



Genetic Testing for Inherited Predisposition to Breast Cancer: Few Benefits, Many Limitations

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Position

Genetic testing for breast cancer risk has limited value in the clinical setting and should only be performed in the context of well-designed clinical trials and research studies. Genetic testing must not be used as a screening tool because it is an unreliable indicator of true risk of developing breast cancer. We do not know how to prevent breast cancer and there are few and limited options available to women who wish to reduce their risk of developing breast cancer. Women considering genetic testing must receive counseling by a certified genetic counselor who provides accurate and unbiased information about the potential benefits and limitations of genetic testing.

Genetic Mutations Associated with Breast Cancer

By studying families with multiple cases of breast cancer, scientists have discovered several genetic mutations associated with a higher risk of developing breast cancer. Mutations in two genes known as *BRCA1* and *BRCA2* ("Breast Cancer genes 1 and 2," also referred to as breast cancer susceptibility genes) are strongly associated with breast cancer risk.

When functioning properly, *BRCA1* and *BRCA2* are thought to help suppress the growth of cancerous cells. People who have certain alterations, or mutations, in these genes have an increased risk of developing breast cancer and several other types of cancer. Mutations in the *BRCA1* and *BRCA2* genes can be inherited and passed on to offspring by both fathers and mothers. These mutations are very rare in the general population but may contribute to the development of several cases of breast and/or ovarian cancer within one family. However, not all individuals with such mutations develop cancer. Despite the association between mutations in these genes and breast cancer, only 5-10% of all breast cancer patients have *BRCA1* or *BRCA2* mutations.¹ Scientists believe there may be other unknown genes that are strongly associated with breast cancer risk. However, the majority of breast cancer cases are "sporadic" cancers, meaning that the individual has no known inherited predisposition to breast cancer.

Susceptibility Genes and Risk of Cancer

Some women have a family history of breast cancer and do not have mutations in either of the breast cancer susceptibility genes *BRCA1* and *BRCA2*. Other women do not have a family history of breast cancer, but do have a mutation in one of these genes. Both of these groups of

women are presumed to have a higher risk of breast cancer than the general population, but the exact amount of risk increase is unknown.²

Several studies of Ashkenazi Jewish women with breast cancer have shown that women with a *BRCA1* or *BRCA2* mutation have between a 55% and 85% risk of developing breast cancer during their lifetime. A large, more recent study of Ashkenazi Jewish women has shown that breast cancer risk in *BRCA1* or *BRCA2* mutation carriers increases with age. Women with a mutation in a *BRCA* gene were found to have a 20% risk of breast cancer by age 40, 55% by age 60, and 82% by age 80 in this study.³

It has been estimated that a woman who has a *BRCA1* or *BRCA2* mutation and a previous diagnosis of breast cancer may have a 24-65% risk of developing cancer in her other (contralateral) breast.⁴ Some data suggests that *BRCA1* and *BRCA2* mutations may also be associated with prostate, pancreatic, and colon cancer risk, but to a smaller degree than breast and ovarian cancer risk.^{5,6}

What Information Can Genetic Testing Provide?

Laboratory tests have been developed that can detect the most common mutations in the *BRCA1* and *BRCA2* genes. These genetic tests cannot predict precisely who will develop breast cancer; they can only attempt to identify those individuals that carry *BRCA1* or *BRCA2* mutations. The tests do not and cannot protect women who carry mutations from developing the disease, nor can they cure existing disease. Furthermore, current genetic testing technology often cannot deliver conclusive results about one's predisposition to disease. For example, a recent research study found that the standard genetic test used to identify *BRCA* mutations in the U.S. was unable to identify 12% of people who carried a potentially dangerous mutation in one of the *BRCA* genes that could lead to breast cancer.⁷ In addition, the sensitivity of currently used selection criteria for testing of the *BRCA1* mutation is in the range of 25% to 30%, meaning that about three-quarters of women who test positive do not actually possess this mutation.⁸

If a woman tests negative for *BRCA1* and *BRCA2* mutations, the finding does not mean that she is protected from getting breast cancer. The large majority of women who develop breast cancer do not have *BRCA1* or *BRCA2* mutations. Even if *BRCA1* and *BRCA2* are thoroughly checked for mutations, it is still possible that a mutation could be present in another breast cancer susceptibility gene, such as *CHEK2* or *TP53*. Thus, a woman with a strong family history who tests negative for *BRCA1* and *BRCA2* mutations may still have an elevated risk of breast cancer.

Why Get Genetic Testing?

Genetic testing may be useful to women if the test results help them make medical decisions that benefit them in some way. A woman may want to undergo genetic testing because she may find relief from knowing the results, particularly if the results are negative. A 2007 study found that among women with a personal or family history of breast cancer, there was a comparable increase in anxiety in both mutation carriers and women who elected not to receive genetic testing, while women with a negative (uninformative) result did not have elevated anxiety levels.⁹ Six months following testing, however, the distress felt by mutation carriers had dissipated.⁹

Unfortunately, there are very limited options available to women to reduce their risk of breast cancer, and none of them are fully protective against the disease. Therefore, there is little use in knowing that one has a high risk of developing breast cancer if there is little one can do about it. Currently, if a woman tests positive for a *BRCA1* or *BRCA2* mutation, health professionals may offer her the following health management options alone or in combination:

- Increased surveillance with mammography and other imaging devices
- Chemoprevention
- Prophylactic surgery (the removal of healthy breasts and/or ovaries)

Prophylactic surgery has been shown to reduce the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.¹⁰ There is some evidence that tamoxifen, raloxifene, and aromatase inhibitors may reduce risk among women considered to be at high risk.¹¹⁻¹³ Unfortunately, there is no long-term data on healthy women who have taken chemoprevention drugs for risk reduction.

Few studies have looked at the effectiveness of these drugs specifically for women with a *BRCA1* or *BRCA2* mutation. In one study, tamoxifen reduced breast cancer risk by 62% in women with *BRCA2* mutations but showed no associated risk reduction for women with *BRCA1* mutations.¹⁴ More research is needed to evaluate the benefits of tamoxifen for women with *BRCA* mutations.

Women must be informed that none of these health management options have been proven in scientific studies to reduce the risk of dying from breast cancer. Furthermore, these medical interventions have risks and side effects that should be thoroughly discussed with a health care provider.

Genetic Discrimination

Until 2008, it was possible that the results of genetic testing could be used as a basis for discrimination in employment and health insurance. However, that year, the Genetic Information Nondiscrimination Act (GINA) became Federal law prohibiting genetic discrimination in relation to health insurance and employment. GINA prohibits employers from making adverse employment decisions based on a person's genes and forbids insurance companies from discriminating through reduced coverage or pricing. Unfortunately, the law does not cover life insurance, disability insurance, and long-term care insurance.¹⁵

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 also addresses the issue of discrimination on the basis of genetic information. This law prohibits group health plans from using genetic information, and other health-status factors, as a basis for denying or limiting eligibility for coverage or for charging an individual more for coverage. However, this law only pertains to discrimination in health insurance in the context of group plans under limited circumstances.¹⁶

Most recently in March 2010, the Affordable Care Act provides a Pre-Existing Condition Insurance Plan (PCIP) to make health insurance available to individuals who have a pre-existing condition.¹⁷ This Act guarantees coverage for preventive services such as counseling about *BRCA* testing for women at higher risk.

Genetic Testing in the Context of Clinical Trials and Research Studies

Currently, the main benefit of genetic testing is that it may identify a subset of women from whom we can learn more about inherited breast cancer risk within the context of well-designed research protocols. Genetic testing research studies should be available to those for whom testing is appropriate, and the results of such studies be published and made available to the wider community. All those who participate in peer-reviewed research protocols must be guaranteed continuing follow-up and provided information regarding further refinements of these tests and therapies associated with the genes. Research study participants also must be guaranteed that their genetic testing results will be kept confidential.

Conclusion

A genetic test for breast cancer should only be utilized with full consideration of its limitations and implications. Genetic testing cannot cure or prevent breast cancer, and cannot accurately predict whether a woman will or will not develop breast cancer. Most women who get breast cancer do not have *BRCA1* or *BRCA2* mutations, and some women with confirmed mutations will never get breast cancer. While the tests may help some women who have a strong family history and who have a *BRCA1* or *BRCA2* mutation make health management decisions, the available medical options are of limited value and have risks and side effects to be considered.

Genetic testing should be done in the context of well-designed clinical trials and research studies and must include an opportunity to meet with a certified genetic counselor who is unbiased and who has the expertise to explain the risks and limited benefits of testing.

It is irresponsible to market and promote the widespread use of genetic tests for breast cancer risk at this time. Research must first focus on finding safe, reliable ways to reduce cancer risk in women. In the future, if women who have *BRCA1* and *BRCA2* mutations can be offered viable health management options, genetic testing may become more useful. Currently, these tests have limited value in the clinical setting and are most useful in the context of research studies.

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- ¹⁶ Genetic Privacy Laws are not enacted in all states and the degree of protections vary among states. To check and see if your state has a genetic privacy law you can go to <http://www.nhgri.nih.gov/PolicyEthics/> the website for the National Human Genome Research Institute to find a state by state analysis of genetic law
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