximately 20%, based on empiric data reported by Myriad Laboratories, the company that offers testing (http://www.myriad.com/gtmp.html). Factors contributing to this estimate are the presence of two family members with breast cancer under age 50 and the Ashkenazi Jewish ethnicity. Three cancer-predisposing mutations (two in the BRCA1 gene and one in the BRCA2 gene) are relatively common in women of Ashkenazi Jewish descent (Jews of Central and Eastern European ancestry), with a cumulative prevalence of about 2.5% (Roa et al. 1996); as a result, Jewish women with significant family history have a higher likelihood of carrying BRCA1/2 mutations than non-Jewish women.

In offering the test to the patient, the benefits and risks of testing as outlined below should be discussed so that the patient can make an informed decision on whether or not to pursue testing.

**Why test?**

Genetic testing offers the opportunity to identify individuals with an increased risk of cancer. This risk information may be helpful in planning decisions about cancer screening or use of prophylactic surgery; some people may want to use information about their personal risk in making family planning or career decisions. However, evidence on the efficacy of interventions to reduce risk is limited. The decision to be tested is thus a subjective one, in which risks and benefits must be weighed in terms of personal values and preferences, in light of many uncertainties. Genetic testing also offers the opportunity to determine which family members have not inherited the cancer predisposition present in the family.

**Who should be offered testing?**

The most appropriate candidates for testing are those who have a high likelihood of carrying a genetic susceptibility to cancer -- i.e., individuals from cancer-prone families showing
characteristics of autosomal dominant inheritance. Estimates of the likelihood of finding a BRCA1 or BRCA2 mutation based on family history can be obtained from the Cancer Gene web site (http://www.swmed.edu/home_pages/cancergene/) or from data based on the experience of the laboratory offering the testing (http://www.myriad.com/gtmp.html).

Optimal testing strategy

1. Test one or more affected relatives.
2. If a mutation is identified, testing for this specific mutation can be offered to unaffected family members at a much lower cost.
3. If an individual does test positive, follow-up counseling should include discussion of interventions to reduce risk (see Table, page 13)

Why test an affected relative first?

If a mutation cannot be identified in an affected family member, further testing will be non-informative and should not be pursued. However, if a mutation can be identified in an affected relative, both negative and positive test results will be informative in unaffected family members.

Need for counseling (Biesecker et al. 1993; Geller et al. 1997)

Genetic testing involves potential risks as well as benefits. Individuals contemplating testing should have the opportunity to consider these issues carefully prior to deciding whether or not to be tested. Knowledge of an inherited predisposition may cause anxiety and family distress, and may also pose a risk for loss of insurance or employment opportunities.

Preventive care options for carriers of BRCA1 and BRCA2 mutations

The benefits of tailored preventive care for individuals with an inherited predisposition to breast and/or ovarian cancer are largely unproven. Most recommendations are made on the basis of a presumed benefit for individuals with a high lifetime risk of cancer (see Table, next page).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer Surveillance</strong></td>
<td></td>
</tr>
<tr>
<td>• Breast self-exam</td>
<td>A consensus panel has recommended early initiation of mammography screening based on expert opinion (Burke et al. 1997). <strong>No systematic study of the risks and benefits of early screening are available.</strong></td>
</tr>
<tr>
<td>• Clinical breast exam, annually or semiannually, beginning at age 25-35</td>
<td></td>
</tr>
<tr>
<td>• Mammography, annually beginning at age 25-35</td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian Cancer Surveillance</strong></td>
<td></td>
</tr>
<tr>
<td>• Pelvic examination, q 6-12 months, beginning age 25-35</td>
<td>A panel has recommended ovarian cancer screening based on expert opinion (Burke et al. 1997). <strong>Studies of these screening methods have not demonstrated outcome benefit and have demonstrated limited sensitivity and specificity.</strong></td>
</tr>
<tr>
<td>• Transvaginal US with color doppler and serum CA-125 level, q 6 -12 months, beginning age 25-35</td>
<td></td>
</tr>
<tr>
<td><strong>Preventive Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>• Breasts: Prophylactic bilateral simple mastectomies + reconstruction</td>
<td><strong>A panel has recommended the offer of prophylactic mastectomy</strong> based on expert opinion (Burke et al. 1997). A retrospective study of prophylactic mastectomies performed at the Mayo Clinic study estimated a 90% reduction in breast cancer risk from the procedure (Hartmann et al. 1999). A subset analysis of BRCA1/2 mutations carriers, reported but not yet published, indicates a similar benefit for this group.</td>
</tr>
<tr>
<td>• Ovaries: Prophylactic bilateral oophorectomy after completion of desired reproduction</td>
<td><strong>A panel has recommended the offer of prophylactic oophorectomy</strong> based on expert opinion(Burke et al. 1997). A small observational study with limited power found no statistical difference in the incidence of ovarian cancer between those that had or did not have an oophorectomy (Strueming et al. 1997).</td>
</tr>
<tr>
<td><strong>Chemoprevention</strong></td>
<td></td>
</tr>
<tr>
<td>• Tamoxifen</td>
<td><strong>No evidence-based recommendation for BRCA1/2 mutation carriers can be made at this time.</strong> A US randomized trial of women selected on the basis of the Gail model (Gail et al. 1989) demonstrated ~ 50% reduction in breast cancer risk over 4 years (Fisher et al. 1998). A smaller UK trial, using more stringent family history criteria for subject selection, failed to demonstrate benefit (Powles et al. 1998).</td>
</tr>
</tbody>
</table>
REFERENCES


Burke W et al. Translating genetics into the language of primary care. Under review.


