
CANCER FACTS

National Cancer Institute • National Institutes of Health
Department of Health and Human Services

Questions and Answers About Estimating Cancer Risk in Ashkenazi Jews

In 1995, scientists from the National Institutes of Health (NIH) discovered that a particular alteration in the breast cancer gene called BRCA1 was present in 1 percent of the general Jewish population. The researchers did a followup study in 1996 to estimate the cancer risk associated with this alteration as well as two other alterations subsequently reported to be present in the Ashkenazi Jewish population. This study was a cooperative effort between the Washington, D.C., Jewish community and scientists from the National Cancer Institute (NCI) and the National Human Genome Research Institute. The following questions and answers serve as background information on the followup study published in the May 15, 1997, issue of *The New England Journal of Medicine*.

1. What was the purpose of the study?

The primary purpose of the study was to estimate the risk of cancer associated with three specific alterations in the breast cancer genes BRCA1 and BRCA2. The study was conducted in the Washington, D.C., Ashkenazi Jewish population (Jews from eastern or central Europe). Two of the alterations tested were in the BRCA1 gene (185delAG and 5382insC), and one was in the BRCA2 gene (6174delT).

The researchers tested the DNA in blood provided by a finger-prick to see which of the 5,318 volunteers had an alteration. Then, using the family cancer histories reported by the volunteers, the scientists estimated the cancer risk by comparing the histories of cancer in the relatives of the volunteers with the alteration to the histories of cancer in the relatives of the volunteers without the alteration.

2. What was unique about the study?

This was the first study to test DNA from volunteers who are not selected for testing because they are part of cancer-prone families and to estimate the cancer risk associated with each alteration. (For years, researchers have studied families with breast cancer throughout several generations to help identify the altered genes passed on from one generation to the next.)



This was the first community-based study in which men and women with varying degrees of family cancer history participated. In fact, 76 percent of the volunteers had no personal or close family history of breast or ovarian cancer. About 8 percent of the women (302 of 3,742) were breast or ovarian cancer survivors.

The scientists who conducted this study had discovered in previous research that one of the alterations (185delAG) in BRCA1 was present in an unusually high proportion of anonymous stored blood samples from the general Jewish population. Even though the frequencies they found were unexpectedly high (see references in question 4), it was impossible to estimate the cancer risk associated with the alterations because the cancer history of the blood donors was not known.

The study described here was designed both to test for the frequency of the alterations and to find out if alteration carriers from the general population were at greater risk for cancer than those without an alteration.

3. What is known about the BRCA1 and BRCA2 genes?

Because family history is the strongest single predictor of a woman's chance of developing breast cancer, researchers turned to cancer-prone families—those with a high incidence of cancer in several generations—to find specific inherited gene alterations that are passed on from one generation to the next. After a long search, two genes were found that are altered in many families with hereditary breast cancer. The first, BRCA1 (for **BR**east **C**Ancer gene), was discovered in 1994, and the second, BRCA2, in 1995. (Alterations in other genes, including p53 and Rb, are also associated with breast cancer susceptibility. Scientists continue to search for additional genes involved in the development of breast cancer.)

Within families with cancer in multiple generations, it had been estimated previously that a woman with an alteration in the BRCA1 gene has about an 85 percent chance of developing breast cancer and a 44 percent chance of developing ovarian cancer by age 70. Prior research in these high-risk families had reported that women with BRCA2 alterations have a lower risk of developing both breast and ovarian cancer than women with BRCA1 alterations. Previous studies had reported an increased risk of colon and prostate cancer among alteration carriers in these same families.

Most alterations result in a shortened protein product that scientists believe prevents the protein from carrying out its normal function in the cell. The precise biological roles of BRCA1 and BRCA2 are not known.

Once the genes were isolated, it was possible to analyze the specific alterations inherited in each cancer-prone family. Today several hundred different alterations scattered throughout BRCA1 have been identified. In general, most families have a unique alteration. A similar pattern is emerging for BRCA2 alterations seen in cancer-prone families; a large number of distinct, family-specific alterations are scattered throughout the gene.

The initial impetus for this study was the observation in late 1994 that three high-risk Ashkenazi families studied at the NIH carried an identical alteration in BRCA1 (185delAG). These families were not known to be related. This observation led to the study which found that 1 percent of the Jewish population has this alteration. This was the first alteration associated with a particular ethnic group. A few other alterations that occur frequently in other ethnic groups (Icelandic, Norwegian, and Dutch) have been found since then.

4. Why were these particular alterations chosen to be tested?

Of the more than 100 alterations identified in each gene (BRCA1 and BRCA2) in families with hereditary breast cancer, a few are found in subgroups of the general population. In particular, three alterations were initially identified in Ashkenazi families with hereditary breast cancer and later were found in an unusually high percentage of the general Jewish population. The estimated frequencies of the three alterations in the general Ashkenazi population, derived from previous studies, are listed below:*

Gene	Alteration	Frequency in Ashkenazi Jews
BRCA1	185delAG	1.0 percent
	5382insC	0.1 percent
BRCA2	6174delT	1.4 percent

In comparison, the percentage of people in the general U.S. population that have any mutation in BRCA1 has been estimated to be between 0.1 percent and 0.6 percent.

5. What were the findings of the 1996 study in Washington?

This study:

- **Supported previous studies testing the frequency of three BRCA1 and BRCA2 alterations in the general Jewish population:** The frequencies reported in this study are consistent with those previously reported for the general Jewish population. The DNA analysis in this study showed that 120 of the 5,318 volunteers had one of the three alterations or about 1 person in 44 (2.3 percent). No individual carried more than one of the three alterations. By comparison, the frequency of all BRCA1 and BRCA2 alterations combined in the non-Jewish population is less than 1 percent.
- **Estimated the average risk of breast and ovarian cancer associated with three BRCA1 and BRCA2 alterations in the general Ashkenazi population:** The researchers found that women carrying one of the three alterations have, on average, a 56 percent chance (a range of 40 percent to 73 percent) of getting breast cancer by the age of 70 (compared with a 13 percent chance without the

* *Nature Genetics* 1995; 11:198–200 and *Nature Genetics* 1996; 14:185–187, 188–190.

alterations) and a 16 percent chance (a range of 6 percent to 28 percent) of getting ovarian cancer by age 70 (compared with a 1.6 percent chance for noncarriers). In other words, the researchers estimate that by the age of 70, slightly more than half of all women with an alteration will develop breast cancer, and about one out of every six carriers will develop ovarian cancer.

The researchers noted that the cancer risks in this study are likely to be overestimates because people with personal or family histories of breast cancer may have been more likely than others to volunteer for the study. They estimated, for example, that the true breast cancer risk for U.S. Ashkenazi women with an alteration may be 50 percent or lower.

- **Found breast and ovarian cancer risks well below previous estimates:** Before this study, small studies of families with cancer in several generations had estimated that women with an alteration had a 76 percent to 87 percent chance of developing breast cancer; for ovarian cancer, the estimated risk ranged from 11 percent to 84 percent.
- **Further explored the link between prostate cancer and the alterations:** Previous studies had suggested a link between BRCA1 and prostate cancer. This study found an association with and showed a significant excess of prostate cancer among men with the alterations. Based on these findings, the researchers estimated that men carrying one of the three alterations have, on average, a 16 percent chance of getting prostate cancer (compared with a 3.8 percent chance for noncarriers) by the age of 70. In other words, by age 70 the researchers estimate that about one out of every six men carrying an alteration will develop prostate cancer. However, the results of subsequent studies have been conflicting. Some studies have shown an association between BRCA1 or BRCA2 alterations and prostate cancer, while others have not.
- **Found the average risks for breast, ovarian, and prostate cancers:** The study estimated the average risk of cancer for alteration carriers *as a group*. The cancer risk for an individual man or woman who carries one of the alterations may be higher or lower than the average.
- **Found no link with colon cancer:** A previous report showed a link between BRCA1 alterations and colon cancer that was not confirmed in this study.
- **Found that each alteration carries a similar breast cancer risk:** Previous reports suggested that the risk of getting breast cancer was different for two of the alterations studied. Specifically, in studies involving Jewish early-onset breast cancer patients, data suggested that the risk associated with the 6174delT mutation (in BRCA2) was considerably lower than the risk associated with 185delAG. In this study, the risk associated with the 6174delT was slightly lower, but the risks for the three alterations were not significantly different from each other.

- **Found that the three alterations account for only a small proportion of breast cancer cases in Jewish women:** Of the women in this study who were breast or ovarian cancer survivors, only 9 percent had one of the alterations. In fact, only about 7 percent of breast cancer in Jewish women is due to the three alterations in BRCA1 and BRCA2.

6. **How is inherited breast cancer different from other genetic diseases?**

For many genetic diseases, such as Huntington's disease, everyone who inherits an alteration in the gene will develop the disease. This is called "complete penetrance." All cases of Huntington's disease are caused by alterations in the Huntington's disease gene. The situation with breast cancer appears to be quite different.

Breast cancer is a common disease, but only a small fraction of cases are due to the inheritance of an alteration in a single gene. In order to isolate cancer-predisposing genes such as BRCA1 and BRCA2, scientists initially studied families with many members affected by breast and ovarian cancer over several generations. Estimates of the risk of breast cancer within these families were often over 80 percent by age 70, and 90 percent to 100 percent over a lifetime. These estimates are similar to other genetic diseases like Huntington's disease, with nearly complete penetrance, but whether they applied to all carriers of BRCA1 and BRCA2 alterations was unknown.

Evidence from this study suggests that they do not apply to all carriers, and that, on average, the risk of breast cancer among carriers is closer to 50 percent. This is called "incomplete penetrance" and suggests that about half of the carriers will not develop breast cancer even if they live to age 70. Other factors, both genetic and nongenetic, are likely to affect whether someone with an alteration will develop cancer or not.

7. **What are the chances that someone with one of these alterations in BRCA1 or BRCA2 will get breast, ovarian, or prostate cancer?**

On average, by the age of 70, women with one of the alterations tested for in this study have between a 40 percent and 73 percent chance of being diagnosed with breast cancer and between an 8 percent and 28 percent chance of developing ovarian cancer. Men with an alteration have about a 16 percent chance of developing prostate cancer by the age of 70. However, for any individual with an alteration, a precise estimate of risk is not possible.

Family history helps to place an individual's cancer risk in perspective, but is also an imperfect tool. For example, family history will be most useful in determining risk if a carrier has multiple relatives affected with breast or ovarian cancer. In this case, a woman's risk of breast cancer may be higher than the average of 56 percent.

If a carrier has little or no family history of breast and ovarian cancer, his or her risk will be much more difficult to assess. This is particularly true of women in small families with very few close female relatives.

Unless someone already has a strong family history of breast or ovarian cancer, it will be very difficult to know his or her precise risk until other risk factors for cancer are identified.

8. What are the implications of this study for non-Jewish populations?

This is the first community-based study to estimate the cancer risk associated with alterations in BRCA1 and BRCA2 in the general population. The researchers found that the risks for breast and ovarian cancer were lower on average in this population than in hereditary breast cancer families. Even though there are no data for other ethnic groups, researchers speculate that future findings may be similar; that is, it is likely that most alterations in BRCA1 or BRCA2 that produce a shortened protein product will increase the cancer risk in the general population, but the average risk will probably not be as high as in cancer-prone families.

9. Do the results have implications for Jews considering whether to be tested for these alterations?

Deciding whether to be tested for a gene alteration is complex and personal. One of the factors to be considered is the cancer risk associated with having a positive or negative test result.

Based on this study, the average risk of breast, ovarian, and prostate cancer for people with BRCA1 and BRCA2 alterations is known more accurately. For example, the average risk of breast cancer is lower than previously thought, but is still significantly higher than for those who don't carry the alteration.

But gene alterations linked to cancer do not have the same effect on each person who carries them. For example, the findings from this study suggest that nearly half of the women with these alterations will not develop cancer, and since BRCA1 and BRCA2 alterations account for only a small portion of breast cancer, many women without an alteration will develop breast cancer.

Part of the complexity of the decision to be tested is that the medical consequences of an individual's test result—positive or negative—are not predictable. This is especially true of a carrier who does not have a personal or family history of cancer.

Besides the cancer risks, other considerations are important. There may be psychological and social effects of both positive and negative results for the individual tested and family members. Individuals should also consider how a positive or negative result might affect them and their relatives, especially if they have a strong history of cancer in the family.

In addition, privacy issues are important, since it is possible that having a positive or negative result may affect health insurance and employment.

Until recently, genetic testing for alterations that increase susceptibility to cancer was performed only in a research setting. However, this kind of testing is now commercially

available. Still, there is no consensus about the circumstances in which genetic testing might be useful, and genetic testing is certainly not routine.

Scientists and physicians are still uncertain about how best to help alteration carriers. Even if the precise risk of cancer for an individual carrier were known, there are no proven effective risk reduction strategies. Physicians are not sure about the best ways to monitor those at high risk to assure early detection if they do develop cancer. More research is needed.

10. Do the results of this study have implications for the prevention or treatment of breast, ovarian, or prostate cancer?

The hope is that these gene alterations as well as any others discovered in future studies will provide novel targets for the development of anticancer drugs. The interaction between gene alterations and environmental factors may also present new strategies for cancer prevention.

11. Where can someone go to get more information about genetic testing?

C Information about genetics and genetic testing may be found on NCI's CancerNet™ Web site at <http://cancernet.nci.nih.gov/> on the Internet. Several publications and other documents are available on this Web site, including the position papers of professional and advocacy organizations on the issue of genetic testing for susceptibility to cancer.

This Web site also includes a searchable directory of genetic counselors, physicians, geneticists, and nurses who have expertise in genetic testing and who will accept physicians' referrals for familial cancer risk counseling and/or genetic susceptibility testing. The search form for the directory is available at <http://cancernet.nci.nih.gov/genesrch.shtml> on the Internet. Because the issues surrounding genetic testing are highly personal and can have far-reaching consequences, a health professional trained in genetics is a good resource for exploring these issues.

C Another resource is NCI's Cancer Information Service (CIS) at 1-800-4-CANCER (1-800-422-6237). The staff can send a booklet called *Understanding Gene Testing* and other printed information, and can answer questions about cancer and cancer genetics. The CIS can also identify facilities offering cancer risk assessment, counseling related to familial cancer and genetic susceptibility to cancer, and centers conducting research.

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1-800-4-CANCER (1-800-422-6237)

TTY (for deaf and hard of hearing callers): 1-800-332-8615

NCI Online

Internet

Use <http://cancer.gov> to reach the NCI's Web site.

LiveHelp

Cancer Information Specialists offer online assistance through the *LiveHelp* link on the NCI's Web site.

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