Gene Scene

Why should primary care physicians know about breast cancer genetics?

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Your patient, a 36-year-old woman, recently learned that her former college roommate was diagnosed with breast cancer. She wants to know if she should have the genetic test her friend mentioned to assess her risk. Her only family history is that her mother has breast cancer at age 72. She mentions that her roommate did not have a family history of breast cancer, "except on her father's side, and that doesn't count."

Summary points

- Women are concerned about breast cancer and often overestimate their risk; they may view themselves as candidates for molecular genetic testing even when their likelihood of having cancer is minimal
- Mutations of the *BRCA1* or *BRCA2* genes are rare, and risk-reduction strategies are not well established by evidence-based medicine
- Certain ethnic groups have a higher prevalence of clinically significant *BRCA1* and *BRCA2* gene mutations
- Testing for *BRCA1* and *BRCA2* cancer-producing mutations is mentioned frequently in the medical and lay press; patients may ask about the availability of this testing
- Molecular genetic testing of the *BRCA1* and *BRCA2* genes is being marketed to physicians

PREVALENCE

The National Cancer Institute estimates that about 1 in 50 women will have breast cancer by age 50 years and that about 1 in 10 women in the United States will develop breast cancer by age 80 years.[1] Excluding cancers of the skin, breast cancer is the most common cancer among women, accounting for 1 of 3 cancer diagnoses. Male breast cancer is rare. The ratio of male breast cancer to female breast cancer is 1:125.

Women commonly overestimate their lifetime risk of breast cancer to a substantial degree,[2-5] and they overestimate the proportion of female deaths attributable to breast cancer.[4,6] In 1 survey, for example, women between ages 40 and 50 years overestimated their short-term risk of dying of breast cancer by 22-fold and their lifetime risk by 12-fold.[4] Concerns about the appropriate use of genetic testing in general are amplified by the milieu of women's concerns about breast cancer. Studies have shown that women are receptive to *BRCA1* and *BRCA2* testing,[7-9] despite the lack of a family history that might justify its use.

ETIOLOGY

Breast cancer is caused by both nongenetic (listed in the box) and genetic factors. Most of these risk factors, with the exception of atypical hyperplasia, produce less than a 2-fold increase in the risk of breast cancer and, thus, may contribute relatively little to risk in women from high-risk families. Other possible risk factors include a diet that is high in fat and low in fiber, fruits, and vegetables; lack of exercise; and induced abortion. The relationship between these risk factors and a genetic predisposition is not yet understood. Some hormonal risk factors such as age of menarche and of menopause could be influenced by polygenic inheritance. A family history of breast cancer is a rare but important contributor to breast cancer risk.

Women at high risk of inherited breast cancer typically have several relatives who had breast cancer diagnosed before age 45 to 50 years and 1 or more relatives affected with bilateral or multifocal breast cancer; they may also have a family history of ovarian cancer or male breast cancer.[10]

BRCA1 AND *BRCA2*

Mutations in the *BRCA1* and *BRCA2* genes have been identified as a cause of inherited susceptibility to breast and ovarian cancer. The estimated lifetime risk of breast cancer associated with *BRCA1* and *BRCA2* mutations ranges from 30% to 85%. Penetrance is probably determined in part by the nature of specific mutations and in part by environmental and genetic modifiers.[11,12] For women in an unselected population found to have a

Nongenetic contributors to breast cancer risk

- Menarche before age 12 years
- Menopause after age 55 years
- First live birth after age 30 years
- Nulliparity
- Previous breast biopsies
- Atypical hyperplasia diagnosed by breast biopsy
- Obesity
- Alcohol use
- Hormone replacement therapy
- Excessive radiation exposure

BRCA1 or *BRCA2* mutation, the predictive value of the test would be less certain and probably at the lower end of the range.[13-16]

Out of 10,000 women, 1,000 will have a mother or sister who has had breast cancer, but only 15 have a *BRCA1* or *BRCA2* mutation that confers high risk. It is estimated that in a primary care practice of 1,000 patients, 1 case of breast cancer will be diagnosed every 1 to 2 years, but 1 case of inherited breast cancer due to *BRCA1* or *BRCA2* mutation will be diagnosed every 20 years.[17]

Other genetic factors

Details of extremely rare genetic syndromes with a high breast cancer risk are given at www.geneclinics.org/profiles/brca/index.html. Current research also suggests a possible risk association between breast cancer and several common genetic variants. Common genetic variants are likely to be considerably more common than high-risk cancer-predisposing mutations and, as a result may have a larger effect on overall population risk. In addition, the effect of genetic variants of this kind is likely to vary with environmental exposures and other nongenetic risk factors.

RISK ASSESSMENT

The risk of breast cancer developing depends on a person's family history and nongenetic risk factors. When taking a family history to be used in estimating breast cancer risk, the physician should obtain a history of all cancers in biologic relatives, especially breast and ovarian cancers. The next box lists aspects of the family history that can be used to identify high-risk individuals.

GENERAL RISK FOR THE DEVELOPMENT OF BREAST CANCER BASED ON FAMILY HISTORY

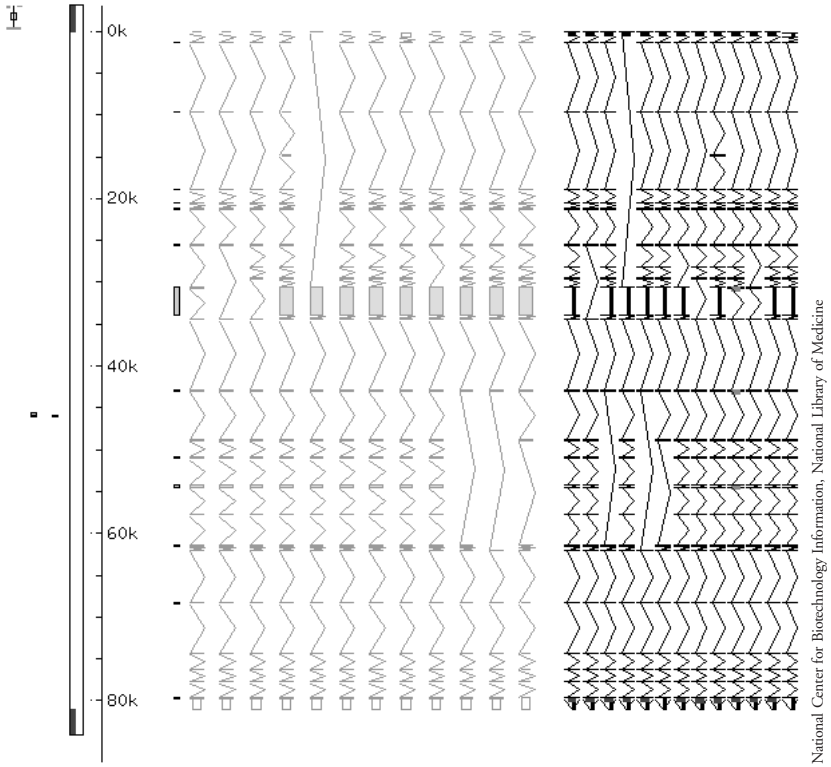
Women can be stratified into high, moderate, and average risk by the family history.

High risk

Women at high risk typically have several relatives who had breast cancer diagnosed before age 45 to 50 years and 1 or more relatives affected with bilateral or multifocal breast cancer; they may also have a family history of ovarian cancer or male breast cancer.[10]

Aspects of the family history useful in risk assessment for breast cancer

- Number of affected relatives
- Presence of cancer in several generations
- Ratio of affected to unaffected relatives
- Closeness of biologic relationship of affected relatives
- Ages at cancer diagnoses
- Presence of bilateral or multifocal breast cancer
- Presence of ovarian cancer
- Case(s) of male breast cancer



BRCA1, human genome sequence

Moderate risk

Women with a single affected first-degree relative who has cancer or more distantly related family members who have breast cancer are usually at only moderately increased risk.

Average risk

Women with a first-degree relative who had cancer diagnosed after age 60 years or 2 second-degree relatives who had cancer diagnosed after age 50 years may have a risk indistinguishable from the average risk.[18]

INTERPRETING FAMILY HISTORY WHEN HIGH-RISK CRITERIA ARE NOT PRESENT

Two empiric models for predicting breast cancer risk are available: the Gail model,[19] which is based on nongenetic factors and limited family history, and the Claus model,[18] which is based solely on family history. Both have limitations, and the risk estimates derived from the 2 models may differ for an individual patient. Despite their limitations, they represent the best methods currently available for individual risk assessment. However, they do not pro-

vide information about the likelihood of having a *BRCA1* or *BRCA2* mutation.

The Gail model projects individualized probabilities of developing breast cancer based on the major predictors of risk: 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. It provides a useful estimate of risk for women who do not have a family history of breast cancer. Because it does not consider second-degree relatives, paternal relatives, ethnicity, ages of diagnosis of breast cancer, or genetically related cancer other than breast cancer, the Gail model is not useful for assessing women whose risk primarily is inherited factors.[20]

The Claus model uses empiric data from the Cancer and Steroid Hormone Study.[21] The risk estimate is based on a woman's current age and the number of first- and second-degree relatives with breast cancer and their age of diagnosis. It does not take into consideration any other factors known to increase breast cancer risk. It is not intended to be used in families with highly penetrant mutations in susceptibility genes such as *BRCA1* or *BRCA2* because it may underestimate risk if the patient does not have sisters, if the inheritance is paternal, or if the family history is of ovarian rather than breast cancer.[20]

The Claus risk model provides the best available estimate of risk based on family history of breast cancer that is not high risk and can be used to reassure most women whose inherited risk is low (table 1). Compared with the average woman's risk of 10% of having breast cancer by age 80 years, the risk is significantly higher only when a relative is affected before age 50 or when several relatives are affected. As a result, most women with a family history, such as the woman in the case example, can be reassured about their risk.

Table 1 *Estimated risk of breast cancer according to family history**

Breast cancer in a mother or sister, by age when affected, yr	Risk of breast cancer by age 79, %	Breast cancer in a mother and sister, both affected at age, yr	Risk of breast cancer by age 79, %
20–29	21	20–29	48
30–39	17	30–39	44
40–49	13	40–49	35
50–59	11	50–59	25
60–69	10	60–69	16
70–79	9	70–79	11

*From Claus et al.[18]

Inherited breast cancer risk

In evaluating the family history for inherited breast cancer risk, consider the following:

Unusual family history of breast cancer
- Before age 50
- Bilateral
- In 2 or more family members
- In males

Father's side as well as mother's

Ovarian cancer, especially
- Breast and ovarian cancer in same person
- Presence of both breast and ovarian cancer in the family

INTERPRETING FAMILY HISTORY WHEN HIGH-RISK CRITERIA ARE PRESENT

There is no simple, well-defined threshold for high risk. In general, the more family history risk factors present, the greater the likelihood that an inherited risk is present. When obtaining a triaged family history (see Gene Scene, *wjm* July 2001;175:48-49), look for red flags that suggest that further evaluation of the patient's family history is indicated (see next box).

Studies indicate that a *BRCA1* or *BRCA2* cancer-predisposing mutation is more likely to be present if the family history includes Ashkenazi Jewish ancestry, breast cancer diagnosed before age 50 years, bilateral breast cancer, breast cancer in a male, ovarian cancer, or the occurrence of both breast cancer and ovarian cancer in the same person.[22-26] (See www.geneclinics.org/profiles/brca1/index.html for more in-depth information.) Because these studies were based on referral populations, the quantitative estimates of mutation frequency cannot necessarily be generalized to patients seen in primary care settings.

A method of calculating the probability of the presence of a cancer-predisposing *BRCA1* or *BRCA2* mutation has been developed. This calculation is based on observations in referral populations in which most women tested were affected with cancer.[26,27] CancerGene software includes these models and a tool for assessing the likelihood of a mutation (www.swmed.edu/home_pages/cancergene/).

GENETIC TESTING

Primary care physicians are faced with the question: To whom should DNA-based genetic testing be offered? The phrasing of the question as "offered" as opposed to "recommended" represents the 2 dynamics of the testing decision. First, is there a medical indication for the testing? and second, how do the benefits and risks of testing coincide with the patient's reasons for testing and manage-

Table 2 *Arguments for and against* BRCA1 *and* BRCA2 *testing in women whose family history indicates high risk*

Arguments for testing	Arguments against testing
In a family with a known mutation (positive *BRCA1* and *BRCA2* test result in a family member with cancer), a negative test result in an at-risk family member means she has not inherited the mutation	In a family without a known mutation, a negative test result does not provide helpful information (noninformative test)
In a cancer patient: A positive test result could benefit relatives A positive test result might affect treatment or screening decisions	In a cancer patient: Alternative approaches, such as DNA banking, might have less negative effect on labeling, psychological harms, etc
Labeling: Patients who have an identifiable mutation can be enrolled in research studies or registries and may be first in line for new therapies A positive test result may reduce feelings of self-blame and provide an explanation for disease	Labeling: A positive test result could have economic repercussions (insurance, employment discrimination) or lead to stigmatization—viewing oneself negatively or being treated differently by others Patient's offspring and other relatives may also be affected by test results
Positive test results may increase patient's health efforts through: Clinical or breast self-examination, screening Lifestyle changes	Negative test results may decrease patient's health efforts through: False reassurance (reduced screening efforts, etc) Failure to relieve anxiety or provide explanation for cancer
Psychological benefits: Increased sense of control Possible decreased anxiety	Psychological harms: Alarm, confusion, anxiety, worry, depression, uncertainty, etc Concern about risk to offspring Disruption of family relationships
Possibility of improved certainty about the cancer risk in family members	Possibility of ambiguous or noninformative results

ment decisions she would make based on the results? (See www.geneclinics.org/profiles/brca1/index.html for a discussion of the efficacy of possible risk-reduction strategies.)

The offer of testing is actually to the patient's family because testing should be offered first to an affected family member. Once a cancer-predisposing mutation has been identified, testing is technically straightforward and can be done through a blood test. However, several factors complicate genetic testing for breast cancer risk. For example:

- The cause of cancer predisposition has not yet been identified in some high-risk families, suggesting that additional genes and mutations have yet to be found. False-negative results are a significant problem.
- Full-scale sequencing for *BRCA1* and *BRCA2* mutations can produce results of unknown clinical significance—such as when a previously undescribed sequence variant is found.
- Full-scale sequencing for *BRCA1* and *BRCA2* mutations costs $2,600. (For women of Ashkenazi Jewish descent, a much less expensive test can be used that tests only for the 3 mutations that are common in this ethnic group.) Health insurance coverage varies.
- Risk prediction for those carrying a mutation is imprecise.

In addition, the results of the test will affect other family members beyond your patient. The importance of providing education and obtaining informed consent before performing testing for cancer-predisposing gene mutations has been emphasized by several expert groups.[28,29] Pretest counseling, often done by genetic counselors, addresses issues of the fees involved in testing and counseling; the meaning of positive and negative test results, including when the test is informative and when it is not; other options besides testing, including future discussion on the topic and/or DNA banking; medical interventions available for patients with high genetic risk; and possible psychological or economic effects of testing for individual and family members. Testing of at-risk asymptomatic relatives who are younger than 18 years is generally not recommended because of concerns about issues of informed consent among minors, the lack of proven surveillance or prevention strategies, and concerns about stigmatization and discrimination. The possible benefits and risks of testing as outlined in table 2 should be discussed so that the patient can make an informed decision on whether or not to pursue testing.

Resources for primary care physicians and patients are listed in the next box.

If there is no other history of breast cancer and no history of ovarian cancer, your patient's risk of having breast cancer based on her family history is similar to that of an average-risk woman. There would be little justification for testing for the

Resources*

- American Cancer Society (www.cancer.org)
  Contact information for regional support groups and programs, cancer information, patient and family education materials, and free mammograms
- Breast Cancer Information Core NHGRI (National Human Genome Research Institute) Cancer Genetics Branch (www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic)
- Cancernet (cancernet.nci.nih.gov)
  Genetics, causes, risk factors, and prevention of breast cancer
- Cansearch Cancer Care (www.cancercareinc.org)
- Facing Our Risk of Cancer Empowered (FORCE) (www.facingourrisk.org)
  A forum specifically for women who are at high risk of developing ovarian or breast cancer
- Gilda's Club (www.gildasclub.org)
- Lifetime Probability of Breast Cancer in American Women (www.meb.uni-bonn.de/cancernet/600056.html)
- National Action Plan on Breast Cancer (www.napbc.org)
- The National Alliance of Breast Cancer Organizations (www.nabco.org)
  An advocacy group that serves as an umbrella for 370 breast cancer groups, it provides information and a newsletter. It also provides funds for programs on early detection and education
- The National Breast Cancer Coalition
  Phone: (202) 296-7477; (800) 935-0434
  An advocacy group seeking public policy change to benefit breast cancer patients and survivors
- National Center for Biotechnology Information
  Genes and Disease (www.ncbi.nlm.nih.gov/disease/Breast-ovary.html)
- National Cancer Institute (www.nci.nih.gov)
- The National Coalition for Cancer Survivorship
  Phone: (301) 560-8868
  A consumer organization that advocates on behalf of all people with cancer
- Ovarian Cancer (National Ovarian Cancer Coalition) (www.ovarian.org)
- Susan G Komen Breast Cancer Foundation
  Phone: (800) 462-9273 (hotline); (214) 450-1777
  Information and referrals to treatment centers
- Y-Me National Organization for Breast Cancer Information
  Phone: (800) 221-2141
  Hotline staffed by counselors and volunteers who have had breast cancer. Information, support, and referrals

*Please see this article on our web site, www.ewjm.com, for a link to more contact information

BRCA1 and *BRCA2* genes in this patient, and testing could cause harm through false reassurance and its consequences. Your patient's likelihood of having a negative test result would be high, which could lead to a mistaken belief that her risk for breast cancer was lower than average because of the negative test result. In fact, her pretest risk estimate would not be changed by a negative test result because she is not expected to have a cancer-predisposing mutation. There has been little population-based testing of *BRCA1* and *BRCA2* (as opposed to testing in high-risk families in which the penetrance has been high). Thus, we could not provide her with accurate risk prediction information if her test results were positive. Therefore, the patient may benefit most from a discussion of risk that allows her to recognize her low short-term risk of breast cancer and a review of recommended breast cancer prevention strategies for the general population (mammography, breast self-examination, and clinician examination). Her lifetime risk of developing breast cancer remains at about 10%.

Your patient also has articulated a common misunderstanding—that a family history of a cancer that occurs predominantly in women is important only if the affected persons are related to the mother. In fact, cancer predisposition that is inherited in an autosomal dominant manner can be transmitted by either the father or the mother. The roommate had a paternal aunt with early-onset breast cancer and 2 paternal cousins with ovarian cancer. After individual and family genetic counseling, the roommate underwent *BRCA1* and *BRCA2* mutation analysis and was found to have a recognized cancer-predisposing mutation in *BRCA1*. The roommate's older brother had chosen to be tested to provide genetic counseling to his 2 daughters. The roommate's 50-year-old sister decided not to have testing because she did not have children, was getting routine mammograms, and was not interested in any other risk reduction interventions.

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