Q&A

The Genetics of Breast and Ovarian Cancer

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What if you could gaze into a crystal ball and learn that breast or ovarian cancer lies in your future? It's a frightening possibility—and one women who come from families with the cancers now face. Today's crystal ball is a high-tech blood test. Analyzed in a lab, the DNA in your white blood cells can reveal mutations in two genes, BRCA1 *and* BRCA2, *that put you at great risk for familial breast or ovarian cancer. And that's the easy part. It's then up to you to make tough health decisions—whether getting frequent mammograms and ultrasound exams of your ovaries or opting for radical surgery to remove your breasts or ovaries.*

Scientists discovered BRCA1 *in 1994 and* BRCA2 *a year later. Now they are unraveling how the genes work—and why they sometimes don't. One researcher at the forefront is* **MARY-CLAIRE KING, Ph.D.,** *a molecular geneticist at the University of Washington. King has analyzed mutations in* BRCA1 *and* BRCA2 *in hundreds of families. She speaks with* **KATHRYN SERGEANT BROWN,** *special correspondent for* SCIENTIFIC AMERICAN, *about the genetics of breast and ovarian cancer. One of King's most important messages is that most breast cancers are not caused by inherited mutations.*

Q ***To understand inherited breast or ovarian cancer, it's important to know how the responsible genes,* BRCA1 *and* BRCA2, *normally work. What do these genes do in the body—and what goes wrong to cause cancer?***

A We don't know, in full, what the genes do. We do know that *BRCA1* and *BRCA2* control the proliferation of breast epithelial cells—that is, the cells that line the milk ducts in the breasts—and ovarian epithelial cells, the cells on the surface of the ovaries. Some scientists have suggested we call *BRCA1* the "cruise control" gene for breast and ovarian cells because it works to keep cells growing and dividing at the right pace. Without normal versions of *BRCA1* or *BRCA2*, breast or ovarian cells can multiply out of control. That's the ultimate consequence. But the mechanism isn't fully understood. Scientists have found hundreds of inherited mutations in *BRCA1* and *BRCA2* that can lead to cancer, and new mutations are found every day.

If a woman inherits a faulty version of* BRCA1 *or BRCA2, how likely is she to get breast or ovarian cancer?

In the U.S. population as a whole, a woman has a 10 percent chance of developing breast cancer by the age of 85. That risk increases to more than 80 percent among women with inherited *BRCA1* or *BRCA2* mutations. In general, fewer than one in 100 women develop ovarian cancer. Women with inherited *BRCA1* or *BRCA2* mutations have at least a 40 percent higher risk for ovarian cancer.

Who's at Risk

When it comes to cancer, genetics is only part of the story. For instance, researchers blame* BRCA1 *and* BRCA2 *for only 5 percent of the 180,000 breast cancer cases that occur every year in the U.S. What explains the rest?

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We know two clear classes of environmental factors play a role in breast cancer. One is exposure to radiation as a young woman. It's a rare event, but it has a dramatic impact on risk. For example, girls surviving the atomic bomb blasts at Hiroshima and Nagasaki subsequently had four times the rate of breast cancer as other Japanese women their age.

The second class of risk factors is related to estrogen. The earlier a woman begins to menstruate and the later she has her first pregnancy, the higher her subsequent risk of breast cancer. And the later her menopause, the higher her postmenopausal risk of breast cancer. In other words, the longer the interval between puberty and childbearing—during which the body makes estrogens—the higher the risk. Estrogen-rich tissue provides a very healthy milieu for breast epithelial cells to divide, including those with mutations. Of course, most of these mutations will be somatic—that is, not inherited.

Early menstruation and delayed childbearing are probably primarily responsible for the increase in breast cancer rates over the past 50 or 60 years. On average, women today begin menstruating at about age 11. Three generations ago the average age of first menstruation in industrial countries was a few years older. The difference is probably attributable to changes in diet. A well-nourished young girl begins to menstruate earlier, when she reaches a critical weight for height.

Also, many women today have their first child in their early or mid-30s, whereas years ago women began childbearing far younger. Breast cancer occurs very rarely in cultures in which women still begin to menstruate late and have their children at a younger age. Unfortunately, the increased risk of breast cancer in modern women is very much a consequence of being a modern woman. There's no single behavioral or environmental assault that, if it vanished, would drastically reduce the incidence of breast cancer.

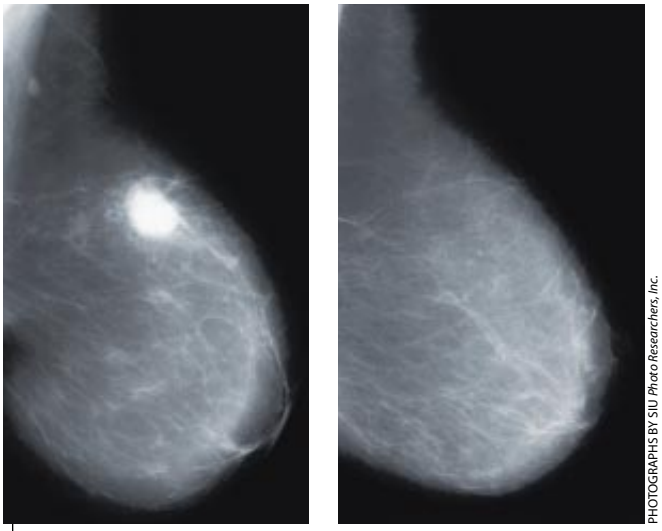
In summary, it's important to note that the vast majority of cancer cases, including breast and ovarian cancer, have nothing to do with inherited predisposition. Most cancers are caused by mutations that occur specifically in cells of a critical tissue, like the breast. Radiation is a mutagen: it causes mutations. Estrogens probably don't cause mutations, but they maintain a cellular environment in which cells can grow and flourish, even if they have mutations.

So far* BRCA1 *and* BRCA2 *have dominated research on the genetics of breast and ovarian cancer. Could another* BRCA *gene be out there waiting to be found?

Certainly. Using mathematical models, we can explain most inherited predispositions to breast cancer—and the vast majority of predispositions to ovarian cancer—by mutations in *BRCA1* and *BRCA2*. But there remain families with many cases of breast or ovarian cancers but no mutations in *BRCA1* or *BRCA2*. If another *BRCA* gene is discovered, it—like *BRCA1* and *BRCA2*—will teach us not only about inherited cancer in some families but also about the general biology of breast and ovarian epithelial cells in women.

Jewish women of eastern or central European descent—Ashkenazi Jews—have an unusually high rate of inherited breast or ovarian cancer. Why? What might these families tell us about how* BRCA1 *and* BRCA2 *cause cancer?

In America the proportion of breast cancer patients with inherited mutations in *BRCA1* or *BRCA2* appears to be highest among Jewish women. Until the past few generations, most Jewish communities tended to intermarry. There are ancient mutations in *BRCA1* and *BRCA2* among people of Jewish ancestry. On the basis of work done in Israel, it appears that at least one of those mutations probably dates back at least 2,500 years.



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Set of mammograms shows a tumor in one of a woman's breasts (left). *Her other breast* (right) *is free of disease. Despite the publicity over the breast cancer genes, only 5 percent of all breast cancer cases are linked to inherited mutations.*

Jewish women with inherited mutations in *BRCA1* and *BRCA2* provide unique insight into the causes of breast cancer. With clinical colleagues in New York City, we have been studying breast cancer patients of Jewish ancestry and their families. About 10 percent of breast cancer patients who identify their ancestry as Jewish have one of these ancient mutations in *BRCA1* or *BRCA2*. By tracing the histories of these mutations in the families of these women, we can ask several important questions. Among women with a *BRCA1* or *BRCA2* mutation, what is the actual risk of breast cancer developing by the age of 30, 40 or 50? What's the risk of ovarian cancer developing by those same ages?

By working with these families, we can also learn how the genes interact with the environment. Are there any differences in environmental exposures among women with *BRCA1* or *BRCA2* mutations who developed breast or ovarian cancer compared with those who have not? Are there other differences in life experiences that can be identified? By first evaluating genetics and then asking questions about nongenetic factors, we hope to get a better handle on both.

Getting Tested

Following the discovery of* BRCA1 *and* BRCA2*, companies scrambled to develop blood tests that could detect cancer-causing mutations in the genes. Today a number of commercial firms offer these DNA tests. How should a woman decide whether to take a test for a* BRCA1 *or* BRCA2 *mutation—and what should she do if the results come back positive?

A woman might consider genetic testing if she's from a family with a severe history of breast or ovarian cancer. In a recent publication in the *Journal of the American Medical Association*, we suggested that in the American population generally, families

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at high risk of having inherited mutations in *BRCA1* or *BRCA2* are families with both breast and ovarian cancers or at least four cases of breast cancer. Some Jewish women consider genetic testing if the family history is less severe because the frequencies of inherited *BRCA1* and *BRCA2* mutations are higher. Also, screening all of *BRCA1* and *BRCA2* involves testing about 18,000 nucleotides, or units, of DNA. Women from populations with ancient mutations often choose to be screened for more common mutations first. Then they may decide to have complete sequencing undertaken. But one can't exclude the possibility of a mutation without screening all of both genes. It's labor-intensive and expensive.

Let's suppose a woman's mother developed breast cancer and has an inherited mutation in *BRCA1* or *BRCA2*. This woman has a 50–50 chance of inheriting a mutation. If she does inherit the mutation, her risk of breast and ovarian cancer is much higher than that of other women, but it's not 100 percent. One of the greatest frustrations in this work is the level of uncertainty that remains about the biology.

If a woman learns she has an inherited mutation in *BRCA1* or *BRCA2,* what are her choices? At present, interventions are close to the extreme. On one hand, she can be screened carefully by mammogram and physical exam for breast cancer—and possibly by ultrasound for ovarian cancer. At the other extreme, she could have prophylactic surgery to remove her breasts (mastectomy) and/or ovaries (oophorectomy). It's very frustrating not to have less drastic but proactive interventions available yet.

Are mastectomy and oophorectomy foolproof ways to stay cancer-free?

Surgeons point out that the removal of the breast does not always remove all cells vulnerable to the development of cancer. Biologically, there is legitimate concern that one hasn't removed the risk completely. Current studies from the Mayo Clinic, however, suggest that prophylactic mastectomy greatly reduces the subsequent risk of breast cancer for women.

One drawback to genetic testing is that a person may later experience discrimination at work or when applying for health insurance. Lawmakers have proposed several bills to prevent health insurers from restricting coverage based on genetic tests. Has genetic discrimination been a big concern to you?

Yes. One thing that makes genetic testing difficult is that it's all bound up in an insurance industry that, until recently, has been able to penalize people on the basis of their genotype. The reality is that all of us carry genes that predispose us to something. We just happen to have identified those genes for breast and ovarian cancer.

It's essential that a woman be able to take advantage of technology to make decisions about health care without worrying that she's preventing her access to that very care. It's life-threatening to be unable to get adequate health care. That's why the legislation to separate the availability of health care from genotype is absolutely critical. I hope that new laws will make this debate moot in the next few months.

In the future, what choices might women have in testing for or treating inherited breast and ovarian cancer?

Two approaches are under investigation. One is very early diagnosis—that is, detection of breast tumors when they're less likely to be invasive, using the combined techniques of molecular biology and screening through mammography and breast exams. Another area is chemoprevention. For example, the tamoxifen prevention trial just indicated that taking the drug tamoxifen, which blocks the estrogen receptors in breast cells, reduces breast cancer risk. Now we need to see whether it works in women with inherited mutations in *BRCA1* or *BRCA2*.

In the next several years, we hope to sort out the biology of familial breast cancer well enough to offer women with *BRCA1* or *BRCA2* mutations a series of intermediate choices between mammography or ultrasound screening and surgery. SA

BRCA Testing Basics

Two companies offer genetic testing for *BRCA1* and *BRCA2* mutations in the U.S.:

Company: Myriad Genetics
Test name: BRACAnalysis
Test types: Full *BRCA1* and *BRCA2* gene analysis for breast and ovarian cancer susceptibility; three-mutation analysis for Ashkenazi Jewish women; single search for known family mutations
Cost: $395–$2,400
Results: Within four weeks
How to get tested: Ask your doctor to order Myriad's test kit and information packet
For more information: 800-469-7423; http://www.myriad.com

Company: OncorMed
Test names: Stage I, Stage II, Stage III, Heritage Panel
Test types: Screening for 98 percent of known *BRCA1* and *BRCA2* mutations, from most to least common: Stage I screens for the top 40 percent of *BRCA1* mutations and 27 percent of *BRCA2* mutations; Stage II, the next 40 and 37 percent, respectively; Stage III, the next 18 and 34 percent; Heritage Panel test screens for three known mutations in Ashkenazi Jewish women
Cost: $300–$800 per test
Results: Within three, four or 10 weeks, depending on the test
How to get tested: Ask your doctor to order OncorMed's test kit and information packet
For more information: 800-662-6763; http://www.oncormed.com

For more information, contact the National Alliance of Breast Cancer Organizations at http://www.nabco.org on the World Wide Web or call 800-719-9154. The National Cancer Institute also has information on breast and ovarian cancer; contact the institute at http://rex.nci.nih.gov or call 800-422-6237.

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