Inheriting a Cancer Risk

curetoday.com/view/inheriting-a-cancer-risk

Amy Paturel, M.S., M.P.H.

Aug 14, 2023
Amy Paturel, M.S., M.P.H.

Family history of breast and other cancers can mean some people are more likely to develop the disease at a younger age. But advances in testing may improve prevention and survival rates.

When Jennifer Fink was a little girl, she was surrounded by cancer. Her grandmother and aunt both developed the disease twice — once in each breast — before she graduated high school. Now a nurse and writer in southeastern Wisconsin, Fink viewed cancer almost like wallpaper. It was always there in the background.

“I don’t remember a time when I didn’t know about my family history of breast cancer,” Fink says. “My grandmother died when I was 5 and my aunt was diagnosed at 39 years old when I was in my teens. Then, when I was in my 20s, my mom was diagnosed with breast cancer, then ovarian cancer 10 years later.”

According to the American Cancer Society, breast cancer will strike more than 350,000 American women in 2023. About 5% of patients with breast cancer carry a genetic mutation that predisposes them to the disease. Although the most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 genes, advances in next-generation sequencing coupled with studies of cancer-prone families have uncovered several milder mutations, including ATM and CHEK2, that are also linked to the disease.

“Many, but not all, familial breast cancers are due to inherited mutations,” says Dr. Wendy Chung, chief of clinical genetics at Columbia University in New York City. “But cancers may also run in families without any known genetic mutation.”

No matter which category a patient may fall into, identifying and personalizing the risk of developing breast cancer is crucial. Being proactive about the best way of sidestepping the disease is important. That is where genetic testing comes in.

Genetic Mutations Linked to Breast Cancer

Everyone is born with two copies of genes in every cell of the body — one copy from each parent. Cells typically contain genes that can suppress tumor growth, but when these genes are mutated, tumors can form and grow.

“Any cell at any time, either as a direct result of something exposure related or just by random chance, can acquire mutations,” says Lisa Madlensky, a genetic counselor and program director of the Family Cancer Genetics Program at Moores Cancer Center at UC San Diego Health in California. “There are billions of pieces of information in trillions of cells, and each time cells grow and divide, it’s like copying volumes and volumes of encyclopedias. That’s not a perfect process.”

The more you copy those encyclopedias, the more opportunity there is for error. So naturally, most cancers are related to age; however, people who carry certain genetic mutations are more susceptible to developing cancer, earlier in life.

Consider BRCA1 and BRCA2, for example: In normal cells, these function as important tumor suppressor genes that help repair damaged DNA. However, Madlensky says, “If you are born with a mutation in one of those inherited genes, you only have one working gene left in each cell to act as a buffer against the kick-starting of a cancer. It’s almost like you’re going up to bat, but you’ve already got one strike against you.

”Studies show that the risk of breast cancer before age 70 among BRCA1 and BRCA2 female carriers ranges from 38% to 87%. Fink falls into that high-risk category. She inherited the BRCA2 mutation from her mother, Pat Wondra, whose initial breast cancer almost went undetected. Wondra did not feel a lump, but her lower breast felt hard to the touch whereas the middle felt bouncy, like a blood vessel. A clinical examination did not sound any alarm bells. But because Wondra’s mom died of breast cancer, her doctor suggested she see a specialist.

“The fact that he remembered my mother had breast cancer was lifesaving,” says Wondra, emphasizing that her diagnosis predated the discovery of the BRCA genes in the 1990s. “The tissue they took out during a biopsy looked healthy, but when they put it under the microscope, there was cancer everywhere. It just never coalesced into a lump.” Pat had a double mastectomy, followed by radiation. Ten years later, she was diagnosed ovarian cancer, which had mysteriously metastasized throughout her abdomen.

“There were thousands of cancerous warts all over my uterus,” Wondra says. “The doctors didn’t expect me to recover.” Nevertheless, they treated her with chemotherapy and she recovered. But 18 months later, doctors discovered a small tumor on her intestines. After surgery to remove the tumor, Wondra received another chemotherapy regimen, first through the vein and then directly into the gut through a port in Wondra’s belly.

Although Wondra, now 85, has had a few scares, she has been free of cancer ever since. Still, she feels tremendous guilt for passing the “cancer gene” to her eldest child, Fink.

“Finding out that she carried the gene broke my heart — that was harder to hear than my own diagnosis,” Wondra says. But inheriting a genetic mutation does not guarantee cancer will happen, especially if a patient carries a gene with a milder risk profile including ATM or CHEK2 “Inherited mutations are only one part of the equation, and with non-BRCA mutations, they may not be that impactful,” says Dr. Steven Narod, a Tier I Canada Research Chair in Breast Cancer, professor in the Dalla Lana School of Public Health and the Department of Medicine at the University of Toronto, and a senior scientist at Women’s College Research Institute.

“With BRCA1 and BRCA2 mutations, the risk of developing breast cancer is about the same, regardless of family history. But with CHEK2, for example, your risk of breast cancer is largely dependent on your family history.” According to the American Cancer Society, having a firstdegree relative (mother, father, sister, or daughter) with breast cancer nearly doubles the risk for women, whereas having two firstdegree relatives with the disease Although Wondra, now 85, has had a few scares, she has been free of cancer ever since. Still, she feels tremendous guilt for passing the “cancer gene” to her eldest child, Fink. “Finding out that she carried the gene broke my heart — that was harder to hear than my

own diagnosis," Wondra says. But inheriting a genetic mutation does not guarantee cancer will happen, especially if a patient carries a gene with a milder risk profile including ATM or CHEK2 "Inherited mutations are only one part of the equation, and with non-BRCA mutations, they may not be that impactful," says Dr. Steven Narod, a Tier I Canada Research Chair in Breast Cancer, professor in the Dalla Lana School of Public Health and the Department of Medicine at the University of Toronto, and a senior scientist at Women's College Research Institute. "With BRCA1 and BRCA2 mutations, the risk of developing breast cancer is about the same, regardless of family history. But with CHEK2, for example, your risk of breast cancer is largely dependent on your family history." According to the American Cancer Society, having a firstdegree relative (mother, father, sister, or daughter) with breast cancer nearly doubles the risk for women, whereas having two firstd-egree relatives with the disease increases the risk threefold.

To Test or Not to Test

Fink was newly married and in her 20s when she felt a lump in her breast. She visited her doctor to get it checked out. Despite explaining that she has a strong family history of breast cancer, he dismissed her.

"I don't remember whether I pushed for a mammogram or an ultrasound, but I do remember the frustration I felt," Fink says. "I had this sense of 'What more do I need to say for you to take this seriously?' " A few years after her mom received her ovarian cancer diagnosis, Fink pushed for genetic testing. "I wanted it documented irrefutably in my chart," says Fink. "I spent my entire life assuming I would eventually get breast cancer, and I'm almost more afraid of the treatment than the diagnosis because I saw what it did to my family members."

But not everyone with a strong family history of breast cancer — or inherited mutations — wants to know. Emma Jarrett, a poet, writer and coach in British Columbia Canada, had little knowledge of her family's history of breast cancer. She knew her grandmother received a diagnosis in her 80s and that her mom's cousin had breast cancer, but she did not think much about a genetic link.

"My family are buttoned-up Brits, so any health issues were all shrouded in mystery," Jarrett says. In fact, when her mom received a diagnosis of breast cancer in 1997, Jarrett learned the news in a letter after she'd already been treated. "She wrote that she'd had a 'little diagnosis' and that it was nothing to worry about," she says. But when Jarrett was 50, she felt little lumps under her armpit.

“They would come and go, and they were never consistent in size, so I figured they were swollen lymph nodes,” she says. “And plenty of ‘Dr. Google’ searches seemed to confirm my theory.” The lumps grew larger, and then painful. “They were no longer ignorable,” Jarrett adds. In July 2016, a mammogram and ultrasound uncovered several suspicious lesions. Jarrett had breast cancer, but decided against genetic testing. At the time of diagnosis, she was convinced her cancer was not driven by a genetic mutation, “and I just didn’t want to know,” she says. Fink’s and Wondra’s siblings seem to feel the same way — none did genetic testing.

“Deciding whether or not to test when you have a family history isn’t always clear-cut,” Madlensky says. “People may have the sense that their family is riddled with cancer. But when you dig deeper into their family history, you discover their father had prostate cancer in his 80s and their mother had breast cancer when she was in her 70s. So that person may not have an elevated inherited risk, but rather cancer struck their family members due to age-related changes.”

Five years after her initial diagnosis, Jarrett still does not have a definitive answer about whether her cancer was driven by an inherited mutation. “But I’m absolutely convinced that if I do have a BRCA mutation, there are lifestyle changes I can make to override it, so that’s where I place my focus,” Jarrett says. Jarrett’s decision “not to know” could get flipped on its head if her 19-year-old daughter does her own testing to uncover whether she has an inherited risk of developing breast cancer. Most genetic counselors recommend against cancer genetic testing in children. With advances in technology occurring rapidly, the findings may not be relevant when the results become important for screening guidelines. But if Jarrett’s daughter chooses to test, and no mutation is identified, she may decide to implement screening guidelines based on family history alone.

“For patients with a strong family history but no known genetic mutation, the general rule is to begin screening 10 years younger than the age when the earliest cancer diagnosis occurred,” Chung says. “If you’re the type of person who seeks information and knowledge, you will self-select for testing. But if you’re not that type of person, no one is going to force you to get tested.”

Management Based on Mutations

No parent wants to pass a genetic mutation to their child. But once people know they have an increased risk of developing cancer, they can take proactive steps to ensure the best outcome.

“We use genetic testing not only to identify whether there’s a breast cancer-associated genetic mutation, but also to understand how high the risk is and at what age it begins,” Chung says. In Fink’s case, genetic testing — and proactive treatments — have allowed her to reduce her risk of developing the disease. But she has been confronted with difficult decisions, ranging from genetic testing to prophylactic mastectomy and/or salpingo-oophorectomy (removal of the ovaries and tubes). Because BRCA-2 and CHEK2-driven cancers are usually estrogen and progesterone positive, removing the ovaries can help protect against a future cancer by reducing circulating estrogen.

“The people who choose to have prophylactic surgeries tend to be the ones who are suffering from the most anxiety,” Narod says. Although these procedures may reduce the risk of developing breast cancer, they are also big decisions that can dramatically affect quality of life — and they may not be appropriate for women with mild-tomoderate-risk genes.

“A lot of women hear that they have a genetic mutation linked to breast cancer and they jump right to prophylactic surgery,” Chung says. “But moderate-risk genes — like ATM and CHEK2 — don’t carry the same risks as the BRCA mutations. And if your lifetime risk of developing breast cancer is 25%, that’s very different than if it’s 75%.”

Even with BRCA1 and BRCA2mutations, pre-emptive surgery is a tough call. In lieu of removing her breasts and ovaries, Fink chose to take tamoxifen for five years beginning at age 43 — a decision that would be expected to reduce her risk of developing breast cancer by 40% or more. At the very least, people with a strong family history or documented genetic mutation may choose to screen for breast cancer more frequently and with more sensitive methods, such as MRI. For people who have received breast cancer diagnoses, inherited mutations are not only relevant to assessing the risk of developing breast cancer, but they can also help guide treatment decisions. Studies show that cancers driven by an inherited BRCA1 or BRCA2 mutation, for example, tend to be more responsive to chemotherapy. BRCA carriers also seem to be highly sensitive to a new class of medications called poly (ADP-ribose) polymerase, or PARP, inhibitors.

“These drugs are specifically for patients with BRCA1 and BRCA2 carriers,” Chung says.

Genetis on the Horizon

The goal of genetic testing in the cancer space is to give people information about their personal risk of developing the disease. But genetic testing is not perfect, and the results may not always provide clear, actionable answers. To complicate matters, genetic tests

that are available to the public, without medical oversight, may only look for a small number of mutations associated with a specific gene.

For example, the Food and Drug Administration has approved a commercial test for BRCA mutations, but it only applies to people of Ashkenazi Jewish ancestry. About 1 in 40 such individuals carry a BRCA mutation compared with 1 in 500 people in the general population. However, there are more than 2,900 variants of BRCA1 and more than 3,400 variants of BRCA2 that scientists have identified as pathogenic, many of which would not be detected by this test.

“People with a negative test result from certain companies might assume they don’t have to be concerned about their risk, when in fact they might still have a different BRCA mutation,” Madlensky says. Accurately determining your genetic risk depends on which specific genes were tested, the laboratory methods used to test those genes, and how long ago the testing was done since there are always improvements in testing technology. To help personalize patients’ risk, scientists are working hard to develop a polygenic risk score.

“This score will put together 100 or more different genetic variants, each of which might represent teeny tiny risks, or even decreased risks,” Chung says. “The idea is to mathematically pair all of those variants with the major players, such as BRCA1 and BRCA2, to provide patients with a more accurate risk score.”

In the meantime, patients often have to make decisions based on incomplete information. But when people learn they have a genetic mutation that increases their risk of cancer, they can arm themselves with information, proactive screening measures and prophylactic procedures to mitigate the risk of getting the disease.

“Even with unexpected genetic test results, studies show that most people have the initial shock, but then they feel empowered,” says Madlensky. “That’s partly because the focus of genetic testing for cancer risk is always on prevention and early detection.” Fink is 50 now, just six years younger than her mom was diagnosed with breast cancer. “When you reach this age, more and more people around you get diagnosed with breast cancer,” she says. “So there’s this voice in my head reminding me that my best-laid plans for the next year, or five years, could change at any point in time. I like to believe that helps me lead my best life.”

For more news on cancer updates, research and education, don’t forget to subscribe to CURE®’s newsletters here.