

# Breast and Ovarian Cancer: Risk Assessment

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## Key Points

- Family history is generally the most important tool in the assessment of breast and ovarian cancer risk.
- Most women with a positive family history of breast cancer have only modestly increased risk. Evaluation of family history information helps to identify rare high-risk families.
- Women are concerned about breast cancer and often overestimate their risk. They may view themselves as candidates for genetic testing when their likelihood of a positive test is very low.
- *BRCA1/BRCA2* mutations are rare in most populations. The likelihood of identifying a *BRCA1/BRCA2* mutation is increased in women of certain populations, including those of Jewish and Icelandic descent.
- Testing for *BRCA1/BRCA2* is mentioned frequently in the medical and lay press. Patients may ask about the availability of gene testing for breast cancer.

## 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;
- Use current breast cancer risk assessment models and understand their limitations.

## 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 multicentric occurrence of breast cancer
- *Information about relatives with breast cancer on the father's side as well as mother's side should be obtained:* breast cancer risk can be inherited from either side of the family.
- *Ovarian cancer is also important:* genetic risk often involves both breast and ovarian 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 [[de Bock 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, the genetic risk increases. (Males who carry *BRCA1* or *BRCA2* mutation 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 of the presence of *BRCA1* or *BRCA2* mutation in the family.)

**Claus model to assess likelihood of developing breast cancer.** The Claus model provides estimates of the probability of developing breast cancer for women with a family history of breast cancer; [Table 1](#) provides an example of risk estimates from this model, which is based on empiric data

from the Cancer and Steroid Hormone Study [[Claus et al 1994](#)]. The model provides cumulative risk estimates for several different family history configurations. However, it does not take other risk factors into account and thus may underestimate breast cancer risk for women with behavioral factors or reproductive histories that increase risk. The Claus model provides useful estimates for most women with a positive family history of breast cancer, but it is not suitable for use with women who have more than two relatives with breast cancer. The [Gail model](#) provides risk estimates based on other risk information and limited family history.

**Table 1. Estimated Risk for Breast Cancer According to Family History**

Breast Cancer in a Mother OR Sister, Affected at Age:	Risk for Breast Cancer by Age 79	Breast Cancer in a Mother AND Sister, both Affected at Age:	Risk for 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%

[Claus et al 1994](#)

**Risk for ovarian cancer according to family history.** Ovarian cancer is a component of inherited breast/ovarian cancer syndromes. In addition, a family history of ovarian cancer may indicate significantly increased risk for ovarian cancer, even when the family history does not suggest an inherited breast/ovarian cancer syndrome. [Table 2](#) provides estimates of the **relative risk (RR)** of ovarian cancer according to family history. This table is most useful in counseling women who have one or two relatives with ovarian cancer, without any family history of breast cancer. A RR of 2 indicates a twofold increased risk compared to women without a family history of ovarian cancer. For comparison, the average lifetime risk for ovarian cancer for American women is approximately 1.8%.

**Table 2. Relative Risk for Ovarian Cancer According to Family History**

Family History of Ovarian Cancer	Relative Risk for Ovarian Cancer
Any 1 <sup>st</sup> degree relative with ovarian cancer (mother, sister, or daughter)	3.1 (95% CI 2.6-3.7)
Daughter with ovarian cancer	1.1 (95% CI 0.8-1.6)
Sister with ovarian cancer	3.8 (95% CI 2.0-5.1)
Mother with ovarian cancer	6.0 (95% CI 3.0-11.9)
More than one affected relative (1st or 2nd degree)	11.7 (95% CI 5.3-25.9)
Second-degree relative with ovarian cancer (aunt or grandmother)	2.5 (95% CI 1.5-4.3)

Stratton et al 1998

## 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

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## Case 1. 36-Year-Old Woman Asks about Genetic Testing To Assess Breast Cancer Risk

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 a genetic test (done after her cancer diagnosis) that indicated she had a genetic predisposition to breast 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.

## Clinical Care Issues

The clinical issue raised by this patient is whether she is among the small subset of women at very high risk for breast cancer.

After non-melanoma skin cancer, breast cancer is the most common cancer in women. The majority of breast cancers occur among women in their 60s and 70s, but about 25% of breast cancers occur before age 50. Women at high risk are also more likely to develop breast cancer at an early age.

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](#)]. Breast self-examination is also commonly recommended, although definitive evidence for benefit in reducing morbidity and mortality from breast cancer is lacking. An important goal of genetic risk assessment is to identify the minority of women who are at high risk. Interventions recommended for these women include early initiation of breast cancer screening utilizing a combination of mammography and MRI screening; consideration of tamoxifen to reduce risk; and consideration of prophylactic mastectomy and/or oophorectomy.

## Risk Assessment

### Relevant risk factors

The patient's risk for breast cancer can be assessed through a review of her family history and other breast cancer risk factors.

[Family history](#) represents the most useful way to identify 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 have only a moderately increased

risk, and can follow the same screening program recommended for the woman with average breast cancer risk. Other risk factors for breast cancer (discussed below) 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.

Breast cancer risk is age dependent. The prevalence of breast cancer increases with age, and most breast cancers occur among women in their 60s and 70s. The Gail and Claus models described below can be used to estimate breast cancer risk over the short term (the next 5-10 years) and long term (to age 80).

### **Gail model for estimating breast cancer risk**

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 [[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](#), [Spiegelman 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 for invasive breast cancer. This same model was used to determine subject eligibility in the NSABP Tamoxifen Breast Cancer Prevention Trial.

While the Gail model is useful in assessing breast cancer risk for most women, it substantially underestimates risk for women with several affected family members, or for those with a history of breast cancer on their father's side. It also ignores the impact of ovarian cancer. For these reasons, it is not a useful tool for identifying women at high risk of having an inherited breast/ovarian cancer syndrome.

## Other risk factors

**Radiation exposure.** Women treated with therapeutic radiation to the chest area — for example, to treat lymphoma — have an increased risk for breast cancer.

**Hormone treatment.** Prolonged exposure to hormone replacement therapy is associated with an increased risk for breast cancer. Epidemiologic data also suggest risk is increased by obesity and a sedentary lifestyle.

See [Cancer.gov](http://www.cancer.gov).

## Genetic Counseling and Testing

### Are there genetic testing options?

Testing for mutations in the *BRCA1* and *BRCA2* genes is clinically available. The sensitivity of testing is limited: about one-third of high-risk families (that is, families in which four or more family members are affected with breast or ovarian cancer in sequential generations, in a pattern indicating inherited risk) do not have an identifiable *BRCA1* or *BRCA2* mutation to explain the inherited risk. [BRCAPRO software](#) includes a tool for assessing the likelihood that a mutation will be detected, using family history and other clinical data. Like other statistical models (such as the Gail and Claus models) this tool may overestimate or underestimate risk in some patients. For further information on inherited breast and ovarian cancer syndromes, see [GeneReview: BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer](#) and the [National Cancer Institute online summary on breast and ovarian cancer genetics](#).

## Should this patient be offered genetic testing?

The patient's only family history of breast cancer is in her aunt, a second-degree relative. Her aunt was diagnosed at age 72. This family history does not suggest increased risk. A family history of ovarian cancer is relevant. Assuming the patient has no family history of ovarian cancer and no further family history of breast cancer (including none on her father's side), the patient's risk of having breast cancer is average, according to the Claus model. (see [Table 1](#)). It would be difficult to justify *BRCA1/BRCA2* testing in this setting. Her likelihood of having a normal test result is very high, and a normal test result could lead to a mistaken belief that the result lowered her risk. In fact, her pre-test risk would not be changed by a normal test result, because she is not expected to have a cancer-predisposing mutation.

Other risk factors, such as those assessed in the Gail model 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 risk based on the Gail model 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.

Note: See [Case 2](#) for discussion of genetic testing in a person with a family history suggesting inherited risk.

## Interventions

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). She should be encouraged to seek medical evaluation if she notes a breast lump, in the context of reassurance that her breast cancer risk is not elevated above the average.

## Ethical/Legal/Social/Cultural Issues

**Common overestimate of breast cancer risk.** An important context for



this case is that women commonly misunderstand their risk for breast cancer. Many significantly overestimate their lifetime risk [Black et al 1995, Pilote & Hlatky 1995, Alexander et al 1996, Bunker et al 1998, McCaul et al 1998] and overestimate the proportion of female deaths attributable to breast cancer as well [Black et al 1995]. In addition, women often see breast cancer as a disease of younger women. In one survey, for example, women between 40 and 50 overestimated their short-term risk of dying from breast cancer by 22-fold and their lifetime risk by 12-fold [Black et al 1995]. Many women also have the mistaken belief that their risk diminishes as they get older [Dolan et al 1997, Fulton et al 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.

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## 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](mailto: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](mailto: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](mailto: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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