BRCA1 and BRCA2

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BRCA1 and BRCA2: Cancer Risk and Genetic Testing

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What are BRCA1 and BRCA2?

BRCA1 and BRCA2 are human genes that produce tumour suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material. When either of these genes is mutated, or altered, such that its protein product either is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer.

Specific inherited mutations in BRCA1 and BRCA2 increase the risk of female breast and ovarian cancers, and they have been associated with increased risks of several additional types of cancer. Together, BRCA1 and BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers (1) and about 5 to 10 percent of all breast cancers (2). In addition, mutations in BRCA1 and BRCA2 account for around 15 percent of ovarian cancers overall (3). Breast and ovarian cancers associated with BRCA1 and BRCA2 mutations tend to develop at younger ages than their nonhereditary counterparts.

A harmful BRCA1 or BRCA2 mutation can be inherited from a person's mother or father. Each child of a parent who carries a mutation in one of these genes has a 50 percent chance (or 1 chance in 2) of inheriting the mutation. The effects of mutations in BRCA1 and BRCA2 are seen even when a person's second copy of the gene is normal.

How much does having a BRCA1 or BRCA2 gene mutation increase a woman's risk of breast and ovarian cancer?

A woman's lifetime risk of developing breast and/or ovarian cancer is greatly increased if she inherits a harmful mutation in BRCA1 or BRCA2.

Breast cancer: About 12 percent of women in the general population will develop breast cancer sometime during their lives (4). By contrast, according to the most recent estimates, 55 to 65 percent of women who inherit a harmful BRCA1 mutation and around 45 percent of women who inherit a harmful BRCA2 mutation will develop breast cancer by age 70 years (5, 6).

Ovarian cancer: About 1.3 percent of women in the general population will develop ovarian cancer sometime during their lives (4). By contrast, according to the most recent estimates, 39 percent of women who inherit a harmful BRCA1 mutation (5, 6) and 11 to 17 percent of women who inherit a harmful BRCA2 mutation will develop ovarian cancer by age 70 years (5, 6).

It is important to note that these estimated percentages of lifetime risk are different from those available previously; the estimates have changed as more information has become available, and they may change again with additional research. No long-term general population studies have directly compared cancer risk in women who have and do not have a harmful BRCA1 or BRCA2 mutation.

It is also important to note that other characteristics of a particular woman can make her cancer risk higher or lower than the average risks. These characteristics include her family history of breast, ovarian, and, possibly, other cancers; the specific mutation(s) she has inherited; and other risk factors, such as her reproductive history. However, at this time, based on current data, none of these other factors seems to be as strong as the effect of carrying a harmful BRCA1 or BRCA2 mutation.

What other cancers have been linked to mutations in BRCA1 and BRCA2?

Harmful mutations in BRCA1 and BRCA2 increase the risk of several cancers in addition to breast and ovarian cancer. BRCA1 mutations may increase a woman's risk of developing fallopian tube cancer and peritoneal cancer (7, 8). Men with BRCA2 mutations, and to a lesser extent BRCA1 mutations, are also at increased risk of breast cancer (9). Men with harmful BRCA1 or BRCA2 mutations have a higher risk of prostate cancer (10). Men and women with BRCA1 or BRCA2 mutations may be at increased risk of pancreatic cancer (11). Mutations in BRCA2 (also known as FANCD1), if they are inherited from both parents, can cause a Fanconi anemia subtype (FA-D1), a syndrome that is associated with childhood solid tumours and development of acute myeloid leukemia (12, 13). Likewise, mutations in BRCA1 (also known as FANCS), if they are inherited from both parents, can cause another Fanconi anemia subtype (14).

Are mutations in BRCA1 and BRCA2 more common in certain racial/ethnic populations than others?

Yes. For example, people of Ashkenazi Jewish descent have a higher prevalence of harmful BRCA1 and BRCA2 mutations than people in the general U.S. population. Other ethnic and geographic populations around the world, such as the Norwegian, Dutch, and Icelandic peoples, also have a higher prevalence of specific harmful BRCA1 and BRCA2 mutations.
In addition, limited data indicate that the prevalence of specific harmful BRCA1 and BRCA2 mutations may vary among individual racial and ethnic groups in the United States, including African Americans, Hispanics, Asian Americans, and non-Hispanic whites (15, 16).

Are genetic tests available to detect BRCA1 and BRCA2 mutations?
Yes. Several different tests are available, including tests that look for a known mutation in one of the genes (i.e., a mutation that has already been identified in another family member) and tests that check for all possible mutations in both genes. DNA (from a blood or saliva sample) is needed for mutation testing. The sample is sent to a laboratory for analysis. It usually takes about a month to get the test results.

Who should consider genetic testing for BRCA1 and BRCA2 mutations?
Because harmful BRCA1 and BRCA2 gene mutations are relatively rare in the general population, most experts agree that mutation testing of individuals who do not have cancer should be performed only when the person's individual or family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2.

In December 2013, the United States Preventive Services Task Force recommended that women who have family members with breast, ovarian, fallopian tube, or peritoneal cancer be evaluated to see if they have a family history that is associated with an increased risk of a harmful mutation in one of these genes (17).

Several screening tools are now available to help health care providers with this evaluation (17). These tools assess family history factors that are associated with an increased likelihood of having a harmful mutation in BRCA1 or BRCA2, including:

- Breast cancer diagnosed before age 50 years
- Cancer in both breasts in the same woman
- Both breast and ovarian cancers in either the same woman or the same family
- Multiple breast cancers
- Two or more primary types of BRCA1- or BRCA2-related cancers in a single family member
- Cases of male breast cancer
- Ashkenazi Jewish ethnicity

When an individual has a family history that is suggestive of the presence of a BRCA1 or BRCA2 mutation, it may be most informative to first test a family member who has cancer if that person is still alive and willing to be tested. If that person is found to have a harmful BRCA1 or BRCA2 mutation, then other family members may want to consider genetic counselling to learn more about their potential risks and whether genetic testing for mutations in BRCA1 and BRCA2 might be appropriate for them.

If it is not possible to confirm the presence of a harmful BRCA1 or BRCA2 mutation in a family member who has cancer, it is appropriate for both men and women who do not have cancer but have a family medical history that suggests the presence of such a mutation to have genetic counselling for possible testing.
Some individuals—for example, those who were adopted at birth—may not know their family history. In cases where a woman with an unknown family history has an early-onset breast cancer or ovarian cancer or a man with an unknown family history is diagnosed with breast cancer, it may be reasonable for that individual to consider genetic testing for a BRCA1 or BRCA2 mutation. Individuals with an unknown family history who do not have an early-onset cancer or male breast cancer are at very low risk of having a harmful BRCA1 or BRCA2 mutation and are unlikely to benefit from routine genetic testing.

Professional societies do not recommend that children, even those with a family history suggestive of a harmful BRCA1 or BRCA2 mutation, undergo genetic testing for BRCA1 or BRCA2. This is because no risk-reduction strategies exist for children, and children's risks of developing a cancer type associated with a BRCA1 or BRCA2 mutation are extremely low. After children with a family history suggestive of a harmful BRCA1 or BRCA2 mutation become adults, however, they may want to obtain genetic counselling about whether or not to undergoing genetic testing.

Should people considering genetic testing for BRCA1 and BRCA2 mutations talk with a genetic counsellor?
Genetic counselling is generally recommended before and after any genetic test for an inherited cancer syndrome. This counselling should be performed by a health care professional who is experienced in cancer genetics. Genetic counselling usually covers many aspects of the testing process, including:

- A hereditary cancer risk assessment based on an individual’s personal and family medical history
- Discussion of:
    - The appropriateness of genetic testing
    - The medical implications of a positive or a negative test result
    - The possibility that a test result might not be informative
    - The psychological risks and benefits of genetic test results
    - The risk of passing a mutation to children

- Explanation of the specific test(s) that might be used and the technical accuracy of the test(s)

What does a positive BRCA1 or BRCA2 genetic test result mean?
BRCA1 and BRCA2 gene mutation testing can give several possible results: a positive result, a negative result, or an ambiguous or uncertain result.
A positive test result indicates that a person has inherited a known harmful mutation in BRCA1 or BRCA2 and, therefore, has an increased risk of developing certain cancers. However, a positive test result cannot tell whether or when an individual will actually develop cancer. For example, some

women who inherit a harmful BRCA1 or BRCA2 mutation will never develop breast or ovarian cancer.

A positive genetic test result may also have important health and social implications for family members, including future generations. Unlike most other medical tests, genetic tests can reveal information not only about the person being tested but also about that person's relatives:

- Both men and women who inherit a harmful BRCA1 or BRCA2 mutation, whether or not they develop cancer themselves, may pass the mutation on to their sons and daughters. Each child has a 50 percent chance of inheriting a parent's mutation.
- If a person learns that he or she has inherited a harmful BRCA1 or BRCA2 mutation, this will mean that each of his or her full siblings has a 50 percent chance of having inherited the mutation as well.

What does a negative BRCA1 or BRCA2 test result mean?

A negative test result can be more difficult to understand than a positive result because what the result means depends in part on an individual's family history of cancer and whether a BRCA1 or BRCA2 mutation has been identified in a blood relative.

If a close (first- or second-degree) relative of the tested person is known to carry a harmful BRCA1 or BRCA2 mutation, a negative test result is clear: it means that person does not carry the harmful mutation that is responsible for the familial cancer, and thus cannot pass it on to their children. Such a test result is called a true negative. A person with such a test result is currently thought to have the same risk of cancer as someone in the general population.

If the tested person has a family history that suggests the possibility of having a harmful mutation in BRCA1 or BRCA2 but complete gene testing identifies no such mutation in the family, a negative result is less clear. The likelihood that genetic testing will miss a known harmful BRCA1 or BRCA2 mutation is very low, but it could happen. Moreover, scientists continue to discover new BRCA1 and BRCA2 mutations and have not yet identified all potentially harmful ones. Therefore, it is possible that a person in this scenario with a "negative" test result actually has an as-yet unknown harmful BRCA1 or BRCA2 mutation that has not been identified.

It is also possible for people to have a mutation in a gene other than BRCA1 or BRCA2 that increases their cancer risk but is not detectable by the test used. People considering genetic testing for BRCA1 and BRCA2 mutations may want to discuss these potential uncertainties with a genetic counsellor before undergoing testing.

What does an ambiguous or uncertain BRCA1 or BRCA2 test result mean?

Sometimes, a genetic test finds a change in BRCA1 or BRCA2 that has not been previously associated with cancer. This type of test result may be described as "ambiguous" (often referred to as "a genetic variant of uncertain significance") because it isn't known whether this specific gene change affects a person's risk of developing cancer. One study found that 10 percent of women who underwent BRCA1 and BRCA2 mutation testing had this type of ambiguous result (18).

As more research is conducted and more people are tested for BRCA1 and BRCA2 mutations, scientists will learn more about these changes and cancer risk. Genetic counselling can help a person understand what an ambiguous change in BRCA1 or BRCA2 may mean in terms of cancer risk. Over time, additional studies of variants of uncertain significance may result in a specific mutation being re-classified as either harmful or clearly not harmful.

How can a person who has a positive test result manage their risk of cancer?
Several options are available for managing cancer risk in individuals who have a known harmful BRCA1 or BRCA2 mutation. These include enhanced screening, prophylactic (risk-reducing) surgery, and chemoprevention.

Enhanced Screening. Some women who test positive for BRCA1 and BRCA2 mutations may choose to start cancer screening at younger ages than the general population or to have more frequent screening. For example, some experts recommend that women who carry a harmful BRCA1 or BRCA2 mutation undergo clinical breast examinations beginning at age 25 to 35 years (19). And some expert groups recommend that women who carry such a mutation have a mammogram every year, beginning at age 25 to 35 years.

Enhanced screening may increase the chance of detecting breast cancer at an early stage, when it may have a better chance of being treated successfully. Women who have a positive test result should ask their health care provider about the possible harms of diagnostic tests that involve radiation (mammograms or x-rays).

Recent studies have shown that MRI may be more sensitive than mammography for women at high risk of breast cancer (20, 21). However, mammography can also identify some breast cancers that are not identified by MRI (22), and MRI may be less specific (i.e., lead to more false-positive results) than mammography. Several organizations, such as the American Cancer Society and the National Comprehensive Cancer Network, now recommend annual screening with mammography and MRI for women who have a high risk of breast cancer.

No effective ovarian cancer screening methods currently exist. Some groups recommend transvaginal ultrasound, blood tests for the antigen CA-125, and clinical examinations for ovarian cancer screening in women with harmful BRCA1 or BRCA2 mutations, but none of these methods appears to detect ovarian tumours at an early enough stage to reduce the risk of dying from ovarian cancer (23). For a screening method to be considered effective, it must have demonstrated reduced mortality from the disease of interest. This standard has not yet been met for ovarian cancer screening.

The benefits of screening for breast and other cancers in men who carry harmful mutations in BRCA1 or BRCA2 is also not known, but some expert groups recommend that men who are known to carry a harmful mutation undergo regular mammography as well as testing for prostate cancer. The value of these screening strategies remains unproven at present.

Prophylactic (Risk-reducing) Surgery. Prophylactic surgery involves removing as much of the "at-risk" tissue as possible. Women may choose to have both breasts removed (bilateral prophylactic mastectomy) to reduce their risk of breast cancer. Surgery to remove a woman's ovaries and fallopian tubes (bilateral prophylactic salpingo-oophorectomy) can help reduce her risk of ovarian

cancer. Removing the ovaries also reduces the risk of breast cancer in premenopausal women by eliminating a source of hormones that can fuel the growth of some types of breast cancer.

No evidence is available regarding the effectiveness of bilateral prophylactic mastectomy in reducing breast cancer risk in men with a harmful BRCA1 or BRCA2 mutation or a family history of breast cancer. Therefore, bilateral prophylactic mastectomy for men at high risk of breast cancer is considered an experimental procedure, and insurance companies will not normally cover it.

Prophylactic surgery does not completely guarantee that cancer will not develop because not all at-risk tissue can be removed by these procedures. Some women have developed breast cancer, ovarian cancer, or primary peritoneal carcinomatosis (a type of cancer similar to ovarian cancer) even after prophylactic surgery. Nevertheless, the mortality reduction associated with this surgery is substantial: Research demonstrates that women who underwent bilateral prophylactic salpingo-oophorectomy had a nearly 80 percent reduction in risk of dying from ovarian cancer, a 56 percent reduction in risk of dying from breast cancer (24), and a 77 percent reduction in risk of dying from any cause (25).

Emerging evidence (25) suggests that the amount of protection that removing the ovaries and fallopian tubes provides against the development of breast and ovarian cancer may be similar for carriers of BRCA1 and BRCA2 mutations, in contrast to earlier studies (26).

Chemoprevention. Chemoprevention is the use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the recurrence of, cancer. Although two chemopreventive drugs (tamoxifen and raloxifene) have been approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of breast cancer in women at increased risk, the role of these drugs in women with harmful BRCA1 or BRCA2 mutations is not yet clear.

Data from three studies suggest that tamoxifen may be able to help lower the risk of breast cancer in BRCA1 and BRCA2 mutation carriers (27), including the risk of cancer in the opposite breast among women previously diagnosed with breast cancer (28, 29). Studies have not examined the effectiveness of raloxifene in BRCA1 and BRCA2 mutation carriers specifically.

Oral contraceptives (birth control pills) are thought to reduce the risk of ovarian cancer by about 50 percent both in the general population and in women with harmful BRCA1 or BRCA2 mutations (30).

What are some of the benefits of genetic testing for breast and ovarian cancer risk?
There can be benefits to genetic testing, regardless of whether a person receives a positive or a negative result.

The potential benefits of a true negative result include a sense of relief regarding the future risk of cancer, learning that one's children are not at risk of inheriting the family's cancer susceptibility, and the possibility that special check-ups, tests, or preventive surgeries may not be needed.
A positive test result may bring relief by resolving uncertainty regarding future cancer risk and may allow people to make informed decisions about their future, including taking steps to reduce their cancer risk. In addition, people who have a positive test result may choose to participate in medical research that could, in the long run, help reduce deaths from hereditary breast and ovarian cancer.

What are some of the possible harms of genetic testing for breast and ovarian cancer risk?
The direct medical harms of genetic testing are minimal, but knowledge of test results may have harmful effects on a person's emotions, social relationships, finances, and medical choices.

People who receive a positive test result may feel anxious, depressed, or angry. They may have difficulty making choices about whether to have preventive surgery or about which surgery to have.

People who receive a negative test result may experience "survivor guilt," caused by the knowledge that they likely do not have an increased risk of developing a disease that affects one or more loved ones.

Because genetic testing can reveal information about more than one family member, the emotions caused by test results can create tension within families. Test results can also affect personal life choices, such as decisions about career, marriage, and childbearing.

Violations of privacy and of the confidentiality of genetic test results are additional potential risks. However, the federal Health Insurance Portability and Accountability Act and various state laws protect the privacy of a person's genetic information. Moreover, the federal Genetic Information Non-discrimination Act, along with many state laws, prohibits discrimination based on genetic information in relation to health insurance and employment, although it does not cover life insurance, disability insurance, or long-term care insurance.

Finally, there is a small chance that test results may not be accurate, leading people to make decisions based on incorrect information. Although inaccurate results are unlikely, people with these concerns should address them during genetic counselling.

What are the implications of having a harmful BRCA1 or BRCA2 mutation for breast and ovarian cancer prognosis and treatment?
A number of studies have investigated possible clinical differences between breast and ovarian cancers that are associated with harmful BRCA1 or BRCA2 mutations and cancers that are not associated with these mutations.

There is some evidence that, over the long term, women who carry these mutations are more likely to develop a second cancer in either the same (ipsilateral) breast or the opposite (contralateral) breast than women who do not carry these mutations. Thus, some women with a harmful BRCA1 or BRCA2 mutation who develop breast cancer in one breast opt for a bilateral mastectomy, even if they would otherwise be candidates for breast-conserving surgery. In fact, because of the increased risk of a second breast cancer among BRCA1 and BRCA2 mutation carriers, some doctors recommend that women with early-onset breast cancer and those whose family history is consistent with a mutation in one of these genes have genetic testing when breast cancer is diagnosed.

Breast cancers in women with a harmful BRCA1 mutation are also more likely to be "triple-negative cancers" (i.e., the breast cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein), which generally have poorer prognosis than other breast cancers.

Because the products of the BRCA1 and BRCA2 genes are involved in DNA repair, some investigators have suggested that cancer cells with a harmful mutation in either of these genes may be more sensitive to anticancer agents that act by damaging DNA, such as cisplatin. In preclinical studies, drugs called PARP inhibitors, which block the repair of DNA damage, have been found to arrest the growth of cancer cells that have BRCA1 or BRCA2 mutations. These drugs have also shown some activity in cancer patients who carry BRCA1 or BRCA2 mutations, and researchers are continuing to develop and test these drugs.

What research is currently being done to help individuals with harmful BRCA1 or BRCA2 mutations?

Research studies are being conducted to find new and better ways of detecting, treating, and preventing cancer in people who carry mutations in BRCA1 and BRCA2. Additional studies are focused on improving genetic counselling methods and outcomes. Our knowledge in these areas is evolving rapidly.

Information about active clinical trials (research studies with people) for individuals with BRCA1 or BRCA2 mutations is available on NCI's website. The following links will retrieve lists of clinical trials open to individuals with BRCA1 or BRCA2 mutations.

- BRCA1 mutation carriers
- BRCA2 mutation carriers

NCI's Cancer Information Service (CIS) can also provide information about clinical trials and help with clinical trial searches.

Do inherited mutations in other genes increase the risk of breast and/or ovarian tumours?

Yes. Although harmful mutations in BRCA1 and BRCA2 are responsible for the disease in nearly half of families with multiple cases of breast cancer and up to 90 percent of families with both breast and ovarian cancer, mutations in a number of other genes have been associated with increased risks of breast and/or ovarian cancers (2, 31). These other genes include several that are associated with the inherited disorders Cowden syndrome, Peutz-Jeghers syndrome, Li-Fraumeni syndrome, and Fanconi anemia, which increase the risk of many cancer types.

Most mutations in these other genes are associated with smaller increases in breast cancer risk than are seen with mutations in BRCA1 and BRCA2. However, researchers recently reported that inherited mutations in the PALB2 gene are associated with a risk of breast cancer nearly as high as that associated with inherited BRCA1 and BRCA2 mutations (32). They estimated that 33 percent of women who inherit a harmful mutation in PALB2 will develop breast cancer by age 70 years. The estimated risk of breast cancer associated with a harmful PALB2 mutation is even higher for women who have a family history of breast cancer: 58 percent of those women will develop breast cancer by age 70 years.

PALB2, like BRCA1 and BRCA2, is a tumour suppressor gene. The PALB2 gene produces a protein that interacts with the proteins produced by the BRCA1 and BRCA2 genes to help repair breaks in DNA. Harmful mutations in PALB2 (also known as FANCN) are associated with increased risks of ovarian, pancreatic, and prostate cancers in addition to an increased risk of breast cancer (13, 33, 34). Mutations in PALB2, when inherited from each parent, can cause a Fanconi anemia subtype, FA-N, that is associated with childhood solid tumours (13, 33, 35).

Although genetic testing for PALB2 mutations is available, expert groups have not yet developed specific guidelines for who should be tested for, or the management of breast cancer risk in individuals with, PALB2 mutations.

Link to National Cancer Institute for more details
http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet

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36. Breast cancer is the most common cancer in women. Like most cancers, the majority of breast cancer occur by chance, but up to 10% can be inherited. Current findings state that up to 50% of hereditary breast cancers could be attributed to BRCA1 and BRCA2 mutations, with the remaining due to other genes (The Cancer Genome Atlas Network, 2012).

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