

BRCA1 and BRCA2 Mutations

- ❖ Cancer is a complex disease thought to be caused by several different factors.

A few types of cancer run in families. These types, called “hereditary” or “familial” cancer, have been linked to changes in genes that can be passed from parents to children.

- ❖ Changes in genes are called mutations.
- ❖ Hereditary breast and ovarian cancer syndrome is a type of familial cancer.
 - It most commonly is linked to mutations in two genes called BRCA1 and BRCA2.
 - Inheriting one of these mutations increases the risk of getting breast cancer, ovarian cancer, and other types of cancer. About 10% of cases of ovarian cancer and 3–5% of cases of breast cancer are due to mutations in BRCA1 and BRCA2.

BRCA Mutations and Cancer

Cancer is a disease that affects the normal growth of cells in the body.

- ❖ Normal, healthy cells grow, divide, and are replaced on a regular basis.
- ❖ Cancer occurs when cells begin to grow out of control.
- ❖ Cancer cells can quickly multiply and form growths or tumors.
- ❖ In some types of cancer, cells spread to other parts of the body, where they can grow to form new cancerous areas.

BRCA1 and BRCA2 are known as tumor suppressor genes.

- ❖ They keep cells from growing too rapidly or in an uncontrolled way.
- ❖ Thousands of mutations in BRCA1 and BRCA2 have been found.
- ❖ Some have been linked to an increased risk of cancer.

How Cancer Genes Work

All genes come in pairs.

- ❖ One copy of each gene in a pair is inherited from the mother, and the other copy is inherited from the father.
 - ❖ Cells need both copies to work normally.
 - ❖ Inheriting one copy of a BRCA1 or BRCA2 mutation increases the risk of getting cancer, but it does not necessarily mean that you will get cancer.
 - ❖ The other copy of the gene without a mutation keeps cells from growing out of control. But if the normal copy of the gene becomes damaged, it can increase the risk that cancer will occur.
- ❖ Genes can be damaged by many factors, including chemicals, radiation, smoking, and sun exposure. Many of the factors that damage genes are unknown.

Who Is Affected?

About 1 in 300 people carry a BRCA1 mutation, and 1 in 800 carry a BRCA2 mutation. These mutations are found more frequently in certain ethnic groups, including people of Ashkenazi (Eastern European) Jewish, French Canadian, and Icelandic backgrounds, but they can occur in anyone.

Effect of BRCA Mutations on Cancer Risk

All women have a certain risk of getting breast cancer or ovarian cancer at some point in their lives. Having a BRCA mutation increases this risk (Table 1).

- ❖ Women who have a BRCA1 or BRCA2 mutation also have an increased risk of cancer of the ovary, fallopian tube, peritoneum, and pancreas.
- ❖ Men who have a BRCA1 or BRCA2 mutation have an increased risk of breast cancer and an increased risk of prostate and pancreatic cancer.

Type of Cancer	Risk for the General Population	Risk With BRCA1 Mutation	Risk With BRCA2 Mutation
Breast Ovary	12% 1.4%	55–65% 39%	45% 11–17%

Tests for BRCA1 and BRCA2 Mutations

All women should be asked specific questions about their personal and family history of breast cancer and ovarian cancer (see box). If answers to these questions suggest that you may have inherited one of these mutations, genetic testing may be offered. Genetic testing requires a DNA sample from blood or saliva. There are several approaches to testing that can be followed.

DNA Sequencing

- ❖ If a relative with breast cancer or ovarian cancer is available, the relative's BRCA genes can be analyzed to find out if a specific BRCA mutation is present. This is called DNA sequencing.
- ❖ Your DNA then can be tested to see if you have the same mutation.
- ❖ This option is the best way to know if you are at risk.
- ❖ If no relative is available, and you and your family belong to an ethnic group with high numbers of people with a specific BRCA mutation, you can be tested for this mutation.
- ❖ If you are not part of a high-risk ethnic group, another option is to have DNA sequencing of your BRCA genes.
- ❖ This option usually is not the first choice because of the time and expense involved.

Before you have genetic testing, a health care provider with expertise in cancer genetics can help you understand how the test is done, what the results may mean, and what you may do depending on the test results.

You also should discuss current laws about genetic discrimination and privacy of genetic information. The Federal Genetic Information Nondiscrimination Act of 2008 protects people against health and employment discrimination based on genetic information. Many states have similar laws.

Understanding Test Results

- ❖ A *positive test* result means that you have the BRCA mutation for which you have been tested.
- ❖ A *negative test* result can mean several things, depending on the testing that you have had performed:

Scenario 1

- If you were tested for a specific BRCA mutation linked to cancer in your family (eg, a family member with cancer has given a DNA sample and a known BRCA mutation is found), and you have a negative test result for that BRCA mutation, you have not inherited the gene.
- You have the same risk of breast and ovarian cancer as the general population.

Scenario 2

- If you have a family history of cancer but no family member with cancer has given a DNA sample, and you have a negative test result for a BRCA mutation, it can mean that your family has a gene that increases cancer risk that is not a BRCA mutation.

- Or, it can mean that your family has a BRCA mutation that cannot be found with current tests.
- With these two possibilities, it remains unclear whether you have an inherited predisposition for cancer. A third possibility is that your family does not have a gene that increases the risk of cancer.
- ❖ You also can have an unclear test result. This means there is a change in a BRCA gene, but it is not known whether the change increases the risk of cancer.
- ❖ Researchers are continuing to study many more BRCA mutations to determine how they may or may not influence cancer risk.
- ❖ If you have a negative result or an unclear result, a genetic counselor may be able to determine which scenario is most likely for you and what risk-reduction strategies may be appropriate.

What a Positive Test Result Means for You and Your Family

A positive test result for a BRCA mutation associated with cancer means that you have an increased risk of getting cancer.

It does not mean that you will get cancer.

- ❖ There is no test currently available that can tell which women with a BRCA mutation will develop cancer or at what age. It is important to discuss your results with your health care provider and learn about preventive strategies that may be available to you to decrease your risk of cancer
- ❖ Having a BRCA mutation means that you can pass the gene to your children. Each child has a 50% chance of getting the gene.
- ❖ Your siblings also may be at risk of having the gene. Each of your siblings has a 50% chance of having inherited the gene.
- ❖ Whether to tell family members that you have a BRCA1 or BRCA2 mutation is your choice.
 - Your health care provider cannot disclose this information to them.
 - You are not obligated to tell your family members, but it often is a good idea to do so.
 - Sharing this information allows your family members to decide whether they want to be tested and to get appropriate preventive care if they also have a mutation.

Should You Be Tested?

If you answer “yes” to any of the following questions, genetic risk assessment IS recommended:

- ❖ Do you have a personal history of breast cancer and ovarian cancer?*

- ❖ Do you have a personal history of ovarian cancer* and a close relative† with ovarian cancer or premenopausal breast cancer or both?
- ❖ Do you have a personal history of ovarian cancer* and are you of Ashkenazi Jewish ancestry?
- ❖ Have you had a breast cancer diagnosis at age 50 years or younger and do you have a close relative† with ovarian cancer * or male breast cancer at any age?
- ❖ Are you of Ashkenazi Jewish ancestry and have you had a breast cancer diagnosis at age 40 years or younger?
- ❖ Do you have a close relative† with a known BRCA1 or BRCA2 mutation?

If you answer “yes” to any of the following questions, genetic risk assessment MAY BE helpful:

- ❖ Have you had a breast cancer diagnosis at age 40 years or younger?
- ❖ Do you have a personal history of ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high-grade, serous histology that was diagnosed at any age?
- ❖ Do you have a personal history of bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger)?
- ❖ Have you had a breast cancer diagnosis at age 50 years or younger and do you also have a close relative† with breast cancer diagnosed at age 50 years or younger?
- ❖ Are you of Ashkenazi Jewish ancestry and have you had a breast cancer diagnosis at age 50 years or younger?
- ❖ Do you have a personal history of breast cancer diagnosed at any age and two or more close relatives† with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger)?
- ❖ Have you never had breast or ovarian cancer but have a close relative† that meets one of the previous criteria?

*Cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.

†Close relative is defined as a first-degree relative (parent or sibling) or second-degree relative (grandparent, grandchild, aunt, uncle, niece, nephew).

Cancer Prevention if You Have a BRCA Mutation

If you test positive for a BRCA mutation, you may want to discuss preventive strategies with your health care provider. Prevention includes screening tests, medications, and surgery.

Screening Tests

Enhanced breast cancer screening for women with BRCA mutations is recommended.

Enhanced breast cancer screening may include the following tests:

- ❖ *Clinical breast exam* by a health care provider twice a year
- ❖ *Annual mammography* and annual breast magnetic resonance imaging (MRI) starting at age 25 years or younger based on the earliest age at which breast cancer was diagnosed in the family
- ❖ *breast self-awareness*: It is also helpful to be aware of how your breasts normally look and feel and report any changes to your health care provider. This is called breast self-awareness.

Screening for ovarian cancer in women with BRCA mutations also may be recommended.

Current screening tests include

- ❖ periodic blood tests for CA 125 (a substance that is made by ovarian cancer cells) and an ultrasound exam of the ovaries.
- ❖ Testing can begin between the ages of 30 years and 35 years or 5–10 years earlier than the age at which ovarian cancer was diagnosed in the youngest affected relative.
- ❖ These screening tests have a limited ability to find ovarian cancer at an earlier, more treatable stage.
- ❖ Test results may be normal even when cancer is present.
- ❖ There also is a high rate of false– positive results (a positive test result in someone who does not have ovarian cancer).

Medications

The use of drugs to help reduce the risk of or delay the occurrence of cancer is called chemoprevention.

- ❖ Taking a medication called tamoxifen has been shown to reduce the risk of breast cancer in women with BRCA2 mutations.
- ❖ Tamoxifen is a drug that is used to treat and prevent “estrogen–positive” breast cancer.
 - Estrogen–positive means that the cancer cells respond to the hormone estrogen.
 - Estrogen in the bloodstream can cause the cancer cells to grow.
 - Tamoxifen blocks the effects of estrogen on these cancer cells.
 - Tamoxifen works well in women with BRCA2 mutations because about 70% of breast cancer tumors in this group are estrogen–positive. Less than 25% of tumors in women with BRCA1 mutations are estrogen–positive.
 - Tamoxifen does not appear to reduce breast cancer risk in women with BRCA1 mutations.

- ❖ Combined hormonal birth control pills (those that contain estrogen and another hormone called progestin) may reduce the risk of ovarian cancer and fallopian tube cancer in women with BRCA mutations.
 - If you are thinking about using combined hormonal birth control pills, you should carefully weigh the risks and benefits for chemoprevention and birth control.

Surgery

Surgery is another preventive option for women with BRCA1 and BRCA2 mutations. This type of surgery is called “risk-reducing surgery.”

- ❖ Risk-reducing bilateral salpingo-oophorectomy is the removal of both ovaries and both fallopian tubes.
 - It can significantly reduce the risk of ovarian cancer, fallopian tube cancer, and peritoneal cancer in women with a BRCA mutation.
 - If it is done before menopause, having this surgery also can reduce the risk of breast cancer.
 - Women with these mutations should consider having this surgery before age 40 years or after they have completed their families.
 - An important consideration to think about is that salpingo-oophorectomy performed before menopause will cause you to experience menopause immediately, rather than over several years.
 - Signs and symptoms of menopause often can be managed with hormone therapy and other treatments. You can discuss these treatment options with your health care provider before your surgery.
- ❖ Bilateral mastectomy (surgical removal of both breasts) reduces the risk of breast cancer by more than 90–95%. The type of mastectomy is important in reducing risk.
- ❖ Total mastectomy, in which the entire breast tissue is removed, including the nipple and areola, is the most effective risk-reducing surgery for breast cancer.

Mastectomy that removes the breast tissue and leaves the nipple and areola also can be considered.

If you are thinking about having preventive surgery, you and your health care provider will consider the risks and benefits. You should discuss the psychological effects as well as short- and long-term complications.

Timing of surgery should be based on your needs, your desire to have children, and the effect that surgery will have on your well-being.

Finding More Information

If you have a personal or family history of breast cancer or ovarian cancer, getting tested for BRCA mutations may be something that you want to consider.

Talk to your health care provider about screening and testing options.

The following organizations offer additional information about BRCA and cancer risk:

American Cancer Society Genetics and Cancer

www.cancer.org/cancer/cancercauses/geneticsandcancer/genetics-and-cancer-landing

Centers for Disease Control and Prevention KNOW: BRCA

www.cdc.gov/cancer/breast/young_women/knowbrca.htm

National Cancer Institute: BRCA1 and BRCA2: Cancer Risk and Genetic Testing

www.cancer.gov/cancertopics/factsheet/Risk/BRCA