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FACT SHEET #48

Cornell University Program on
Breast Cancer and Environmental Risk Factors
in New York State (BCERF)

Family History, Inheritance, and Breast Cancer Risk

All breast cancer results from multiple gene mutations. The initial mutation can be inherited from one's parents (familial breast cancer) or occur after conception (sporadic breast cancer). Inherited gene mutations play a role in about 27% of all cases of breast cancer. Mutations in two different genes, called BRCA1 and BRCA2, have been associated with early breast cancer in some families. These mutated genes can act alone and the families that carry either of these mutations may have as many as half of their women members with breast cancer. But these families are rare and are thought to account for only about 4% of all breast cancer cases. Most inherited breast cancer risk results from the interaction of several mutated genes. Families with this pattern of inheritance will contain only a few members with breast cancer. These mutated genes by themselves are associated with only a small increase in breast cancer risk, but when several of these genes are inherited together they can lead to a significant increase in breast cancer risk. Diet and lifestyle may modify inherited breast cancer risk but more study is needed to identify and understand how this happens.

How are inheritance and a family history involved in breast cancer risk?

Most women do not develop breast cancer. When it does develop it results from mutations in multiple cancer-associated genes. The first of these mutations can be either inherited from ones parents (familial cancer) or they can occur after conception (sporadic cancers). A few of the inherited mutations – called high penetrance mutations – are associated with a prominent family history of breast cancer and high breast cancer risk. However, most of the inherited mutations are associated with a smaller increase in the risk of breast cancer and a less prominent family history of breast cancer (these mutations are called low penetrance mutations). Most breast cancer cases (about three forths) are known as sporadic, meaning that rare mutations have occurred. In these cases the initial rare cancer gene mutations occurred after conception; these cases have no connection to family history. (Figure 1)

How large a role does inheritance of breast cancer risk play in a woman's chance of developing breast cancer?

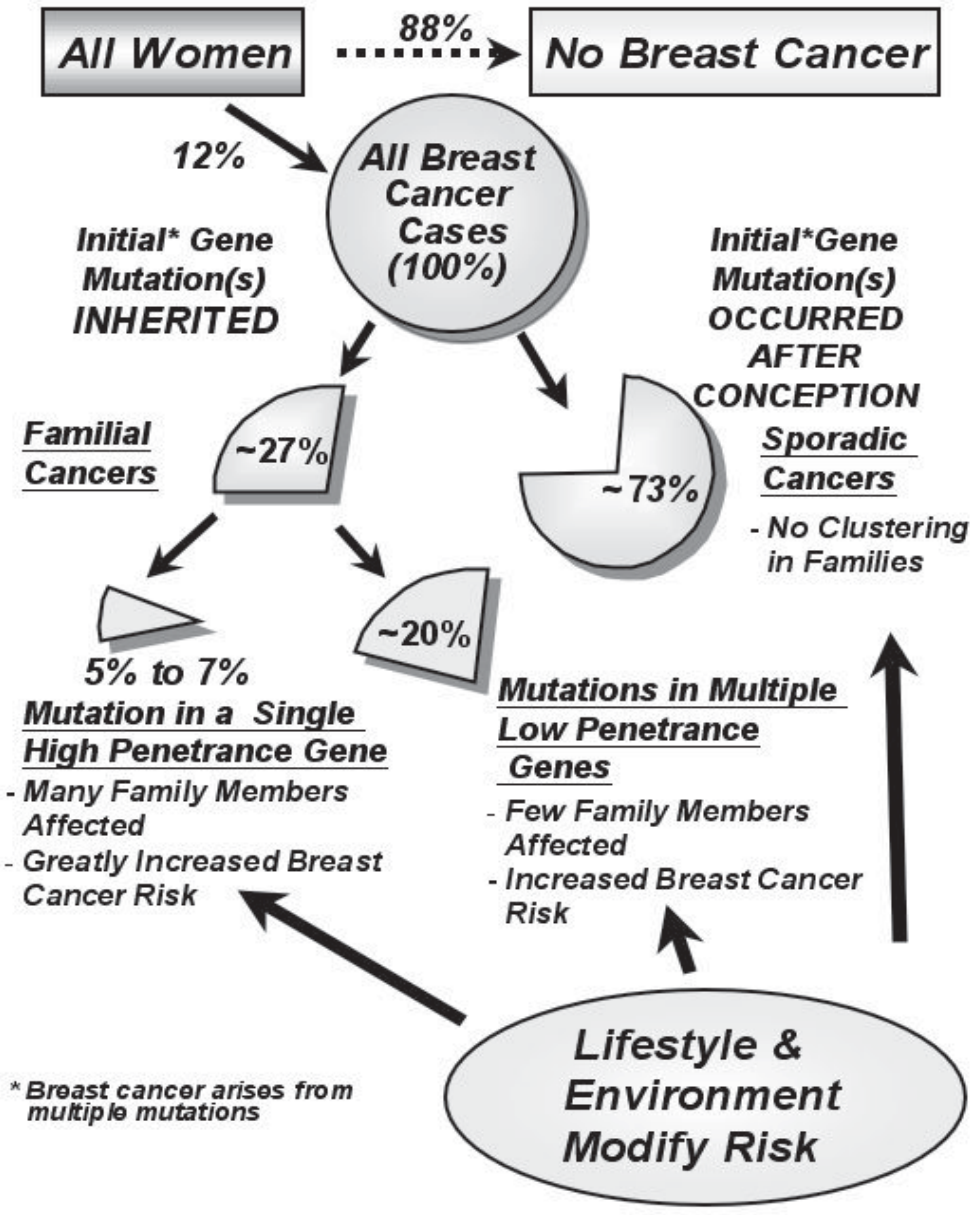
Study of the differences in breast cancer risk between identical and non-identical twins has allowed a very good estimate of how much of all breast cancer risk is inherited. A recent large study using data from twin and cancer registries in Sweden, Denmark, and Finland (547 pairs of identical twins and 1075 pairs of non-identical twins) reported that about one quarter (27%) of the total risk of breast cancer was due to inherited factors. While the results are most applicable to these Scandinavian countries, they would be expected to be similar in other Western countries.

How large a role does a family history of breast cancer play in a woman's chance of developing breast cancer?

Having a family history or family member with breast cancer, does not play a large role in most women's chances of developing breast cancer. Women with a family history of breast cancer make up only 5 to 7 percent of all women with breast cancer.

The mutated genes associated with a strong family history of breast cancer are known as *high penetrance genes*. A breast cancer gene's penetrance is the likelihood that someone with a mutated gene will develop breast cancer during their lifetime. A person with a high penetrance breast cancer gene has a high risk of breast cancer and a strong family history of breast cancer Because high penetrance genes are thought to largely act alone, diseases associated with them are sometimes called single gene disorders. But the effects of these genes can be modified by other genes as well as by the environment inside and outside the body.

Inherited breast cancer risk seen in families with only a few cases of breast cancer results from a second type of mutated genes, *low penetrance genes*. Low penetrance genes are much more common than high penetrance genes. The breast cancer risk of women who carry these genes depends largely on the interactions of the low penetrance genes with other genes and



with the body's internal and external environments. Since low penetrance genes are much more common than the high penetrance genes, low penetrance genes account for more cases of breast cancer overall.

If inherited mutations are only responsible for about one quarter of all breast cancer risk (27%), what is the source of the rest of the risk?

Three quarters of cases of breast cancer are not due to inheritance. Instead, they are the result of biological and environmental factors to which women are exposed. These factors can include: reproductive hormone levels and how long women are exposed to them (for example, age of menarche and menopause); women's child-bearing patterns (for example, at what age they bear children, how long they breast feed and

how many children they have); medical treatments associated with breast cancer risk (for example, oral contraceptives, or postmenopausal hormone treatment); women's physical characteristics (for example, body weight and where fat is carried on the body); exposure to toxic chemicals associated with breast cancer risk; exposure to radiation, especially at young ages, and parts of the diet associated with breast cancer risk (for example, alcohol use). These environmental and lifestyle factors may also act together with genetic factors.

What are breast cancer families?

Breast cancer families are families in which breast cancer is inherited and family members are at greater than average risk of breast cancer. Simply finding several cases of breast cancer within one family does not mean a pattern of genetic inheritance. Determination of family inheritance requires a detailed examination of breast cancer in present and earlier generations by someone trained in genetic analysis. Breast cancer is common enough (affecting one in eight or 12% of all American women over their lifetimes) that several cases could occur within a family merely by chance alone. For example, if a woman with breast cancer has ten female relatives who have lived to 80 years old, there is a 50% chance that one of them will also have developed breast cancer.

Breast cancer families are frequently described as families with three or more close relatives with breast cancer. Members of these families are at high risk for developing breast cancer at a young age that may affect both breasts. The existence of breast cancer families has been noted since the mid-1800s.

Several types of family patterns exist. There are families with breast cancer alone, families with both breast and ovarian cancer, and families with several types of cancer including breast cancer. Breast cancer families also differ in the number of family members affected with cancer. Some families have many members with breast cancer and very high risk and other families have fewer family members affected and lower, but still, higher than average breast cancer risk.

Have specific genes been linked to the high breast cancer risk seen in breast cancer families?

Mutations in two genes strongly associated with inherited breast cancer risk were identified among members of breast cancer families with the highest risk. These genes are called BRCA1 and BRCA2. Mutations in BRCA1 and BRCA2 have been linked to: the occurrence of breast cancer at a young age; the number of cases of breast cancer in a family; the occurrence of ovarian cancer as well as breast cancer in families; and breast cancer among men in the family.

BRCA1 and BRCA2 mutations are found much more often in the rare breast cancer families that have many members with breast cancer. Studies of such families have reported presence of BRCA1 or BRCA2 in as many as 87 % of the cases. However, in breast cancer families with fewer cases of breast cancer, the presence of BRCA1 or BRCA2 mutations is much lower (15 to 20 % of the cases). Mutations in other unidentified genes have also been implicated in these families. BRCA1 and BRCA2 mutations have rarely been found in the sporadic cancers of women with no family history of breast cancer.

How high is the risk of breast cancer for women with BRCA1 and BRCA2 mutations?

The risk of getting breast cancer for women who have BRCA1 and BRCA2 mutations is very high compared to women without these mutations – but how high is still uncertain. Early studies of the breast cancer risk associated with the mutated forms of BRCA1 and BRCA2 focused on women from the rare high risk breast cancer families with many cases of breast cancer. Their extremely high risk made these families ideal for identifying breast cancer-associated genes. Following identification of BRCA1 and BRCA2, initial estimates indicated that all women with mutations in these genes would have breast cancer risk similar to that of women in these high breast cancer risk families. With more study, it became apparent that women in the general population with mutated versions of these genes were at higher risk of breast cancer but their risk was lower than that seen in the rare families with many cases of breast cancer.

More recent studies have evaluated the rate of occurrence of BRCA1 and BRCA2 mutations and breast cancer in women without such a strong family history of breast cancer, who were more like women in the general population. These studies have estimated that from 36 % to 68 % of the women with BRCA1 mutations in the general population would be expected to have breast cancer by age 70. The risk associated with BRCA2 ranged between no change in risk to 37 % of the women developing cancer by age 70. Overall, women with a BRCA1 and BRCA2 mutations make up 15 % to 20 % of women with a family history of breast cancer. Please see "What is a woman's breast cancer risk if she has relatives who have been diagnosed with breast cancer?", below, for a discussion of breast cancer risk for women with a genetically undefined family history of breast cancer.

Are there countries or racial/ethnic groups with more women with BRCA1 and BRCA2 mutations?

Breast cancer incidence varies as much as 8-fold between countries, yet in most countries 6 % to 10 % of all breast cancers are related to BRCA1 or BRCA 2 mutations. There is a considerable country-to-country difference in the proportion of cases of breast cancer in breast cancer families that are due to BRCA1 or BRCA2. Almost 80 % of cases with a family history of breast and ovarian cancer (familial cases) in Russia have BRCA1 mutations whereas in other European countries, less than 30 % of these familial cases are due to mutations in this gene. In the United States and Canada about 40 % of the familial cases involve BRCA1. In the Ashkenazi Jewish population in Israel BRCA1 mutations are involved in about 50 % of familial cases. Iceland has a high percentage (64 %) of breast and ovarian cancer families affected by BRCA2 mutations. In the United States and Israel approximately 25 % of breast and ovarian cancer families are due to BRCA2 mutations; in most other countries the proportion is below 20 %.

Different racial/ethnic groups have different prevalences of BRCA1 and BRCA2 mutations. The best studied racial/ethnic group is the Ashkenazi Jews. More than 90 % of the Jewish people in the United States are Ashkenazis. There are two BRCA1 mutations and one BRCA2 mutation observed frequently in Ashkenazi Jews. These mutations are also seen in the general population regardless of race or ethnicity but they are 10 to 50 times more frequent in women with an Ashkenazi background. Although Ashkenazi women are more likely to be carriers of these mutations, the occurrence of these mutations is rare enough such that the risk of breast or ovarian cancer for Ashkenazi women is not higher than that of non-Jewish Caucasian women.

How are mutations in BRCA1 and BRCA2 thought to increase breast cancer risk?

The majority of mutations in BRCA1 and BRCA2 have been found to result in changes in the size and function of the proteins produced by these genes. These proteins have been shown to have roles in a number of different biological processes centered around the stability of genes and the cellular response to gene damage. These are processes whose loss could be associated with increased cancer risk and may explain their linkage to high risk breast cancer families. This is an active area of research and more definite answers should arise in the near future.

Is breast cancer seen in families with other types of inherited cancer?

Breast cancer has been associated with the following familial cancer syndromes, ataxia-telangiectasia, Muir-Torre syndrome, Cowden syndrome, Li-Fraumeni syndrome and Peutz-Jehger syndrome. These cancer syndromes are very rare, and their contribution to the total number of cases of breast cancer is very small.

Low penetrance genes are thought to play a major role in breast cancer susceptibility but have any of these genes been identified?

The study of low penetrance genes is still in its infancy. Low penetrance genes that may be associated with breast cancer risk have been discovered, but are not yet well understood. Studies have focused on different forms (variants) of these genes, which are known as polymorphisms. Polymorphisms have been shown to have varying levels of biological activity. The different levels of biological activity of polymorphisms might link them with differing breast cancer risk. A number of classes of genes with polymorphisms have been evaluated, including genes whose products play a role in reproductive hormone action, repair gene mutations, detoxify cancer-causing chemicals, or induce or prevent cancer themselves. This area of research has the potential to identify other groups of women with increased breast cancer susceptibility.

What is a woman's breast cancer risk if she has relatives who have been diagnosed with genetically undefined breast cancer?

A woman whose close relatives have been diagnosed with breast cancer has a higher risk of breast cancer than women with no close relatives with breast cancer. The size of the breast cancer risk depends on the woman's current age, the age of relatives when they were diagnosed, and the number of relatives who were diagnosed. Table 1 (next page) shows the how a woman's risk of breast cancer depends on her age and the number of first-degree relatives (mothers, fathers, sisters, and brothers) with breast cancer she has.

For instance, 7.8 % of 20 year olds, with *no* first degree relative with breast cancer, will *develop* breast cancer by the time they are *80 years old*. Twenty-one percent of 20 year olds with *two* first degree relatives will develop cancer by age 80. Since the table looks at the percentage of women who will develop breast cancer by age 80, the percentage decreases as the woman gets older (current age increases). Most women who develop breast cancer do so after age 50, whether or not they have a family history.

It is important to note that most of the women in these studies who developed breast cancer did not die from it. The lifetime risk of *dying* from breast cancer was 2.3% for women with no first degree relatives, 4.2% for those with one first-degree relative, and 7.6% for those with two first degree relatives.

TABLE 1: Familial Breast Cancer Risk Depends on Both the Age of the Potentially Affected Woman and the Number of First-Degree Relatives Diagnosed With Genetically Undefined Breast Cancer

	Percentage Of Women Developing Breast Cancer By Age 80		
	Number of First-Degree* Relatives Affected		
Woman's Current Age	***None***	***One***	***Two***
20 years	7.8%	13.3%	21.1%
30 years	7.7%	13.0%	20.7%
40 years	7.3%	12.0%	18.9%
50 years	6.1%	9.8%	14.7%
60 years	4.5%	7.1%	10.4%
70 years	2.5%	4.2%	5.7%

*First-degree relatives include mothers, sisters and daughters.

Lancet *358*, 1389-1399, 2001.

Studies have also examined how a woman's relative breast cancer risk depends on which of her family members were diagnosed with breast cancer. Women with family members with breast cancer had in general about twice the breast cancer risk of women with no family history of breast cancer. Which of a woman's relatives was diagnosed with breast cancer had a small effect on the woman's breast cancer risk.

Is survival from breast cancer different for women with a family history of breast cancer?

No conclusive result can be derived from studies that have examined survival from breast cancer among women with a genetically undefined family history relative to similar-aged women with breast cancer but no family history. It is also uncertain if survival of women with BRCA1 or BRCA2 mutations is different from women diagnosed at the same age with breast cancer who do not have these mutations.

Who should get tested for BRCA1 and BRCA2 mutations?

The decision to be tested for mutations in BRCA1 or BRCA2 is best made in consultations with a genetic counselor and medical geneticist. The National Society of Genetic Counselors maintains a web site that provides the names and locations of genetic counselors including those who specialize in cancer genetics. The address for this web site is: http://www.nsgc.org/resourcelink.asp

Are there ways that women with a family history of breast cancer can modify their breast cancer risk?

Studies of women with mutations in BRCA1 and BRCA2 argue that there are factors that modify the risk of breast cancer for women with these mutations, as well as women with a genetically undefined family history of breast cancer. Women from the same family with the same BRCA1 or BRCA2 mutation can have different patterns of disease. Differences in whether cancer develops at all, the age of cancer diagnosis, and in whether they develop breast or ovarian cancer, can be observed. The most likely explanation for these patterns is different exposures to lifestyle and other environmental factors that modify these women's risk. However, genetic differences between these women may also contribute to differences in risk.

Many studies have evaluated whether the established risk factors for breast cancer (such as age of menarche, age of menopause, age of first child's birth) might affect women with a family history of breast cancer differently. The results of these studies have been inconsistent. However a collaborative study pooled and reanalyzed the data from 52 different studies of 58,200 women with a first-degree (mother, daughter or sister) family history of breast cancer. In this reanalysis the established breast cancer risk factors did not affect these women with a family history of breast cancer to a greater extent than women without a family history. These results support the idea that family history acts largely by itself as a risk factor.

A few studies have examined eating habits and breast cancer risk for women with a family history of breast cancer. A promising large cohort study, part of the Nurses Health Study, reported on women with a family history of breast cancer. In this study, postmenopausal women with a family history of breast cancer who ate 5 or more servings of fruits and vegetable a day decreased their breast cancer risk by 71%; no effect was reported for women without a family history. A second, more recent study of these women reported decreased risk associated with carotene rich foods (such as carrots, sweet potatoes and broccoli). This study also reported a decrease in risk from breast feeding and strenuous activity as a young adult. Some but not all reports associated increased risk with alcohol consumption for women with a family history of breast cancer.

Another large cohort study based in Iowa found a synergistic link between family history and waist-to-hip ratio (the size of the waist divided by the size of the hips; see BCERF Fact Sheet, #42, *A Woman's Body Type and the Risk of Breast Cancer.*). Women with a high waist-to-hip ratio (sometimes called apple shaped) and a family history of breast cancer had a 3.2-fold increase in breast cancer risk relative to women without this body characteristic or family history. In contrast women with the same waist to hip ratio but without a family history of breast cancer had little or no increase in breast cancer risk.

A number of studies have specifically examined women with BRCA1 and BRCA2 mutations. Several have evaluated how these women's reproductive histories affected their breast cancer risk. The results of these studies have been inconclusive. Other studies have examined the effect of cigarette smoking and alcohol use on breast cancer risk in BRCA1 and BRCA2 mutation carriers; no conclusion could be made since the results of these studies differed. The effect of oral contraceptive use on these women's breast cancer risk is also undecided. Oral contraceptive use is an area of contention as some reports have suggested an association of oral contraceptive use with decreased ovarian cancer in women with these mutations.

More study of how various factors might affect breast cancer risk in women with a family history of breast cancer is needed.

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World Wide Web sites with breast cancer incidence and mortality information can be found on the BCERF web site at: http://envirocancer.cornell.edu/

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