

New Data on *BRCA* Mutations and Prophylactic Surgeries

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Treatment choice is highly individual

Barbara, aged 44 years, always knew that breast cancer ran in her family. She lost her mother to the disease when she was 9 years old, and her mother's first cousin also died of it. When the cousin's daughter developed breast cancer and tested positive for the *BRCA1* mutation, it became clear that Barbara's mother also had been a carrier. Still, after both Barbara's siblings and her maternal aunt and uncle all tested negative, she thought she was safe. She was wrong. "I had the same genetic mutation as my cousin, who was then fighting a difficult battle against ovarian cancer," she says.

Barbara did not hesitate to undergo a total hysterectomy at age 41 followed by a double mastectomy at age 42. "When I learned my high probability of getting cancer, I was not going to play Russian roulette," she adds. "To me, there was no decision. Quite honestly, I should have done it when I was younger." She put off taking the test because she had hoped to marry and have children before having to deal with the possibility of the surgeries, but, with her cousin dying of ovarian cancer, she could put it off no longer.

A Difficult Choice

Many women who test positive for *BRCA1/2* genetic mutations confront the same choice. Although not all of them will develop breast or ovarian cancer, they do have a 60% lifetime risk of developing breast cancer (5 times higher than the general population) and a 15% to 40% risk of developing ovarian cancer, compared with a 1.4% risk for the general population, according to the National Cancer Institute (NCI), although these risk percentages may change with further research.

Because ovarian cancer has such a poor prognosis and no proven screening methods, oophorectomy is considered a mandate for patients who carry *BRCA1/2* mutations and who have completed their childbearing or are aged 40 years and older. Prophylactic mastectomies are an individual choice, experts note.

Some women, particularly those who are young, have not completed their families, and have never had cancer, may opt for intensive screenings, including both mammograms and magnetic resonance imaging (MRI), versus undergoing a bilateral mastectomy. Others may not want to wait. "You have to individualize these recommendations in the context of women's lives," says Susan Domchek, MD, director of the Cancer Risk Evaluation Program at the University of Pennsylvania's Abramson Cancer Center in Philadelphia.

She points to a recent study that compared survival outcomes of patients who underwent oophorectomy and prophylactic mastectomy versus those treated with oophorectomy and intensive breast screenings using sophisticated computer modeling.[1] The difference in mortality was small, and MRI screening with oophorectomy at age 40 was found to be very effective in improving survival. The study's authors are developing a program that will enable *BRCA* mutation carriers to enter their own data to estimate differences in projected survival based on risk reduction choices.

Dr. Domchek and colleagues have conducted a number of studies related to the *BRCA1/2* mutations. When the mutations were first discovered in the mid-90s, many people questioned the value of testing if it was only going to cause anxiety and stress among those who tested positive. "It was our job in the research community to prove that there are interventions that can reduce the risk of cancer," she says.

A Look at the Data

Early studies were retrospective in nature, but Dr. Domchek and colleagues recently published a study that prospectively examined women with the mutations who had not had prior breast cancers and who opted to have their ovaries or breasts removed.[2] The study followed approximately 2500 women with these genetic mutations identified between 1974 and 2008. Participants were followed

until the end of 2009. The median follow-up for women was 3.65 years among those who underwent surgery and 4.29 years in controls who did not undergo surgery.

Of the 257 women who underwent risk-reducing mastectomies, no breast cancers were diagnosed, whereas 7% of women who did not opt for the mastectomies were diagnosed with breast cancer. Of the 993 women who underwent salpingo-oophorectomies, 1.1% were subsequently diagnosed with ovarian cancer, 11.4% were subsequently diagnosed with breast cancer, and 3% subsequently died from any cause; in women who did not undergo the surgery, 5.8% were diagnosed with ovarian cancer, 19.2% were diagnosed with breast cancer, and 10% died.

In the United States, approximately 20% of *BRCA1/2* mutation carriers who have not had cancer opt for prophylactic mastectomies. In addition, approximately 40% to 45% percent of women with prior breast cancers choose oophorectomies, with that rate noted to increase significantly by age 50, Dr. Domchek says. She points out that there continue to be many unknowns. For example, the long-term effects of oophorectomy on women's bone and cardiovascular health are unknown and researchers do not know the optimum age at which to remove the ovaries.

The conclusion, she says, is "there should no longer be a sense of nihilism about genetic testing for *BRCA1/2*. If we can identify the women who have these genetic mutations, we can improve their overall mortality with these interventions."

Future Interventions

A key goal for future research is to determine why some *BRCA1/2* carriers develop breast cancer at age 30, others at age 50, and others never develop it. There may be other genetic modifiers that are inherited that might alter disease development, which would require specific recommendations for individual risk profiles, Dr. Domchek notes.

Improving screening methods for ovarian cancer and developing preventive medicines for cancer also are priorities. Researchers are interested in studying poly adenosine diphosphate-ribose polymerase inhibitors in women with *BRCA1/2* mutations. In addition, ensuring that the "right" women are tested for the mutations is another important goal. "There are women who get tested who have never had cancer, but the right person to test is their mother or sister who has had cancer—that gives us much more information and is more cost-effective," Dr. Domchek explains. "We need to educate providers about how best to evaluate these families." Although most women will test negative for these mutations, the challenge is to find out what is going on in the remaining families with a history of these diseases, she adds.

References

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2. Domchek SM, Friebel TM, Singer CF. Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA.* 2010; 304:967-975.

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A Diverse Vegetable Diet May Decrease Lung Cancer Risk for Smokers



Researchers have discovered more evidence to support a diet high in fruits and vegetables. A recent study reported that eating a variety of vegetables appears to decrease the risk of getting lung cancer, while eating a variety of fruits and vegetables may decrease the risk of developing squamous cell lung cancer, particularly among smokers.

Using data from the ongoing European Prospective Investigation into Cancer and Nutrition (EPIC) study, researchers evaluated 452,187 patients, 1613 of whom were diagnosed with lung cancer. Information was reviewed for 14 commonly eaten fruits and 26 commonly eaten vegetables, including fresh, canned, and dried products. Investigators found that the risk of lung cancer decreased when a variety of vegetables were eaten, regardless of the amount. Meanwhile, the risk of squamous cell carcinoma decreased substantially when a variety of fruit and vegetables were eaten.

"Fruits and vegetables contain many different bioactive compounds, and it makes sense to assume that it is important you not only eat the recommended amounts but also consume a rich mix of these bioactive compounds," said coauthor H. Bas Bueno-de-Mesquita, MD, MPH, PhD, senior scientist and project director of cancer epidemiology at the National Institute for Public Health and the Environment in the Netherlands, in a news release issued by the American Association of Cancer Research.

Researchers caution, however, that the only proven way to reduce lung cancer risk is to avoid all forms of tobacco.

Reference

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Experts Weigh in on *BRCA1/2* Mutations and Prophylactic Surgeries



Gail Tomlinson, MD, PhD, interim director of the Greehey Children's Cancer Research Institute at the University of Texas Health Science Center, San Antonio, and coauthor of the prospective *BRCA1/2* mutation study.[2]

"For women and families at risk of developing these cancers, this study shows a very real benefit to these prophylactic surgeries, allowing women to concentrate on other aspects of their lives, such as their families, children, and jobs.

"Women with *BRCA1* mutations have a higher percentage of triple-negative tumors that don't respond to tamoxifen or aromatase inhibitors and can be very aggressive, so some of these women may be less willing to run the risk of waiting [rather than undergo one or both surgeries].

"We need to see if, after 20 to 30 years, women still feel good about having had these surgeries."



Martha Thomas, MS, certified genetic counselor at the University of Texas Health Science Center at San Antonio

"No genetic testing is perfect. *BRCA* analysis will detect up to 90% to 92% of all mutations. The *BRCA* rearrangement test came out in 2007, and it looks for large deletions and duplications in the gene. A lot of women have had to come back to have this new test.

"The Genetic Information Nondiscrimination Act of 2008 prevents people from discrimination by insurers and employers based on genetic test results, but it doesn't include life insurance. But, I think because these tests are relatively new, unless you're getting a multimillion-dollar policy, rarely does it come up.

"I had one woman who, when she got her positive results back, wanted to go to the operating room immediately. But the doctor I work with says, 'Prevention is never an emergency.'

"A lot of people's concerns are for their children. Except under extreme circumstances, we don't recommend testing under age 18. The earliest is about 25.

"Even after a prophylactic mastectomy, there is still a 5% to 10% residual risk of developing breast cancer. And if women decide to keep their nipple, there's a slight additional residual risk."



Kelly Hunt, MD, chief of the surgical breast section at The University of Texas MD Anderson Cancer Center in Houston, Texas

"Recommendations are re-evaluated every year, and these study results certainly will make those recommendations stronger. In the past, there was less data showing that these surgeries reduce mortality. There have been ads encouraging women to get genetic testing, and that brings in women who may not need to be tested. Also, just because a woman tests negative for *BRCA1* or *2* doesn't mean she still isn't high risk. That's why women considering the test should get counseling.

"The mutation location, a patient's family history, and her age at diagnosis will all affect relative risk. Older women won't benefit as much from oophorectomy after menopause. Also, breast cancer patients who have been treated with chemotherapy that leads to menopause may not receive much benefit from oophorectomy.

"It's always important to consider how many quality years you're gaining with this surgery. Individuals need to know what life changes will occur, especially with young women who have oophorectomies now that it is less clear whether they should take hormone replacement therapy."



Christina Finlayson, MD, professor of surgery and director of the Diane O'Connor Thompson Breast Center at the University of Colorado Cancer Center in Aurora

"As we're testing more people, we're finding more mutations. The initial families we tested were at very high risk. Now, if a patient is diagnosed with breast cancer under age 45, it's an indication to test even if there's no family history. So, we're picking up family members with the mutation that may or may not have as high a risk as the original group we studied.

"Locally, I see many more women choosing prophylactic mastectomies than high-risk screening. But there also has been a pendulum shift in the general population away from breast conservation toward mastectomy. Prevention is becoming a more accepted way to manage your health.

"Women with the mutations who have cancer in 1 breast will choose bilateral mastectomies because they have a 40–50% chance of getting cancer in the other breast in the next 10 years.

"It's important that women realize that reconstruction after mastectomy is not the same as breast augmentation. We can do a lot to make the breasts look better, but they will never feel the same—the breast area is numb and the nipple, if we save it, is still numb.

"It's important for women undergoing prophylactic mastectomy to do a little grief therapy, because it is a loss. I think they underestimate the scope of the operation—it takes a lot out of you, and there are lifelong changes you have to cope with. Having good emotional support is very important."

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