Understanding Breast Density and Breast Cancer Risk

By Judy Peres

It’s been nearly 40 years since radiologist John Wolfe, M.D., first observed that women with mammographically-dense breasts have a higher risk of developing breast cancer. Since then, dozens of studies have confirmed the association. And yet, physicians have made little progress in understanding how patients might reduce their risk.

That has not stopped politicians and their constituents from taking action, based on the little that is known. At least three states—Connecticut, Texas and Virginia—have passed laws requiring doctors to notify women if their mammograms show high density, which applies to an estimated 30% to 40% of all women. This has many experts concerned.

“At this point, we can’t tell a woman with high density what she can do to reduce her risk,” said Rulla Tamimi, Sc.D., a researcher at Harvard Medical School. “All you do is increase her anxiety.”

That dilemma led California Gov. Jerry Brown to veto a breast density reporting law last year. Critics worried such legislation would lead women to get expensive follow-up tests that might not be scientifically warranted. Still another issue is related to the fact that there is no standardized, automated method for measuring mammographic density. According to Celia Byrne, Ph.D., an epidemiologist at the Uniform Services University of the Health Sciences, “If states are going to mandate it, that’s a problem. What I measure could be different from what someone else measures.”

Researching Density
Research is underway in a number of areas, including epidemiology, molecular biology and genetics, with the aim of providing answers to some of the most basic questions: What causes a woman to have dense breasts? Why does density change (generally decrease) over time? What is dense breast tissue composed of? How does it promote cancer? How can density be measured reliably in the clinic?

The only classification of mammographic density currently in clinical use in the U.S. is BI-RADS (Breast Imaging Reporting and Data System), a qualitative classification developed by the American College of Radiology. But according to Norman Boyd, M.D., of the University of Toronto, a pioneer of breast density research, BI-RADS may be the least reliable of all the available methods. In research settings, radiologists or technicians often outline the white (radiodense) patches in digitized mammograms with computer guidance, which yields a quantitative score.

However, this system, while more precise, is too labor intensive for routine clinical use.

According to Karla Kerlikowske, M.D., of the University of California, San Francisco, several research groups and companies are developing methods of automating mammographic density assessment that, if combined with risk assessment, could make their way into the clinic in the near future.

Some researchers believe there is information in the pattern of density in addition to the extent of it. Maryellen Giger, Ph.D., professor of radiology at the University of Chicago, has been conducting “radiographic texture analysis” on digital mammograms in the region behind the nipple. She looked at mammograms from two groups of women—those deemed at low risk, based on their personal and family history, and those at high risk because they have already had breast cancer or carry a BRCA gene mutation. In the high-risk group, she said, “the mammographic density patterns tend to be coarse and low in contrast.”

A Strong Risk Factor
Women at the high end of the density spectrum (>75%) have a 10-year breast cancer risk 4 to 6 times greater than that of same-age women at the low end (<10%). That makes breast density—usually defined as the percentage of radiodense areas on a mammogram—one of the biggest risk factors for a cancer that threatens 1 in 8 U.S. women over their lifetime. Only age and mutations in the BRCA cancer-susceptibility genes have a bigger influence on breast cancer risk.

Further, mammographic density may be an indication of localized risk. “It appears as if a woman’s overall breast density is not just a marker or correlate of her breast cancer risk,” said Valerie McCormack, Ph.D., of the International Agency for Research on Cancer in Lyon, France. “In women who have breast cancer, the tumors are located precisely in those areas of the breast that were dense several years prior to diagnosis, strongly suggesting that dense tissue has a biologically causal relationship with breast cancer risk.”

To be sure, researchers know from twin studies that some of the extent of mammographic density is hereditary. It’s also possible that critical periods of exposure, when density is amenable to modification, may occur relatively early in life. Nevertheless, some breast density is at least potentially modifiable.
Mammographic density increases with older age at first birth, fewer children, and the use of combined (estrogen and progesterin) postmenopausal hormone therapy.

Breast density is also inversely correlated with BMI: Heavier women tend to have large, fatty breasts, and fat is radiolucent (non-dense). But, gaining weight is not a viable option for reducing breast cancer risk.

Breast cancer patients who are overweight or obese appear to have more local recurrence, even if they have low mammographic density, said Kerlikowske. Postmenopausal women with high body mass index are also more likely to be diagnosed with breast cancer.

Including some measure of density, along with other known factors, in risk prediction models, such as the Gail Model, has been found to improve accuracy. But integrating breast density into risk assessment and risk management is cumbersome, and the goal of using density to tailor screening and prevention programs for individual women remains elusive.

According to Kerlikowske, standardizing and automating breast density measures will make that much easier. And it can’t come too soon for her and other experts, who see manifold clinical applications: deciding at what age and how often individual women should get mammograms, whether to add ultrasound or magnetic resonance imaging to standard mammography screening, whether to embark on chemoprevention, and whether to start or stop postmenopausal hormone therapy.

However, using density measurements to help a woman or her radiologist decide when to start screening mammography, or how often to have mammograms, contains a kind of Catch 22: She has to get a mammogram first to determine her density. Jeanne Mandelblatt, M.D., of Georgetown Lombardi Comprehensive Cancer Center, is concerned this could lead some organizations to recommend a baseline mammogram at age 35.

The International Breast Cancer Intervention Study I (IBIS-I) reported that women on tamoxifen who experienced a significant reduction in breast density also had a significantly reduced risk of developing breast cancer; those who had smaller reductions in density did not reap the same benefit. The authors suggested that a baseline measure of breast density and a subsequent measure 12 to 18 months after initiation of tamoxifen could be used to assess response to treatment.

The Biology of Breast Density
Breast cancer arises in epithelial cells, and the number and proliferative nature of these cells may influence both the radiological density of the breast and the probability of genetic damage that can give rise to cancer. But the appearance of dense breast tissue under the microscope is remarkably heterogeneous, suggesting that high mammographic density may reflect more than one biological process.

One hypothesis being studied is that breast density is a surrogate for the number of at-risk cells (i.e., stem cells). Simply put, “If you have more tissue at risk, you’re more likely to get breast cancer,” said Tamimi. Another hypothesis is that density reflects the proliferation of breast epithelium and stroma in response to stimulation by hormones and growth factors.

Gretchen Gierach, Ph.D., an investigator at the National Cancer Institute, in a 2010 JNCI editorial, noted growing evidence that the microenvironment surrounding epithelium is important in carcinogenesis. Molecular assessment of epithelial proliferation, apoptosis and differentiation; fibroblast secretion of growth factors and hormones; and analysis of collagen composition may all be important in assessing breast cancer risk, she said.

Dense breast tissue is typically composed of epithelial cells and connective tissue (collagen and fibroblasts), whereas non-dense tissue is mostly fat. Kerlikowske’s colleague at UCSF, Thea Tlsty, Ph.D., is especially interested in the connective tissues. She has found that the collagen in high-density breasts turns over much more rapidly than the collagen in low-density breasts. She is also investigating the possibility that the fibroblasts in dense breasts may send growth signals to the epithelium, much as they do in cancerous breasts.

The Genetics of Breast Density
Some researchers are seeking to identify genetic variants associated with breast density. According to Boyd, of the 12 single-nucleotide polymorphisms (SNPs) reproducibly associated with risk for breast cancer, at least three have been linked to breast density as well.

Tamimi’s group is looking at both genetic and molecular predictors of breast density, “and if there are factors that interact with breast density to influence breast cancer risk.”

“We’ve found some genetic predictors,” she said. “They’re statistically significant, but they don’t predict the large variability [in mammographic density].”

Tamimi believes physicians may some day be able to counsel women about individualized breast cancer risk factors that differ according to their breast density. “Women in the Nurses’ Health Study with high breast density and high circulating hormones are at higher risk [for breast cancer],” she said. “There is also evidence that the elevated risk of breast cancer associated with hormone therapy is greater for women with high breast density.

So you may be able to have health recommendations targeted at women based on their density,” she said.

McCormack would go a step further. “For peri- and postmenopausal women who are taking combined hormone therapy,” she said, “it may be worth considering stopping if they have very dense breasts. Similarly, it may be especially inadvisable for women with very dense breasts to commence combined hormone therapy, thus increasing their density and their breast cancer risk further.”

McCormack said the association between hormone therapy and breast density is a good illustration of the potential role of mammographic density in research. “The increased breast cancer risk associated with the use of combined hormone therapy could have been predicted much earlier had the increase in density been considered as a surrogate outcome,” she said.