Making Breast Cancer Risk Assessment Personal

By Cori Vanchieri

Priscilla A. Furth, M.D., can imagine a day when breast cancer risk assessment is as simple and accurate as testing for heart disease risk. Like a blood test to check cholesterol levels, fine-needle aspiration could remove a few cells from the breast to look at genetic markers in young women.

“You wouldn’t even need a piece of tissue, just some cells,” said the professor of oncology and medicine at Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, D.C. “It’s a little dreamy, but it’s feasible.”

Furth and many others are working hard to improve breast cancer risk assessment. But so far, the only well-tested way to gauge breast cancer risk is through models that use a few self-reported factors, including age, reproductive history (age at onset of menstruation, first live birth), whether a mother or sister had breast cancer, and previous history of breast cancer. The Breast Cancer Risk Assessment Tool (BCRAT), also known as the Gail model, is one example. Unfortunately, existing models are more helpful in looking at populations than at specific women.

“Our ability to assess risk at an individual level is somewhat lacking,” said Eitan Amir, M.D., who recently evaluated six assessment tools with his colleagues from the Division of Medical Oncology and Hematology at Princess Margaret Hospital in Toronto. “We need to improve those models.”

Genomewide association studies linked several genetic variations, single-nucleotide polymorphisms (SNPs), to breast cancer. Adding those to the assessments makes sense. But the known genetic variations, except for the clearly influential BRCA1 and BRCA2 mutations, don’t yet give enough information to make them worthwhile, according to a National Cancer Institute study published in March in the New England Journal of Medicine.

Meanwhile, the pressure is mounting; several companies are selling their versions of genetic tests to physicians or directly to the public (see sidebar).

The mammography debate (whether screening should begin at age 40 or 50 years) is moving this field along as well. “Risk assessment is sexy again because of the issues related to the U.S. Preventive Services Task Force routine mammography recommendations,” said Susan M. Domchek, M.D., associate professor of medicine at the Abramson Cancer Center at the University of Pennsylvania, Philadelphia. The task force did not recommend screening mammography until age 50 years, in contrast to guidelines from some other groups, such as the American Cancer Society. “Every single person would like to be told what they should do in their own life. They don’t want to know population-based statistics,” Amir said. In a May 19, 2010, article in JNCI, Amir and colleagues compared the ability of six models to assess individuals’ risk of breast cancer over time. Is one better than another? Should a woman at high risk use a different model than one at average risk?

These models can go only so far because they all rely on known risk factors, even though up to 60% of breast cancers occur in women with no known risk factors. Plus, most do not include many of the known risk factors unrelated to family history, such as hormone use, mammographic density, obesity, and diet.

No model really outshone the others, according to Amir’s review. Several underestimated risk of breast cancer, especially in women with a single first-degree relative with the disease. Amir’s team developed a flowchart to help physicians decide which model may make more sense for their patients. They noted that researchers are making incremental improvements to the models, such as adding hormone use, although the improved versions still need validation in large populations.

Adding SNPs?

Adding genetic variants is one way to improve the models. “With the rapidly emerging information on common genetic variants that increase risk, it’s a natural time to ask, ‘Could we do better?’” said Patricia Hartge, Sc.D., deputy director of the epidemiology and biostatistics program in NCI’s Division of Cancer Epidemiology and Genetics. She and other NCI colleagues, the authors of the March New England Journal of Medicine

Women who attend family history clinics would like to be told what they should do in their own life. They don’t want to know population-based statistics.”

Eitan Amir, M.D.
Selling Genetic Testing to Consumers

The genetic testing genie is emerging from the bottle and regulators are trying to contain it

• Pathway Genomics announced in May that it would sell kits that assess genetic risk for several diseases, including breast cancer, direct to consumers through 60,000 Walgreens stores. The U.S. Food and Drug Administration immediately responded that FDA approval is required, and the launch was put on hold until the company resolves the issue with the FDA. Congress has announced an investigation of personal genetic test kits as well.

• A few companies are selling similar direct-to-consumer genetic testing kits on the Internet. In June, the FDA sent letters to five companies—23andme, Navigenics, deCODE Genetics, Illumina, and Knome—saying that the kits are considered medical devices and require FDA approval for marketing. The agency did not demand that the kits be taken off the market immediately.

• Another company, Intergenetics, offers its Oncovue test only to physicians (see news story).

• The University of California, Berkeley, announced in May that it will offer genetic testing to incoming freshmen. Students can have their saliva checked for genes that regulate the ability to metabolize alcohol, lactose, and folates. The school says that it’s an effort to engage the students in a common intellectual experience, but ethicists, including Arthur Caplan, Ph.D., at the University of Pennsylvania, Philadelphia, have called making genetic test results available without counseling a mistake. What if a student learned that he was not alcohol intolerant and decided that he could binge drink?

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Meanwhile, the private sector is moving forward. Companies such as 23andme and Navigenics offer genetic screening tests directly to consumers through the Internet, a practice that the U.S. Food and Drug Administration is now questioning (see sidebar). Intergenetics offers the Oncovue test, “a genetic-based breast cancer risk test” marketed only to physicians. It screens for 22 SNPs from 19 genes and asks about personal history. The Oncovue model adds “quite a lot to clinical breast cancer prediction,” said Eldon R. Jupe, Ph.D., vice president at Inter-genetics. Among a high-risk population of women in Marin County, Calif., they identified 51% more cases as elevated risk than the Gail model alone in a retrospective study presented at the 2009 San Antonio Breast Cancer Symposium. Jupe is hoping to collaborate with other groups to do further analyses.

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Susan M. Domchek, M.D.

Back to the Future

Georgetown’s Furth isn’t discouraged that studies aren’t further along. “The world needs to understand that the genome is very complex. Maybe we should be looking at different SNPs, or maybe it’s more than SNPs, such as small RNAs or methylation. Maybe there are interacting factors.”

In a move toward her vision of early testing of breast tissue, Furth has developed mouse models of breast cancer to narrow her search for the most important genes. In a May 15 article in Cancer Research, she reported that small variations in expression of the genes for p53 and estrogen receptor α appear to be associated with breast cancer development. She can see them used together as biomarkers to predict future breast cancer risk.

There’s still a lot to do, however: Validate mouse model findings for human disease, figure out how to do the test in people, determine how many cells are needed. After that, researchers would have to determine when and how often women would need the test. Maybe it could be like a Pap smear, Furth said: three negative results and then testing less often. Finally, marketing experts would need to figure out whether such a test would be acceptable to women and whether insurers would pay.
While researchers debate the benefits of each model and of adding genetic variations, Domchek sees a bigger problem to address: Most women don’t get risk assessment at all. “We can quibble about whether models are good enough and work to make them better,” she said. But most people don’t even hear about risk assessment and don’t understand prevention options. “We need better ways of getting risk assessment out there.”

“Down the pike, I hope to see some version of SNP panels, but maybe not the ones we have now. Maybe better ones tailored to certain ethnic populations,” Domchek said. “We could add breast density, which we know matters, but we don’t know how to use it yet. It’s an exciting field because people are working and progress is being made.”

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