NIH NATIONAL CANCER INSTITUTE

BRCA Gene Changes: Cancer Risk and Genetic Testing

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What are *BRCA1* and *BRCA2*?

BRCA1 (BReast CAncer gene 1) and *BRCA2* (BReast CAncer gene 2) are genes that produce proteins that help repair damaged DNA. Everyone has two copies of each of these genes—one copy inherited from each parent.

People who inherit a harmful change (also called a mutation or pathogenic variant) in one of these genes have increased risks of several cancers—most notably breast and ovarian cancer, but also several other types of cancer (1, 2). People who have inherited a harmful change in *BRCA1* or *BRCA2* also tend to develop cancer at younger ages than people who do not have such a variant.

Nearly everyone who inherits a harmful change in the *BRCA1* or *BRCA2* gene from one parent has a normal second copy of the gene inherited from the other parent. Having one normal copy of either gene is enough to protect cells from becoming cancer. But the normal copy can change or be lost during someone's lifetime. Such a change is called a somatic alteration. A cell with a somatic alteration in the only normal copy of one of these genes doesn't have sufficient DNA repair ability and can become cancer.

How much does an inherited harmful change in *BRCA1* or *BRCA2* increase the risks of breast and ovarian cancer?

The risks of developing breast and ovarian cancer are markedly increased in people who inherit a harmful change in *BRCA1* or *BRCA2* (1, 3–7).

- **Female breast cancer:** More than 60% of women who inherit a harmful change in *BRCA1* or *BRCA2* will develop breast cancer during their lifetime (2). By contrast, about 13% of women in the general population will develop breast cancer during their lifetime.

  Among women who have been diagnosed with breast cancer, those who have an inherited harmful change in *BRCA1* or *BRCA2* have an increased risk of developing cancer in the opposite (contralateral) breast in the future compared with those who do not have such a change (8). About 30%–40% of breast cancer survivors with inherited *BRCA1* changes and 25% of those with inherited *BRCA2* changes will develop contralateral breast cancer by 20 years after their first breast cancer diagnosis, compared with about 8% of those in the general population (2, 9).
- **Male breast cancer:** About 0.2%–1.2% of men with an inherited harmful change in *BRCA1* and 1.8%–7.1% with an inherited harmful change in *BRCA2* will develop breast cancer by age 70 (2). By contrast, about 0.1% of men in the general population will develop breast cancer by age 70. Given the rarity of

breast cancer in men with harmful BRCA changes, their risk of contralateral breast cancer has not been estimated.

- **Ovarian cancer:** About 39%–58% of women who inherit a harmful change in *BRCA1* and 13%–29% of women who inherit a harmful change in *BRCA2* will develop ovarian cancer (which includes fallopian tube cancer and primary peritoneal cancer) during their lifetime (2). By contrast, about 1.1% of women in the general population will develop ovarian cancer during their lifetime.

What other cancers are linked to inherited harmful changes in *BRCA1* and *BRCA2*?

People who inherit harmful changes in *BRCA1* or *BRCA2* have an increased risk of several additional cancers (1, 10–12).

- **Pancreatic cancer:** Up to 5% of individuals with harmful changes in *BRCA1* and 5%–10% of those with harmful changes in *BRCA2* will develop pancreatic cancer during their lifetime (2). By contrast, about 1.7% of people in the general population will develop pancreatic cancer during their lifetime.
- **Prostate cancer:** About 7%–26% of men with harmful changes in *BRCA1* and 19%–61% of those with harmful changes in *BRCA2* will get prostate cancer by age 80 (2). By contrast, about 10.6% of men in the general population will develop prostate cancer by age 80.
- **Other cancers:** Some studies have suggested that people with harmful changes in the BRCA genes have increased risks of melanoma (both skin and eye), stomach cancer, and a rare type of endometrial cancer called uterine serous carcinoma (4, 13–15). However, these associations are not yet certain.

  In addition, individuals who inherit genetic changes in both copies of their *BRCA1* or *BRCA2* gene develop subtypes of Fanconi anemia, a rare syndrome that is associated with solid tumors and the development of acute myeloid leukemia, often in childhood (16–18).

Individuals who inherit a harmful change in each of the BRCA genes (one in *BRCA1* and one in *BRCA2*)—although rare—appear to have cancer risks that resemble those of individuals that inherit harmful changes in *BRCA1* (19). Inheritance of harmful mutations in both *BRCA1* and *BRCA2* is more common in populations that have a higher prevalence of inherited BRCA mutations (e.g., Ashkenazi Jewish population).

Does the likelihood of having a BRCA gene mutation differ among populations?

Yes. The prevalence of harmful BRCA gene changes in the general population is about 0.2%–0.3% (or about 1 in 400). However, in certain populations that are geographically or culturally distinct, the prevalence of specific BRCA mutations—called founder mutations—is higher. For example, about 2% of people of Ashkenazi Jewish descent carry a harmful change in one of these two genes, with the change usually being one of three specific mutations. Other populations, such as Norwegian, Dutch, Icelandic, Hispanic, West African, African American, Sephardi Jewish, and Bahamanian people, also have founder mutations (20–28).

Different racial, ethnic, and geographic populations may carry different changes in these genes. For instance, African Americans have *BRCA1* changes that are not seen in other racial or ethnic groups in the United States (29–31).

Who should consider genetic counseling and testing for inherited harmful changes in *BRCA1* and *BRCA2*?

Anyone who is concerned that they may have inherited a harmful change in the *BRCA1* or *BRCA2* gene should discuss their concerns with their health care provider or a genetic counselor to see if testing for an inherited change, sometimes called germline genetic testing, may be right for them. Expert groups recommend that testing be focused on those who have a higher likelihood of carrying a harmful change in *BRCA1* or *BRCA2* (2, 32, 33).

Testing can be appropriate for both people without cancer and people who have been diagnosed with cancer. If someone knows they have inherited a harmful change in one of these genes, they can take steps to reduce their risk of developing cancer or to detect cancer early. If they have cancer, the information about the genetic change may be important for selecting treatment. Also, people can share the results of testing with blood relatives, who can then better understand their own cancer risk. Genetic counseling will allow for a discussion of the implications of testing for BRCA changes so that someone can give informed consent to the process.

Before having testing, people should discuss with their genetic counselor both the benefits and possible downsides of genetic testing.

A risk assessment is usually done before testing, in which a person and their genetic counselor or other health care provider review factors that make it more likely that they inherited a harmful change in *BRCA1* or *BRCA2*. These factors include

- having a family member with an inherited harmful change in the *BRCA1* or *BRCA2* gene
- having Ashkenazi Jewish heritage
- having a personal or family history of breast cancer at age 50 or younger
- having a personal or family history of ovarian cancer, male breast cancer, pancreatic cancer, or metastatic or high-risk prostate cancer

Professional groups do not recommend that children under age 18 undergo genetic testing for *BRCA1* and *BRCA2* changes. This is because there are no risk reduction strategies that are specifically meant for children, and children are very unlikely to develop a cancer related to an inherited BRCA change.

How is genetic testing for harmful changes in *BRCA1* and *BRCA2* done?

Testing for inherited harmful changes in *BRCA1* and *BRCA2* may be done using a blood or saliva sample. That is because when a mutation is inherited, it is found in every cell in the body, including blood cells and cells that are present in saliva. Sometimes people with cancer find out that they have a harmful change in *BRCA1* or *BRCA2* when their tumor is tested to see if they are a candidate for treatment with a particular targeted therapy. Because harmful BRCA changes found in the tumor may have been inherited or may have arisen later in someone's lifetime, someone with such a change in their tumor should consider getting tested to find out if the change was inherited.

If a genetic counselor or other health care professional is ordering the testing, you will generally provide a sample at the doctor's office.

People can also have germline genetic testing on their own, through direct-to-consumer (DTC) testing or via direct access (patient-initiated) testing. Genetic counseling is recommended for people who pursue DTC testing to help them understand the test results and to make sure the most appropriate test is done. People should also be aware that because some DTC tests do not test for every harmful change in the two genes, it is possible that someone could have a harmful change in *BRCA1* or *BRCA2* that the DTC test doesn't detect.

Does health insurance cover the cost of genetic testing for changes in *BRCA1* and *BRCA2*?

People considering testing for inherited harmful changes in *BRCA1* and *BRCA2* may want to confirm their insurance coverage for genetic counseling and testing. Genetic counselors can often help answer questions about insurance coverage for genetic testing.

Some genetic testing companies may offer testing for inherited changes in *BRCA1* and *BRCA2* at no charge to patients who lack insurance and meet specific financial and medical criteria.

What do *BRCA1* and *BRCA2* genetic test results mean?

Testing for inherited changes in *BRCA1* and *BRCA2* can give several possible results: a positive result (a harmful change in the gene is present), a negative result (no harmful gene change is present), or a gene change (variant) of uncertain significance (VUS) result.

Positive result. A positive test result indicates that a person has a harmful change in *BRCA1* or *BRCA2* (these are typically called "pathogenic" or "likely pathogenic" variants on laboratory test reports) and has an increased risk of developing certain cancers. However, a positive test result cannot tell whether or when the tested individual will develop cancer. Some people who inherit a harmful change in *BRCA1* or *BRCA2* never develop cancer.

Negative result. A negative test result can have several meanings, depending on the personal and family medical history of the person who is tested and whether a harmful genetic change has already been identified in the family.

- If a close blood relative of the tested person is known to carry a harmful change in *BRCA1* or *BRCA2* and the laboratory was aware of that variant when performing the testing, a negative test result is clear: it means the tested person did not inherit the harmful change that is present in the family and cannot pass it to their children. A negative test result does not mean that a person will not get cancer They still have the same cancer risks as those in the general population and, depending on their family history, may still be at elevated risk for cancer.
- If the tested person has no personal history of cancer or their family isn't known to carry a harmful variant, then the negative result does not provide additional information about their risk of cancer beyond what is known about their family history and other risk factors they may have.

Variant of uncertain significance (VUS) result. Sometimes, a genetic test finds a change in *BRCA1* or *BRCA2* for which there is not enough data available to conclude that it increases cancer risk. This type of test result is called "a variant of uncertain significance," or VUS. Most often, as more data become available VUS are reclassified as being benign (do not increase cancer risk). Until a VUS is reclassified, whether as harmful or benign, management of cancer risk should be based on family history and other risk factors. Genetic counseling can help a person understand what any of these results may mean for the tested person and their blood relatives, including future generations.

How can a person who has inherited a harmful change in *BRCA1* or *BRCA2* manage their risk of cancer?

Individuals who have inherited a harmful change in *BRCA1* or *BRCA2* have several options for reducing cancer risk. These include enhanced screening, risk-reducing surgery (sometimes referred to as prophylactic or preventive surgery), and taking medication to reduce their risk.

Enhanced screening. Professional groups generally recommend that women who have inherited harmful changes in *BRCA1* and *BRCA2* start breast cancer screening at younger ages and have screening with magnetic resonance imaging (MRI; with or without contrast) in addition to mammography.

No effective ovarian cancer screening methods are known. In the past, some doctors recommended transvaginal ultrasound and blood tests for the CA-125 antigen (which can be present at higher-than-normal levels in women with ovarian cancer) for ovarian cancer screening in women with harmful changes in *BRCA1* or *BRCA2*. However, neither method appears to detect ovarian tumors early enough to improve long-term survival (34).

Men with harmful inherited changes in a BRCA gene should discuss screening options with their health care provider. Some guidelines recommend that men who carry harmful changes in *BRCA1* or *BRCA2* undergo screening for breast and prostate cancers (2). This includes an annual mammogram and prostate cancer screening, particularly for men with harmful changes in *BRCA2*, and possible prostate screening for men with harmful changes in *BRCA1*.

Some organizations recommend the use of ultrasound or MRI/magnetic retrograde cholangiopancreatography to screen for pancreatic cancer in people who are known to have inherited a harmful change in *BRCA1* or *BRCA2* and who have a close blood relative with pancreatic cancer (2, 35–37). Studies are ongoing to investigate whether screening people at increased risk for pancreatic cancer reduces their risk of dying from the disease.

These screening approaches all have potential harms as well as possible benefits. For example, MRI is more likely than mammography to result in false-positive findings.

Risk-reducing surgery. Risk-reducing, or prophylactic, surgery involves removing as much of the "at-risk" tissue—that is, the tissue where cancer may develop—as possible. Women may choose to have both breasts removed (bilateral risk-reducing mastectomy) to reduce their risk of breast cancer. Surgery to remove the ovaries and fallopian tubes (bilateral risk-reducing salpingo-oophorectomy) can help reduce the risk of ovarian cancer and, possibly, breast cancer. (Ovarian cancers often originate in the fallopian tubes, so they are removed along with the ovaries.) Salpingectomy—the removal of the fallopian tubes only with preservation of the ovaries until after menopause—has been found to reduce the risk of ovarian cancer in the general population and is being studied as an option for premenopausal women with harmful changes in *BRCA1* or *BRCA2* who are not yet ready for a full salpingo-ophorectomy (38).

Such surgeries are irreversible, and each has potential complications or harms. These include bleeding or infection, concerns about body image (bilateral risk-reducing mastectomy), and early menopause in premenopausal women (bilateral risk-reducing salpingo-oophorectomy).

Risk-reducing surgery does not guarantee that cancer will not develop because these procedures cannot remove all of the tissue that may become cancerous.

Risk-reducing medications (sometimes called chemoprevention). Tamoxifen and raloxifene are approved by the Food and Drug Administration to reduce breast cancer risk in women who, based on their personal and family medical history, have an elevated risk of breast cancer. It is not yet clear whether these medications can be used to prevent breast cancer in women with greatly increased risk due to inherited harmful mutations in *BRCA1*, *BRCA2*, or other genes (39). However, tamoxifen may lower the risk of contralateral breast cancer among *BRCA1* and *BRCA2* variant carriers previously diagnosed with breast cancer (40). And there is evidence that tamoxifen reduces the risk of estrogen receptor–positive breast cancer among *BRCA2* mutation carriers (41).

Even though these medications are not indicated for women with BRCA gene mutations, they may be an option for women who cannot or choose not to undergo risk-reducing surgery.

Oral contraceptives are another potential option to reduce the risk of ovarian cancer. Both women in the general population, as well as those with harmful *BRCA1* or *BRCA2* variants, who have ever used oral contraceptives (birth control pills) have about a 50% lower risk of ovarian cancer than women who have never used oral contraceptives (42). Potential harms of oral contraceptives include an increased risk of breast cancer, an increased risk that a human papillomavirus (HPV) infection will become cervical cancer, and possible cardiovascular effects among older reproductive-age women.

Another form of birth control, the levonorgestrel intrauterine device, has been associated with a reduced risk of ovarian cancer in people at average risk of the disease (43–45). Whether this device reduces ovarian cancer risk in people with harmful changes in *BRCA1* or *BRCA2* is not yet known.

Do inherited BRCA changes affect cancer treatment?

Anticancer agents that act by damaging DNA, such as cisplatin, can be effective treatments for tumors that develop in people who have inherited harmful changes in *BRCA1* or *BRCA2* because the mutated genes cause defective DNA repair (46). Cancer cells that cannot repair DNA damaged by cisplatin or similar chemotherapy drugs are more likely to be killed by these drugs.

Cancer cells that have harmful changes in *BRCA1* or *BRCA2*—whether the changes are inherited or occur during life—can also be treated effectively with drugs called PARP inhibitors, which block the repair of DNA damage. Four PARP inhibitors—olaparib (Lynparza), rucaparib (Rubraca), niraparib (Zejula), and talazoparib (Talzenna)—are approved by the FDA to treat certain cancers bearing harmful changes in *BRCA1* or *BRCA2*.

Breast cancers in people with inherited harmful changes in *BRCA1* are more likely than breast cancers that develop in people without these gene changes or people in the general population to be triple negative (that is, to lack estrogen receptors and progesterone receptors and to have little or no HER2/neu protein). Because triple-negative breast cancers lack these treatment targets, they are harder to treat and have a poorer prognosis than other types of breast cancer.

If someone has tumor genetic testing that reveals the presence of a harmful change in *BRCA1* or *BRCA2* in the tumor, they should discuss with their health care provider whether to consider having a germline genetic test to determine if the change was inherited or if it occurred during development of the tumor. Knowing if the change was inherited is important for that individual to understand their risks to potentially develop other cancers in the future. It can also provide an opportunity for family members to learn about their own cancer risks.