Dense Breasts Linked to Higher Breast Cancer Risk, But Clinicians Unsure of Application

By Renee Twombly

High breast density is emerging as one of the strongest risk factors for breast cancer, and not just because thick tissue can mask small tumors on a mammogram.

A spate of recent studies have shown that density—the amount of epithelial tissue and connective tissue relative to fat—is an independent risk factor for breast cancer, topped only by age and the rare breast cancer susceptibility genes BRCA1 and BRCA2. The research suggests that about a third of breast cancers are related to high breast density. Having breasts that are made up primarily of dense breast tissue increases breast cancer risk by up to fivefold, compared with a woman with little dense breast tissue.

The idea that breast density is related to breast cancer risk is not new. It was first postulated in 1976 by Detroit hospital radiologist John Wolfe, M.D., who speculated that women with the densest breasts may be more likely to develop cancer. The supposition piqued the interest of investigators, who steadily built the case that breast density is indeed an important risk factor. To date, more than 60 studies have been devoted to the issue, and the field is expanding to include the genetics and biochemical pathways of dense breasts.

“While a small number of people have been studying this for some time, many breast cancer researchers have ignored this strong risk factor, often because of the added complexity to being able to make an assessment,” said Celia Byrne, Ph.D., an assistant professor at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, D.C. “[We hope] further recognition will make it more difficult to ignore.”

“The fact that people are finally paying more attention to breast density as an independent risk factor is wonderful,” said Norman Boyd, M.D., a cancer epidemiologist at Toronto’s Princess Margaret Hospital and the Ontario Cancer Institute who has studied the issue for years.

But the question remains about what to do now that researchers know that dense breasts are an important risk factor. Attempts to incorporate density into breast cancer risk models have shown that it offers only moderately increased predictive power over commonly used risk factors. Also, radiologists often lack training in how to measure breast density on mammograms and so they don’t collect that information, or, if they do, they don’t use a standardized method. And while certain agents can lower...
breast density, no one has determined whether doing so will lower cancer risk.

**Short-term Mask, Long-term Risk**
Among the issues Boyd has examined are whether breast density is a risk factor because it masks tumors in screening mammograms—dense tissue looks white on the films, just as tumors do. His findings, published Jan. 18 in the *New England Journal of Medicine*, suggest that spotting tumors on first mammograms taken of dense breasts is indeed harder. But he also concluded that the risk of developing breast cancer remained elevated for at least 8 years past that first mammogram, whether cancer was detected by screening or other means. This finding means that there is a true underlying association of density with risk, he said.

Boyd’s team reviewed three studies of 1,112 Canadian women with breast cancer and an equal number of women without breast cancer. All participants had a mammogram every year or two for the previous 8 years, and none was diagnosed with breast cancer on the basis of the first of those mammograms. They found that women whose breast tissue is composed of 75% or more dense tissue were up to five times more likely to be diagnosed with breast cancer during the study period. Boyd said this finding indicates that tumors may have been hidden in the first mammogram but appeared on the later tests once they had grown larger and that dense breasts might harbor faster-growing tumors because some of the tumors were found between screenings.

**Hormones Not to Blame**
Other researchers have sought to understand why, masking aside, density might increase cancer risk. One recent study has shown that it isn’t simply because women with dense breasts have increased estrogen production, as many people thought. A study published in the Aug. 1 issue of *JNCI* (J. Natl. Cancer Inst. 2007;99:1178–87) found that density and hormone levels are independent risk factors for breast cancer. In the study of 773 postmenopausal women, the research team found that the relative risk of developing breast cancer in postmenopausal women with dense breasts was fourfold higher and that high versus low levels of hormones (estrogen and testosterone) increased the relative risk by 200%. If both density and high hormone levels were present, a woman’s risk of developing breast cancer increased by 600%, compared with women having both low breast density and low hormone levels.

This finding probably means that each risk factor increases breast cancer risk by a different biochemical pathway, said Byrne, the coauthor. “The fact of the independence of risk from those associated with circulating hormones suggests an alternate breast cancer pathway that may be very important,” she said.

Several different theories exist for why dense breasts might increase a woman’s risk of developing breast cancer, she said. Among them is the fairly simple notion that dense tissue has more epithelial cells and thus more chances that one or more of these cells will become cancerous. Another theory is that dense tissues have more cross-talk between connective tissue cells in the breast, which produce a variety of hormones and growth factors, and more potentially susceptible epithelial cells in the tissue, which is where most breast cancer develops.

“We need to incorporate breast density into studies of breast cancer so we might better understand these different or alternative pathways of the disease,” Byrne said.

**Trait in the Genes**
From studies of twins conducted by Boyd and others, scientists have previously estimated the total influence of genes on breast density at about 60%. Another recent study has offered a genetic clue that may account for up to 22% of the variability in breast density between individuals. Looking at the DNA of 889 people in 89 multigenerational families, researchers at the Mayo Clinic in Rochester, Minn., and H. Lee Moffitt Cancer Center in Tampa, Fla., located a region on chromosome 5 that may harbor a gene(s) for dense breast tissue.

This study, published in the Sept. 1 issue of *Cancer Research*, is the first reported family study that attempts to identify possible locations for genes influencing breast density, and the results confirm past data suggesting that density is genetically influenced, said the study’s lead investigator, epidemiologist Celine Vachon, Ph.D., of the Mayo Clinic.

Further examination of genes in this region may help explain the origins of breast cancer in some women, Vachon said. One interesting candidate was a gene that encodes the receptor for prolactin, a hormone that helps enlarge mammary glands during pregnancy and is involved in milk production. Boyd and colleagues previously demonstrated an association between prolactin levels and density in postmenopausal women. Vachon now proposes to correlate the genetic variation in all candidate genes in their region, including the prolactin receptor, with density in the hopes that
one or more of these genes have an association with both breast density and breast cancer. However, she does not expect definitive results for several years, while she waits for other studies to confirm findings.

**Acting on Risk**

It is too soon to tell how much mammographic density can contribute to predicting a woman’s individual risk. Too many unresolved issues remain about how to calculate density from a mammogram and how to standardize those readings, researchers say. Still, that hasn’t stopped researchers from trying to incorporate density readings into breast cancer prediction models—but only after the researchers have gone back and laboriously calculated breast density from old mammograms.

Two studies published in the September 2006 issue of JNCI (Vol. 98; 1204–14, 1215–26) tried to incorporate breast density into a risk model. Mitchell Gail, M.D., Ph.D., of the National Cancer Institute, collaborated with others to include mammographic density in a new version of his classic Gail model to predict individualized risk over a 5- or 10-year period. The new relative risk model was based on mammographic density measurements in 8,206 women in the Breast Cancer Detection and Demonstration Project. Discriminatory accuracy (the measure of how different the distribution of risk is in women who develop breast cancer from the distribution of risks in women who do not develop breast cancer) improved only modestly in the breast density model compared with the older model. “Mammographic density is a strong and good risk factor, as strong as having two affected first-degree relatives, but this shows that even for a strong risk factor like that, it is hard to improve discriminatory accuracy of a risk model,” Gail said.

A second study from the Breast Cancer Surveillance Consortium evaluated more than 1 million women who had undergone screening mammography. The research team, led by William Barlow, Ph.D., of Cancer Research and Biostatistics in Seattle, also found that breast density is strongly associated with the risk of developing breast cancer within 1 year—almost as important as age. However, it yielded only moderate discriminatory accuracy in the models.

Both Gail and Boyd believe that breast density will ultimately be used to help gauge breast cancer risk if reliable standardized methods to assess mammographic density become available. The Breast Imaging Reporting and Data System (BI-RADS), a quality-assurance tool published by the American College of Radiology, incorporates density measurements, but no formal training has been offered in how to assess this variable. “Our study was a proof of principle that if people can overcome the measurement problems, it should improve accuracy,” Gail said. “But it remains to be seen what the best technology will be that is practical and reproducible.”

Even if breast density can be easily measured, Boyd said, the question remains what to do about the risk. Some agents, like tamoxifen, can decrease breast density, but “the Holy Grail here is knowing whether changing density changes risk,” he said. “Unlike almost everything else known about breast cancer, density is a strong risk factor that accounts for a large fraction of the disease, and could be changed, but we don’t know whether changing density is a useful thing to do.”

“If you going to measure density, there needs to be some clinical reason to do so, and we’re not there yet,” said Robert A. Smith, Ph.D., director of cancer screening at the American Cancer Society. “However, it is quite reasonable to expect that patients should be informed about the limitations of mammography in their individual case if they do have significant breast density, and if appropriate, other imaging methods should be considered in order for the patient to have confidence that she has had a complete screening exam.”