Genetics

About 5% to 10% of breast cancers are thought to be hereditary, caused by abnormal genes passed from parent to child.

Genes are short segments of DNA (deoxyribonucleic acid) found in chromosomes. DNA contains the instructions for building proteins. And proteins control the structure and function of all the cells that make up your body.

Think of your genes as an instruction manual for cell growth and function. Changes or mistakes in the DNA are like typographical errors. They may provide the wrong set of instructions, leading to faulty cell growth or function. In any one person, if there is an error in a gene, that same mistake will appear in all the cells that contain the same gene. This is like having an instruction manual in which all the copies have the same typographical error.

There are two types of DNA changes: those that are inherited and those that happen over time. Inherited DNA changes are passed down from parent to child. Inherited DNA changes are called germ-line alterations or mutations.

DNA changes that happen over the course of a lifetime, as a result of the natural aging process or exposure to chemicals in the environment, are called somatic alterations.

Some DNA changes are harmless, but others can cause disease or other health issues. DNA changes that negatively affect health are called mutations.

BRCA1 and *BRCA2* genetic mutations

Most inherited cases of breast cancer are associated with mutations in two genes: *BRCA1* (BReast CAncer gene one) and *BRCA2* (BReast CAncer gene two).

Everyone has *BRCA1* and *BRCA2* genes. The function of the *BRCA* genes is to repair cell damage and keep breast, ovarian, and other cells growing normally. But when these genes contain mutations that are passed from generation to generation, the genes don't function normally and breast, ovarian, and other cancer risk increases. *BRCA1* and *BRCA2* mutations may account for up to 10% of all breast cancers, or 1 out of every 10 cases.

Having a *BRCA1* or *BRCA2* mutation doesn't mean you will be diagnosed with breast cancer. Researchers are learning that other mutations in pieces of chromosomes -- called SNPs (single nucleotide polymorphisms) -- may be linked to higher breast cancer risk in women with a *BRCA1* mutation as well as women who didn't inherit a breast cancer gene mutation.

Women who are diagnosed with breast cancer and have a *BRCA1* or *BRCA2* mutation often have a family history of breast cancer, ovarian cancer, and other cancers. Still, most people who develop breast cancer did not inherit a genetic mutation linked to breast cancer and have no family history of the disease.

You are substantially more likely to have a genetic mutation linked to breast cancer if:

- You have blood relatives (grandmothers, mother, sisters, aunts) on either your mother's or father's side of the family who had breast cancer diagnosed before age 50.
- There is both breast and ovarian cancer on the same side of the family or in a single individual.
- You have a relative(s) with triple-negative breast cancer.
- There are other cancers in your family in addition to breast, such as prostate, melanoma, pancreatic, stomach, uterine, thyroid, colon, and/or sarcoma.
- Women in your family have had cancer in both breasts.
- You are of Ashkenazi Jewish (Eastern European) heritage.
- You are African American and have been diagnosed with breast cancer at age 35 or younger.
- A man in your family has had breast cancer.
- There is a known abnormal breast cancer gene in your family.

If one family member has a genetic mutation linked to breast cancer, it does not mean that all family members will have it.

The average woman in the United States has about a 1 in 8, or about 12%, risk of developing breast cancer in her lifetime. Women who have a *BRCA1* mutation or *BRCA2* mutation (or both) can have up to an 80% risk of being diagnosed with breast cancer during their lifetimes. Breast cancers associated with a *BRCA1* or *BRCA2* mutation tend to develop in younger women and occur more often in both breasts than cancers in women without these genetic mutations.

Women with a *BRCA1* or *BRCA2* mutation also have an increased risk of developing ovarian, colon, and pancreatic cancers, as well as melanoma.

Men who have a *BRCA2* mutation have a higher risk of breast cancer than men who don't -- about 8% by the time they're 80 years old. This is about 80 times greater than average.

Men with a *BRCA1* mutation have a slightly higher risk of prostate cancer. Men with a *BRCA2* mutation are 7 times more likely than men without the mutation to develop prostate cancer. Other cancer risks, such as cancer of the skin or digestive tract, also may be slightly higher in men with a *BRCA1* or *BRCA2* mutation.

Other genes

Mutations in other genes are also associated with breast cancer. These genetic mutations are much less common and don't seem to increase risk as much as *BRCA1* and *BRCA2* mutations, which are considered rare. Still, because these genetic mutations are even rarer, they haven't been studied as much as the *BRCA* mutations.

- ***ATM***: The *ATM* gene helps repair damaged DNA. DNA carries genetic information in cells. Inheriting two mutated copies of this gene causes the disease ataxia-telangiectasia, a rare disease that affects brain development. Inheriting one mutated *ATM* gene has been linked to an increased rate of breast cancer and pancreatic cancer in some families because the mutation stops the cells from repairing damaged DNA.
- ***BRIP1***: The *BRIP1* gene also works to repair DNA. Inheriting one mutated *BRIP1* gene is associated with higher risk of both breast and ovarian cancer.
- ***CDH1***: The *CDH1* gene makes a protein that helps cells bind together to form tissue. A mutated *CDH1* gene increases the risk of a rare type of stomach cancer at an early age. The lifetime risk is up to 83%. Women with a *CDH1* mutation also have a 39% to 52% lifetime risk of invasive lobular breast cancer.
- ***CHEK2***: The *CHEK2* gene provides instructions for making a protein that stops tumor growth. A *CHEK2* mutation can at least double breast cancer risk, double colon cancer risk, and increase prostate cancer risk.

- ***MRE11A***: Along with the *RAD50* and *NBN* genes, the *MRE11A* gene forms the MRN complex, which helps repair DNA damage in cells. An *MRE11A* mutation is linked to ataxia-telangiectasia-like disorder, a rare disease that affects brain development. The disease also weakens the immune system and increases cancer risk.
- ***MSH6***: The *MSH6* gene provides instructions for making a protein that helps repair DNA damage. Studies have found that mutations in the *MSH6* gene are linked to Lynch syndrome and a higher risk of ovarian cancer. Having Lynch syndrome increases the risk of many types of cancer, particularly colorectal, endometrial, ovarian, stomach, small intestine, liver, gallbladder, upper urinary tract, and brain. In 2018, research found that women with a *MSH6* mutation had double the breast cancer risk of the average woman.
- ***NBN***: Along with the *MRE11A* and *RAD50* genes, the *NBN* gene forms the MRN complex, which helps repair DNA damage in cells. An *NBN* mutation causes Nijmegen breakage syndrome, a condition that causes slow growth in infancy and early childhood. People with Nijmegen breakage syndrome are shorter than average; have a higher risk of several types of cancer, including breast cancer; and many other health problems. Of the three genes in the MRN complex, researchers think that an *NBN* mutation has the strongest link to breast cancer.
- ***PALB2***: The *PALB2* gene is called the partner and localizer of *BRCA2*. It provides instructions to make a protein that works with the BRCA2 protein to repair damaged DNA and stop tumor growth. Research published in 2014 found that a *PALB2* mutation increases breast cancer risk 5 to 9 times higher than average, almost as high as a *BRCA1* or *BRCA2* mutation. Women with a *PALB2* mutation have a 33% to 58% lifetime risk of developing breast cancer. In comparison, women with a *BRCA1* mutation have a 50% to 70% risk of developing breast cancer by age 70. Women with a *BRCA2* mutation have a 40% to 60% risk of developing breast cancer by age 70.
- ***PMS2***: The *PMS2* gene provides instructions for making a protein that helps repair DNA damage. Studies have found that mutations in the *PMS2* gene are linked to Lynch syndrome and a higher risk of ovarian cancer. Having Lynch syndrome increases the risk of many types of cancer, particularly colorectal, endometrial, ovarian, stomach, small intestine, liver, gallbladder, upper urinary tract, and brain. In 2018, research found that women with a *PMS2* mutation had double the breast cancer risk of the average woman.
- ***PTEN***: The *PTEN* gene helps regulate cell growth. A *PTEN* mutation causes Cowden syndrome, a rare disorder in which people have a higher risk of both benign (not cancer) and cancerous breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries. The lifetime breast cancer risk for women with a *PTEN* mutation is up to 85%.

  In 2015, a *SEC23B* mutation also was linked to Cowden syndrome. The *SEC23B* gene also helps regulate cell growth.
- ***RAD50***: Along with the *MRE11A* and *NBN* genes, the *RAD50* gene forms the MRN complex, which helps repair DNA damage in cells. An *RAD50* mutation has been linked to a higher risk of breast cancer in some families because the abnormal gene stops the cells from repairing damaged DNA.
- ***RAD51C***: The *RAD51C* gene repairs DNA damage. People who have inherited one mutated copy have higher risk of breast and ovarian cancer.
- ***STK11***: The *STK11* gene helps regulate cell growth. An *STK11* mutation causes Peutz Jegher syndrome, a rare disorder in which people tend to develop a type of polyp, called a hamartomatous polyp, mostly in the small intestine but also in the stomach and colon. People with Peutz Jegher syndrome are at higher risk not only of gastrointestinal cancers, but also breast and lung cancer and ovarian tumors. People may also develop freckling around the eyes, nose, and mouth, as well as inside the mouth.
- ***TP53***: The *TP53* gene provides instructions to the body for making a protein that stops tumor growth. Inheriting a *TP53* mutation causes Li-Fraumeni syndrome, a disorder that causes people to develop soft tissue cancers at a young age. People with this rare syndrome have a higher-than-average-risk of breast cancer and several other cancers, including leukemia, brain tumors, and sarcomas (cancer of the bones or connective tissue). The cancer risk in women with a *TP53* mutation is up to nearly 100%. In men, it is up to 73%. This gender difference is mostly due to the high breast cancer risk in women.

Inheriting two abnormal copies of the *BRCA2, BRIP1, MRE11A, NBN, PALB2, RAD50,* or *RAD51C* genes causes the disease Fanconi anema, which suppresses bone marrow function and leads to extremely low levels of red blood cells, white blood cells, and platelets. People with Fanconi anemia also have a higher risk of several other types of cancer, including kidney cancer and brain cancer.

Genetic testing

There are genetic tests available to determine if someone has a *BRCA1* or *BRCA2* mutation. A genetic counselor also may order testing for *ATM, CDH1, CHEK2, MRE11A, MSH6, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, SEC23B,* or *TP53* mutations, individually or as part of a larger gene panel that includes *BRCA1* and *BRCA2*.

For more information, visit the Breastcancer.org Genetic Testing pages.

Steps you can take

If you know you have an abnormal gene linked to breast cancer, there are lifestyle choices you can make to keep your risk as low it can be:

- maintaining a healthy weight
- exercising regularly
- limiting alcohol
- eating nutritious food
- never smoking (or quitting if you do smoke)

These are just a few steps you can take. Review the links on the left side of this page for more options.

Along with these lifestyle choices, there are other risk-reduction options for women at high risk because of abnormal genetics.

Hormonal therapy medicines: Two SERMs (selective estrogen receptor modulators) and two aromatase inhibitors have been shown to reduce the risk of developing hormone-receptor-positive breast cancer in women at high risk.

- Tamoxifen has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in both postmenopausal and premenopausal women at high risk. Certain medicines may interfere with tamoxifen's protective effects. Visit the Tamoxifen page to learn more.
- Evista (chemical name: raloxifene) has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in postmenopausal women. Visit the Evista page to learn more.
- Aromasin (chemical name: exemestane), an aromatase inhibitor, has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in postmenopausal women at high risk. Aromasin isn’t approved by the FDA for this use, but doctors may consider it a good alternative to tamoxifen or Evista. In 2013, the American Society of Clinical Oncology (ASCO) released new guidelines on using hormonal therapy medicines to reduce breast cancer risk in high-risk women. These guidelines recommend that doctors talk to high-risk postmenopausal women about using Aromasin to reduce risk. ASCO is a national organization of oncologists and other cancer care providers. ASCO guidelines give doctors recommendations for treatments that are supported by much credible research and experience. Visit the Aromasin page for more information.
- Arimidex (chemical name: anastrozole), also an aromatase inhibitor, has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in postmenopausal women at high risk. Like Aromasin, Arimidex isn’t approved by the FDA for this use, but doctors may consider it a good alternative to tamoxifen, Evista, or Aromasin. Visit the

Arimidex page for more information.

Hormonal therapy medicines do not reduce the risk of hormone-receptor-negative breast cancer.

More frequent screening: If you're at high risk because of an abnormal breast cancer gene, you and your doctor will develop a screening plan tailored to your unique situation. You may start being screened when you're younger than 40. In addition to the recommended screening guidelines for women at average risk, a screening plan for a woman at high risk may include:

- a monthly breast self-exam
- a yearly breast exam by your doctor
- a digital mammogram every year starting at age 30 or younger
- an MRI scan every year starting at age 30 or younger

Women with an abnormal breast cancer gene need to be screened twice a year because they have a much higher risk of cancer developing in the time between yearly screenings. For example, the Memorial Sloan-Kettering Cancer Center in New York, NY recommends that women with an abnormal *BRCA1* or *BRCA2* gene have both a digital mammogram and an MRI scan each year, about 6 months apart (for example, a mammogram in December and an MRI in June).

A breast ultrasound is another powerful tool that can help detect breast cancer in women with an abnormal breast cancer gene. This test does not take the place of digital mammography and MRI scanning.

Talk to your doctor, radiologist, and genetic counselor about developing a specialized program for early detection that addresses your breast cancer risk, meets your individual needs, and gives you peace of mind.

Protective surgery: Removing the healthy breasts and ovaries -- called prophylactic surgery ("prophylactic" means "protective") -- are very aggressive, irreversible risk-reduction options that some women with an abnormal *BRCA1* or *BRCA2* gene choose.

Prophylactic breast surgery may be able to reduce a woman's risk of developing breast cancer by as much as 97%. The surgery removes nearly all of the breast tissue, so there are very few breast cells left behind that could develop into a cancer.

Women with an abnormal *BRCA1* or *BRCA2* gene may reduce their risk of breast cancer by about 50% by having prophylactic ovary and fallopian tube removal (salpingo-oophorectomy) before menopause. Removing the ovaries lowers the risk of breast cancer because the ovaries are the main source of estrogen in a premenopausal woman’s body. Removing the ovaries doesn’t reduce the risk of breast cancer in postmenopausal women because fat and muscle tissue are the main producers of estrogen in these women. Prophylactic removal of both ovaries and fallopian tubes reduces the risk of ovarian cancer in women at any age, before or after menopause.

Research also has shown that women with an abnormal *BRCA1* or *BRCA2* gene who have prophylactic ovary removal have better survival if they eventually are diagnosed with breast or ovarian cancer.

The benefit of prophylactic surgeries is usually counted one year at a time. That’s why the younger you are at the time of surgery, the larger the potential benefit, and the older you are, the lower the benefit. Also, as you get older you’re more likely to develop other medical conditions that affect how long you live, such as diabetes and heart disease.

Of course, each woman's situation is unique. Talk to your doctor about your personal level of risk and how best to manage it.

It's important to remember that no procedure -- not even removing both healthy breasts and ovaries at a young age -- totally eliminates the risk of cancer. There is still a small risk that cancer can develop in the areas where the breasts used to be. Close follow-up is necessary, even after prophylactic surgery.

Prophylactic surgery decisions require a great deal of thought, patience, and discussion with your doctors, genetic counselor, and family over time -- together with a tremendous amount of courage. Take the time you need to consider these options and make decisions that feel comfortable to you.

For more information, visit the Breastcancer.org Prophylactic Mastectomy and Prophylactic Ovary Removal pages.
