Breast and Ovarian Cancer: Inherited Risk

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Key Points

- Evaluation of family history information helps to identify rare families in which a mutation in the *BRCA1* or *BRCA2* gene causes a high risk for breast and ovarian cancer.
- In evaluating family history, it is important to consider affected relatives on the father's side.
- The likelihood of identifying a mutation in the *BRCA1* or *BRCA2* gene is increased in women who have breast cancer and are of Jewish and Icelandic descent.

Learning Objectives

Participants will be able to:

- Evaluate family history information to identify women with an increased risk for breast and ovarian cancer;
- Describe important features of autosomal dominant inheritance, including incomplete penetrance and the potential for inheritance of risk through the paternal side;
- Evaluate management strategies for women with a high risk for breast or ovarian cancer.

Family History Issues

Key elements in the family history of breast and ovarian cancer include (see Pinsky et al 2001):

- *Unusual breast cancer history:*
  - Two or more relatives with breast cancer
  - Early onset of breast cancer (before age 50)
  - Breast cancer in a male relative
  - Bilateral or multifocal occurrence of breast cancer
- *Father's family history:* breast cancer risk can be inherited from either the mother's or the father's side of the family.

- *Ovarian cancer history in family members:* genetic risk often 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 inherited risk. One expert group (deBock et al 1999) recommends genetics consultation if family history includes:

- 2+ relatives with breast cancer, at least one affected before age 50 years, or
- 3+ relatives with breast cancer at any age.

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

The US Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (*BRCA*) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*). The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing (see USPSTF Guidelines).

In addition, if **both breast and ovarian cancer** are present, or if **male breast cancer** is present, genetic risk increases. (Males who have *BRCA1*/*BRCA2* mutations also have an increased risk for prostate cancer; however, because prostate cancer is very common, a family history of prostate cancer is not highly predictive.)

Red Flags

Some clinical presentations raise the question of inherited breast/ovarian cancer:

- Breast cancer occurring at a young age — for example, breast cancer before age 45
- Two or more cancers in a single individual — for example, bilateral

breast cancer, or breast and ovarian cancer
- Breast cancer in a male

Case 2. A Jewish Woman Asks about the "Breast Cancer Gene"

At the time of her annual physical, a 30-year-old woman asks about the "breast cancer gene." She is Jewish, and has been reading in the papers that Jewish women may be more likely to have this gene. 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 50. A first cousin (daughter of her father's sister) was diagnosed with breast cancer a year ago at age 42. Her father is in good health at 62. She has two older sisters, aged 33 and 35 years, who are also worried about their risk.

Clinical Care Issues

After non-melanoma skin cancer, breast cancer is the most common cancer in women. Most breast cancers occur among women in their 60s and 70s, but about 25% of breast cancers occur before age 50.

Early detection of breast cancer increases survival. To aid in early detection, current US screening recommendations call for the initiation of mammography screening and clinical breast examination for all women at age 40 [USPSTF Screening for Breast Cancer, ACS Cancer Detection Guidelines]. Initiation of screening before age 40 is recommended for some women, based on family history or other factors indicating increased risk.

When a family history suggests a high risk for breast or ovarian cancer, further evaluation is merited, including detailed evaluation of family history over several generations and consideration of genetic testing (see Genetic Counseling and Testing) because additional preventive measures may be appropriate (see Interventions).

Risk Assessment

Relevant risk factors

Family history (see above; US Surgeon General's Family History Initiative) represents the most useful way to identify women who may have an inherited predisposition to breast cancer. However, the implications of a positive family history are variable. Many women with a positive family history of breast cancer have only a moderately increased risk, and can follow the same screening program recommended for women with average breast cancer risk.

Other risk factors for breast cancer include a history of breast biopsies, a prior diagnosis of atypia on a breast biopsy, a history of high radiation exposure to the chest (for example, from therapeutic radiation), exposure to prolonged hormone replacement therapy, and reproductive factors such as early menarche, late menopause, nulliparity, and birth of first child after age 30. A breast cancer risk assessment tool developed by the National Cancer Institute provides an estimate of risk based on some of these factors.

Family history in this patient

This patient's 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 father or mother. In evaluating the patient's family history, it is useful to bear in mind the characteristics of family history associated with the inheritance of mutations in the *BRCA1* and *BRCA2* genes, which confer a high lifetime risk for breast and ovarian cancer.

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% risk of inheriting the predisposition.
- Males and females inherit the cancer predisposition with equal frequency.
- Males with a *BRCA1* or *BRCA2* mutation usually do not develop cancer. However, they can still pass the mutation (and hence, predisposition) on to their children as above. Men with a *BRCA2* mutation have a 60-fold increased risk of developing breast cancer (about a 6% lifetime risk) compared with men of average risk. Men with a *BRCA1* or *BRCA2*

mutation also have an increased risk for prostate cancer.
- Lifetime breast cancer risk is estimated to 50% to 85% for women who inherit a *BRCA1* or *BRCA2* mutation. The term "incomplete penetrance" is used to refer to the situation in which a woman with a *BRCA1* or *BRCA2* mutation does not develop cancer.

Diagramming a pedigree can help in evaluation of the family. Based on the information the patient has provided, the pedigree is as follows (with the patient indicated by an arrow):

The two cases of early breast cancer in the family raise the possibility of an inherited risk. Further evaluation of the family is merited. The evaluation approach taken in a medical genetics clinic is outlined below.

Genetic Counseling and Testing

Pedigree assessment

As a first step in a genetic evaluation of the patient's risk, a **pedigree assessment** is undertaken. This process includes a search for additional family history information that might clarify the patient's risk. The patient is often encouraged to talk to family members to clarify medical information. Medical records or death certificate are often sought for any family member with a history of cancer, to confirm the type of cancer and, if possible, the age at diagnosis. The potential implications of additional family history for

this patient can be illustrated by considering the likelihood of inherited risk with and without additional affected family members. The patient's ethnicity is also a factor, as summarized below.

The information the patient has provided identifies two relatives (her grandmother and her cousin) with early-onset breast cancer. If both her grandmother and her cousin have the same cancer-predisposing mutation, we would have to assume that her cousin's mother (her paternal aunt) has the mutation but is unaffected (that is, she represents an instance of incomplete penetrance). This finding is uncommon, but has been described for both *BRCA1* and *BRCA2* mutations. However, we want to be sure that we have accurate information about this aunt's medical history.

Assuming that further evaluation confirms that no additional cancer is present in the family, we can use a statistical program (BRCAPRO) to estimate the likelihood that a *BRCA1* or *BRCA2* mutation is present in the family. Like other statistical modeling programs, BRCAPRO may overestimate or underestimate risk in some patients; however, it provides a rough estimate of the likelihood of an inherited breast/ovarian cancer syndrome in the family. This model starts with an affected family member (for example, the patient's grandmother), and calculates the likelihood of a *BRCA1* or *BRCA2* mutation being present, based on published studies of personal and family history characteristics of women with these mutations.

For the pedigree above, the estimate is very different depending on whether the person with cancer is of Ashkenazi Jewish ancestry. The higher risk for Ashkenazi Jews reflects the higher prevalence of specific *BRCA1* and *BRCA2* mutations in this population: three mutations (two in the *BRCA1* gene and one in the *BRCA2* gene) are estimated to have a cumulative prevalence of 2.5% [Roa et al 1996].

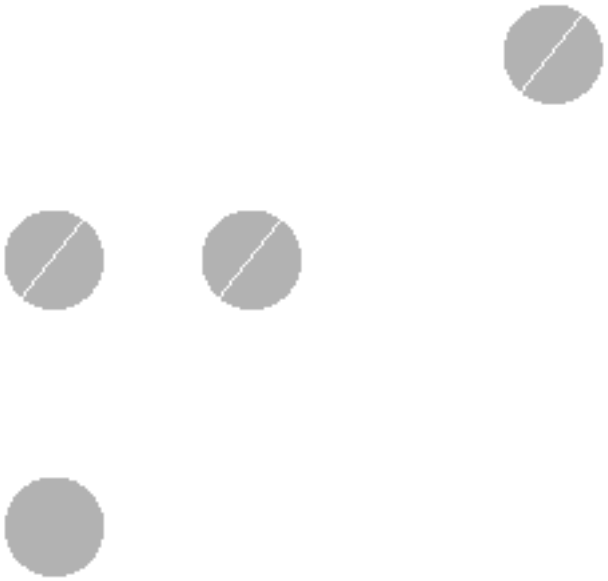
The BRCAPRO estimate of the likelihood of *BRCA1* or *BRCA2* mutation in the grandmother, based on initial pedigree data, is:

- Ashkenazi Jewish ancestry: 43.7%
- No Ashkenazi Jewish ancestry: 2.8%

If a mutation is present in the family, we assume that the father had a 50% of inheriting it from his mother, and the patient has a 50% risk of inheriting it from her father. Thus, for an Ashkenazi Jewish patient with this family history, the likelihood of inheriting a *BRCA1* or *BRCA2* mutation would be 0.437 x 0.5 x 0.5 = .11, or 11%. The likelihood would be much lower for a

patient who was not of Ashkenazi Jewish ancestry.

But what if further exploration of family history reveals additional cases of cancer? For the purposes of illustration, let's assume that further exploration of the family history reveals ovarian cancer in two relatives, as follows:



This additional family history is significant, because it greatly increases the likelihood that a *BRCA1* or *BRCA2* mutation is present in the family. Again using BRCAPRO, the estimated likelihood of a *BRCA1* or *BRCA2* mutation in this patients' grandmother is:

- Ashkenazi Jewish ancestry: 96.3%No Ashkenazi Jewish ancestry: 77.2%

In this case, the likelihood that the patient inherited a *BRCA1* or *BRCA2* mutation is estimated to be 24% if she is of Ashkenazi Jewish ancestry (0.963 x 0.5 x 0.5) and 19% (0.772 x 0.5 x 0.5) if she is not.

Genetic testing

Given the estimates outlined above, it is reasonable to offer *BRCA1*/ *BRCA2* testing to this patient. However, the offer of testing is actually to the patient's family, as testing should ideally be offered first to an affected

family member. In addition, the results of the test will affect the assessment of risk for other people in the family as well as the patient. In offering the test to the patient, the benefits and risks of testing should be discussed, as outlined below, so that the patient can make an informed decision about whether to pursue testing.

Why test? Genetic testing offers the opportunity to identify individuals with a very high risk for breast or ovarian cancer. Breast cancer may occur at a young age. This risk information may be helpful in planning decisions about cancer screening, the use of tamoxifen as a preventive treatment, or use of prophylactic surgery. In addition, some people may want to use information about their personal risk in making family planning or career decisions. Genetic testing also offers the potential to determine which family members have not inherited the cancer predisposition present in the family. The decision to be tested is one in which risks and benefits must be weighed in terms of personal values and preferences, as well as medical considerations.

Who should be offered testing? The most appropriate candidates for testing are those who have a high likelihood of having a genetic susceptibility to cancer — that is, individuals from cancer-prone families showing characteristics of autosomal dominant inheritance. In this family, the best person to undergo initial testing would be the patient's 43-year-old cousin, who was diagnosed with breast cancer at age 42.

Why test an affected relative first? If a causative mutation cannot be identified in an affected family member, testing an at-risk relative will be uninformative and should not be pursued. However, if a causative mutation can be identified in an affected relative, both negative and positive test results will be informative in unaffected family members. When a specific causative mutation is found, others in the family can be tested for the specific mutation — at much lower cost than the initial testing — to determine whether they have inherited the cancer-predisposing mutation.

Exception: Because three specific mutations are relatively common in Ashkenazi Jewish populations, it may be reasonable to test an unaffected family member for these three mutations, without first testing the affected family member. However, if this approach is used, a negative test result will be uninformative, because true negatives and false negatives cannot be distinguished. (A true negative would mean that the patient had not inherited the cancer-predisposing mutation present in the family; a false negative would mean that the patient had inherited the mutation, but it was not detected by the test.)

Interventions

Several interventions are recommended for women who have a *BRCA1* or *BRCA2* mutation. These interventions are supported by expert opinion and retrospective and prospective observational data, including both cohort and case-control studies. A detailed review of the evidence related to these interventions can be found in the National Cancer Institute PDQ review: Genetics of Breast and Ovarian Cancer. These interventions include:

- **Breast cancer screening.** Mammography screening has not been extensively evaluated in high-risk women; prospective studies of MRI screening suggest that it has higher sensitivity than mammography but may occasionally miss cancers seen on mammography. Most experts recommend that screening be initiated by age 30, and that mammography and MRI screening be used alternately on a six-monthly basis.
- **Ovarian cancer screening.** Methods for screening include vaginal ultrasound and measurement of serum CA-125 level. These strategies have limited sensitivity and specificity, and are of uncertain benefit.
- **Tamoxifen.** A US randomized trial demonstrated reduction in breast cancer occurrence over four years of treatment among women with increased risk as estimated by the Gail statistical model [Gail et al 1989]. A subset analysis suggested that women with a *BRCA2* mutation may benefit from this treatment, but women with a *BRCA1* mutation may not.
- **Risk-reducing mastectomy.** Both retrospective and prospective observational studies indicated that breast cancer risk is substantially reduced (>90%) by this surgery. Observational studies suggest that only a minority of women elect to have this surgery prior to a cancer diagnosis.
- **Risk-reducing oophorectomy.** Both retrospective and prospective observational studies indicate that ovarian cancer risk is substantially reduced (>90%) by this surgery.

Ethical/Legal/Social/Cultural Issues

Genetic testing involves potential risks as well as benefits [Biesecker et al 1993, Geller et al 1997]. Individuals contemplating testing should have the opportunity to consider these issues carefully prior to deciding whether 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.

Family communication is an important issue. Some patients may be reluctant to contact an affected family member to initiate the process, or to discuss test results. Yet some experts have suggested that when a genetic risk is identified in the family, there may be a duty to disclose the potential for shared risk with other family members.

Do health care providers have a duty to contact family members about a possible inherited risk? This question is currently controversial. The American Society of Clinical Oncology (ASCO) has suggested that when a patient is identified to have an inherited risk for cancer, the health care provider's duty to other family members is limited to counseling the patient about the family risk and encouraging the patient to discuss the genetic risk and genetic testing options with family members [ASCO 2003].

Resources

- **American Cancer Society**
  Provides contact information for regional support groups and programs, cancer information, patient and family education materials, and free mammograms.
  1599 Clifton Rd NE
  Atlanta, GA 30329
  Phone: 800-227-2345

- **Breast Cancer Information Core** **NHGRI (National Human Genome Research Institute) Cancer Genetics Branch**
  Breast cancer resources on the Web

- **NCI (National Cancer Institute) Breast Cancer Home Page**

- **CancerCare**
  275 7th Avenue
  New York, NY 10001
  Phone: 212-712-8080; 1-800-813-HOPE (4673)
  Fax: 212-712-8495
  Email: info@cancercare.org

- **Facing Our Risk of Cancer Empowered (FORCE)**
  A discussion forum specifically for women who are at a high risk of developing ovarian cancer or breast cancer.
  934 N University Dr, PMB #213
  Coral Springs, FL 33071
  Phone: 954-255-8732
  Email: info@facingourrisk.org

- **Genetics of Breast and Ovarian Cancer (PDQ)**
  A service of the National Cancer Institute

- **Gilda's Club**
  322 Eighth Avenue, Suite 1402
  New York, NY 10001
  Phone: 1-888-GILDA-4-U
  Fax: 914-304-0549
  Email: info@gildasclub.org

- **Mid-Atlantic Cancer Genetics Network: Breast / Ovarian Cancer**

- **The National Alliance of Breast Cancer Organizations**
  An advocacy group that serves as an umbrella for 370 breast cancer groups nationwide. Provides information, a newsletter, and treatment information. Also provides grants for programs on early detection and education.
  9 East 37th Street, 10th Floor
  New York, NY 10016
  Phone: 212-889-0606; 888-806-2226
  Fax: 212-689-1213
  Email: NABCOinfo@aol.com

- **National Breast Cancer Centre Home Page-Australia**

- **The National Breast Cancer Coalition**
  An advocacy group seeking public policy change to benefit breast cancer patients and survivors
  1701 L St NW, Suite 1060
  Washington DC 20036
  Phone: 202-296-7477; 800-935-0434

- **NCBI Genes and Disease Webpage: Breast cancer**

- **National Cancer Institute**

- **The National Coalition for Cancer Survivorship**
  A consumer organization that advocates on behalf of all people with cancer
  1010 Wayne Avenue, Suite 770
  Silver Spring, MD 20910
  Phone: 877-NCCS-YES (877-622-7937)
  Fax: 301-565-9670
  Email: info@cansearch.org

- **National Library of Medicine Genetics Home Reference: Breast cancer**

- **Ovarian Cancer (National Ovarian Cancer Coalition)**
  500 NE Spanish River Blvd, Suite 14
  Boca Raton, FL 33431
  Phone: 1-888-OVARIAN; 561-393-0005
  Fax: 561-393-7275
  Email: nocc@ovarian.org

- **Susan G Komen Breast Cancer Foundation**
  Information, referrals to treatment centers. Answers questions from recently diagnosed women and provides emotional support. Funds research and programs for women who do not have adequate medical service and support.
  Occidental Tower
  5005 LBJ Freeway, Suite 370 LB74
  Dallas, TX 75244
  Phone: 800-462-9273 (hotline); 214-450-1777
  Email: helpline@komen.org

- **US Preventive Services Task Force Guidelines on Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility**

- **Y-Me National Organization for Breast Cancer Information**
  Hotline staffed by counselors and volunteers who have had breast cancer. Information, referrals, support.
  212 West Van Buren St, Suite 500

Chicago IL 60607
Phone: 800-221-2141
Fax: 312-294-8597

- **Cancernet: PDQ® Cancer Information Summaries: Genetics**
- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReview:* BRCA1/BRCA2 Hereditary Breast/Ovarian Cancer**
- **GeneTests Resources for Breast and Ovarian Cancer**

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