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Exploring the Relationship Between Mammographic Breast Density and Breast Cancer

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by Victoria A. Fisher, M.P.H.

Over the past several decades, DCEG has developed an interdisciplinary research program to unravel the epidemiologic, molecular, and pathologic underpinnings of mammographic breast density (MBD), one of the stronger risk factors for breast cancer among women. Senior investigator Gretchen Gierach, Ph.D., M.P.H., and colleagues employ a range of technologies and approaches to improve the measurement of density, delineate risk factors that influence density, and understand mechanisms that mediate its relationship to breast cancer risk.

Gretchen Gierach

MBD refers to the appearance of breast tissue on a mammogram. Dense breasts contain more fibrous and glandular tissue (which shows up white or bright on imaging) than fat (which appears dark). Breast cancer and some benign breast conditions are denser than fat and also appear white on a mammogram. In general, women of child-bearing age tend to have denser breasts than postmenopausal women. Studies of the natural history of the breast have shown that density typically decreases as a woman ages. Breasts that are denser may be harder to screen successfully for early signs of tumorigenesis, since the white of the fibrous tissue can mask an emerging cancer.

MBD was identified as a risk factor for breast cancer before it became widely used to measure density at the time of screening. In the 1970s, Robert Hoover, M.D., Sc.D., Louise Brinton, Ph.D., M.P.H., Catherine Schairer, Ph.D., along with colleagues from the American Cancer Society, established one of the first prospective cohorts capable of evaluating relationships between MBD and risk of developing breast cancer. In the Breast Cancer Detection Demonstration Project (BCDDP) cohort, they found that women who had a breast density of 75 percent or greater at the time of their baseline mammogram had an almost five-fold increased risk of breast cancer compared with women with no visible dense breast tissue (Byrne, 1995). This effect persisted for 10 or more years in this screened population, and was observed for premenopausal and postmenopausal women of all ages.

"Until that point, there were a lot of questions as to whether density was truly a causal risk factor or whether there was some bias that was being caused by density masking a tumor," Dr. Gierach said. "We now know that high MBD is a strong and independent breast cancer risk factor. However, the mechanisms driving this relationship are not clear, and we are still trying to figure out why."

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Density Assessment

Historically, most analyses of MBD have employed subjective visual categorizations or computer-assisted quantification of two-dimensional images (area density); both approaches ignore breast volume. Additionally, the measures themselves have evolved with time; today, most U.S.-based physicians use the American College of Radiology's Breast Imaging-Reporting and Data System (BI-RADS) scoring system, in which radiologists visually classify density into four groups, ranging from almost entirely fatty to extremely dense. Supplementing this scoring system with standardized automated and quantitative assessment of volumetric MBD may allow for improvements in the utility of MBD as a marker of risk. "We decided to explore a novel approach to measure MBD in three dimensions, as a volume," Dr. Gierach said.

In 2006, Dr. Gierach began collaborating with Dr. Brinton and Dr. Mark Sherman (formerly of the NCI, now at the Mayo Clinic, Florida) to develop the Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project, a project funded through a competitive award from the Stamp Act Fund. This complex field effort considered both the radiologic features of the breast through mammography and the histologic, molecular, and biochemical characteristics of breast tissue among women undergoing diagnostic image-guided breast biopsies at the University of Vermont (UVM) College of Medicine and its affiliated academic medical center, the UVM Medical Center. They found that volumetric MBD measures, assessed using a density phantom, were correlated with two-dimensional area density measurements and shared important associations with several epidemiological factors (Gierach, 2014). However, the data also revealed some differences; most notably, among obese women, measured absolute density was higher with volumetric methods, suggesting that breast cancer risk assessments may vary between these techniques.

Dr. Gierach is working to refine methods for measuring MBD as a volume in tissue surrounding lesions targeted for biopsy. Little is known about the spatial distribution of dense breast tissue and whether there are areas within the breast that are "riskier" dense regions. "We found that regional differences in MBD clearly occur among women diagnosed with benign breast disease," she said (Gierach, 2016). In the future, she will conduct studies to further characterize regional heterogeneity in MBD among women whose biopsy results range from benign to cancerous.
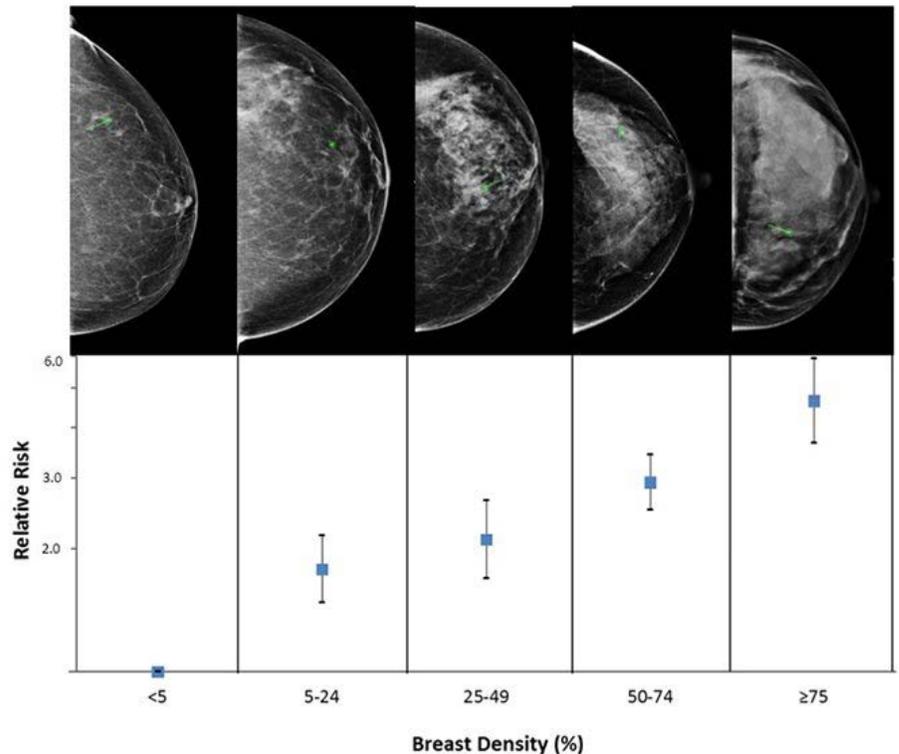
Risk of breast cancer according to percent mammographic breast density. Shown on the y-axis are the combined relative risks (95% confidence intervals) from a meta-analysis of percent breast density and its association with incident breast cancer (McCormack, 2006). Representative mammograms of varying degrees of percent mammographic breast density from participants in the BREAST Stamp Project are shown (Gierach, 2014). Figure adapted from Santen, 2005.

Investigators are also assessing non-ionizing imaging technologies, such as magnetic resonance imaging (MRI) and ultrasound, which may be better suited for safely measuring volumetric density particularly among young or high-risk women, or in other situations where it is desirable to perform more frequent measurements. Dr. Gierach recently completed the clinically-focused field effort of the Ultrasound Study of Tamoxifen, in which she and colleagues used novel ultrasound tomography to determine changes in volumetric breast density within the first year of tamoxifen therapy. They found ultrasound tomography sound speed estimates to be highly reproducible surrogate measures of volumetric breast density (Khodr, 2015). These results will inform the development of methods for serial assessment of density, an important area for future investigation as density changes may translate into changes in breast cancer risk.
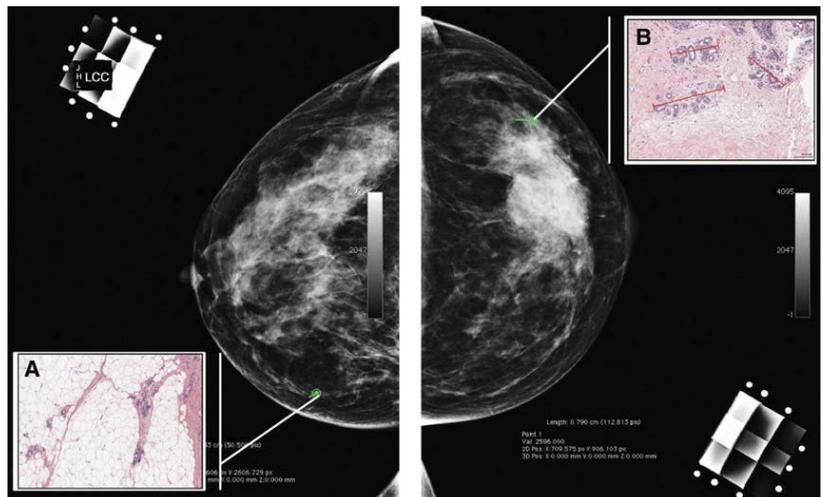
Molecular Epidemiology

As the measurements of MBD continue to improve, a parallel effort is underway to determine how density influences risk, tumor initiation and/or progression at the molecular level.

"One thing we're trying to understand is if there are patterns or markers within the breast tissue that can differentiate women with high density who will go on to develop breast cancer versus women with high density who don't develop breast cancer," said postdoctoral fellow Maeve Mullooly, Ph.D., M.P.H.

To correlate MBD to tissue-level biomarkers, investigators have tapped into data from the DCEG Polish Breast Cancer Study. They have collected mammograms for density assessment from a subset of the cases from whom snap-frozen breast tissues were collected for molecular profiling studies (Sun, Gierach, 2013). "Importantly, we and others have observed that density is similar for both hormone receptor-positive and -negative breast cancers," Dr. Gierach said. "These findings give broad relevance to MBD as a general marker of breast cancer risk" (Razzaghi, 2013).

Dr. Gierach is also exploring the relationships among circulating hormones, MBD, and terminal duct lobular unit (TDLU) involution in the BREAST Stamp Project. TDLUs—milk-secreting structures in the breast—are the tissue of origin for most breast cancers. TDLU involution, or a reduction in the number and size of TDLUs and their secretory substructures called acini, is a normal process of aging.

Representative full-field digital mammograms from two premenopausal participants in the BREAST Stamp Project. The digital mammogram is acquired with the density phantom in the corner of the image to allow for automated computation of volumetric MBD. Panel A represents a breast biopsy specimen with high TDLU involution. Panel B depicts a breast biopsy specimen with limited TDLU involution, as reflected in the increased number of TDLUs and number of acini within the TDLUs. (Gierach, 2016)

Dr. Gierach and colleagues have found that quantitative measures of TDLU involution and MBD are correlated markers of breast cancer risk (Gierach, 2016). These relationships might reflect cumulative exposure to endogenous hormones (Oh, 2016; Gierach, 2015; Sampson, 2017) and growth factors (Horne, 2016). "Our latest findings suggest that elevated estrogens are associated with higher MBD, reduced TDLU involution, and increased breast cancer risk, particularly among postmenopausal women," she said.

In addition, the team is combining digital pathology and novel, deep learning approaches to examine histological features of breast tissue (Bejnordi, 2017). "This technology allows us to examine patterns of tissue organization that may be associated with breast density, and can complement the visual interpretation of the tissue by a pathologist," Dr. Mullooly said. Using data from the BREAST Stamp Project, investigators are applying these novel approaches to examine if there are unique features of breast biopsy tissues that are associated with localized volumetric density measures, that may also be associated with differential breast lesion diagnoses.

Investigators use convolutional neural networks (a type of deep learning model) to classify histologic features of breast tissue and examine their relationships with breast density. Green, orange and red represent fat, stroma, and epithelium, respectively. (Bejnordi, 2017)

Breast Density in Asian Populations

Breast cancer is known to vary significantly by race and ethnicity. Though scientists have established MBD as a strong risk factor for breast cancer, most of these studies have targeted white women in Western countries. Senior investigator Xiaohong Rose Yang, Ph.D., M.P.H., postdoctoral fellow Hyuna Sung, Ph.D., M.A., Dr. Gierach, and Dr. Mullooly are working to describe this relationship in Asian populations.

"In general, Asian women have denser breasts than white women, and yet, they experience lower breast cancer incidence overall," Dr. Yang said. "It is possible that a variety of complex factors contribute to the unique features of breast cancer among Asian women, including cohort/period effects, distinct genetic or non-genetic exposures, and tumor biology."

Dr. Yang and colleagues are utilizing the resources of a breast cancer screening program in China, through a collaboration with the Hospital of the Chinese Academy of Medical Sciences (CHCAMS). Radiologists at CHCAMS assessed MBD on digital mammograms and categorized results using BI-RADS. Researchers would like to study the risk associated with MBD; however, the screening program is only available in limited areas in China and will not have long-term follow-up, which precludes their ability to comprehensively address this question.

Xiaohong Rose Yang

Instead, they are investigating the associations between known breast cancer risk factors and MBD among screening program participants. They are also evaluating the association between MBD and breast cancer subtypes using breast cancer patient data collected at CHCAMS. "This type of analysis has been conducted in Caucasian populations, where the general agreement is that MBD is associated with increased risk for all tumor subtypes," Dr. Yang said. "But, we don't know if that's true in Chinese women."

As BI-RADS scoring is a subjective visual assessment metric for MBD, Drs. Yang and Gierach have also installed automated quantitative density measurement software at CHCAMS to obtain volume density metrics that have been associated with breast cancer risk in other populations. Investigators plan to use the software in future studies and hope to expand the effort to other screening sites around China.
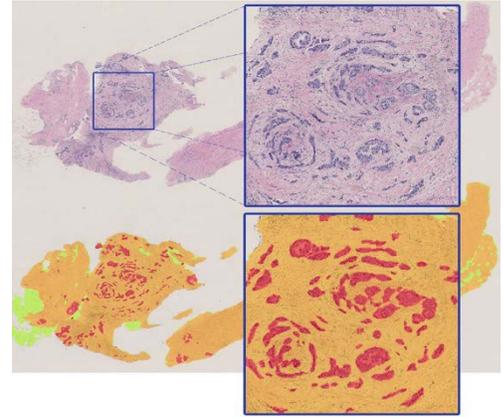
Hyuna Sung

Translational Relevance

MBD may also be an important consideration for women already diagnosed with breast cancer, particularly estrogen-receptor positive breast cancer which is the most common subtype diagnosed. Emerging evidence suggests that MBD decline could serve as a potential biosensor of response to tamoxifen treatment. In a recent study within Kaiser Permanente Northwest, led by former DCEG fellow Dr. Sarah Nyante (now an Assistant Professor at University of North Carolina, Chapel Hill), Dr. Gierach, Dr. Hoover, Amy Berrington, D.Phil., and colleagues, reported that patients who experienced large reductions in MBD following tamoxifen treatment had improved prognosis (Nyante, 2015). "This finding suggests that serial MBD measures could have value for clinicians and patients when deciding whether to continue tamoxifen therapy or change clinical management," Dr. Gierach said. The potential translational implications of this work were recently highlighted in a *Journal of Clinical Oncology* commentary led by Dr. Mullooly (Mullooly, 2016).

Maeve Mullooly

Contralateral breast cancer is the most common second cancer among women with primary breast cancer. However, it's unclear whether MBD changes are associated with risk for development of a second primary contralateral breast cancer among breast cancer patients. Dr. Gierach, Dr. Mullooly, Dr. Berrington and colleagues are developing a new study within the Kaiser cohort to address this question. "There is a growing number of breast cancer survivors and we need to better understand what breast density means in those women," Dr. Mullooly said.

In a separate analysis of breast cancer patients within the U.S. Breast Cancer Surveillance Consortium, Dr. Gierach found that, after accounting for patient and tumor characteristics, elevated MBD was not associated with risk of death—an important and reassuring message for women with high MBD (Gierach, 2012). This work suggests that risk factors for the development of breast cancer may not necessarily be the same as factors influencing the risk of death after breast cancer has developed.

In the future, Dr. Gierach and colleagues will continue to build an integrative approach to investigate key issues in breast cancer and MBD research. "Ultimately, the goal of our research is to facilitate the development of improved strategies for risk stratification, prevention, early detection, and treatment of breast cancer," Dr. Gierach said. "There's still so much to learn."

For a full list of references, go to: https://dceg.cancer.gov/breast-density#references