Radiology

Beyond Breast Density: Radiomic Phenotypes Enhance Assessment of Breast Cancer Risk

Katja Pinker, MD, PhD

From the Department of Radiology, Breast Imaging Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 and Medical University Vienna, Department of Biomedical Imaging Engineering and Image-guided Therapy, Division of Molecular and Gender Imaging, Waehringer Guertel 18-20, 1090 Vienna, Austria. Received October 3, 2018; revision requested October 8; final revision received October 9; accepted October 9. **Address correspondence to** the author (e-mail: pinkerdk@mskcc.org).

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See also the article by Kontos et al in this issue.

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Breast density, or breast composition, reflects the amount of fibroglandular tissue in relation to the amount of fatty tissue in the breast. It varies greatly throughout a woman's life, influenced by endogenous (eg, age, parity, body mass index, ethnicity) and exogenous factors (eg, smoking, alcohol, obesity, sedentary lifestyle, oral contraception, hormone replacement therapy) (1). On the mammogram, fatty components appear radiolucent, whereas fibroglandular components appear radiopaque. Unfortunately, women with dense breasts have a lower sensitivity for breast cancer detection because normal breast tissue may overlap with tissue asymmetries and underlying tumors on the mammogram. Women with dense breasts face a higher rate of false-negative and false-positive findings as well as recall rates (1,2).

Nevertheless, the risk for breast cancer associated with dense breasts cannot be attributed merely to the masking bias that reduces the sensitivity of mammography. The fibroglandular components consist of epithelial and glandular structures where most breast cancers originate. Thus, having dense breasts on its own elevates the risk of developing breast cancer, that is, the more epithelial tissue, the greater the chance that cancer may arise in one of the epithelial cells. Several studies have yielded consistent findings that breast density is an independent and strong risk factor for breast cancer (1–3). Compared with other much stronger but far less common risk factors, such as a mutation carrier or high-risk status, breast density significantly contributes to cancer risk. This emphasizes the potential for risk prediction and stratification of breast density. Yet breast cancer risk estimation tools, such as the Gail and Tyrer-Cuzick models (4,5) that currently do not include breast density, have not been able to reliably identify women at higher risk of developing breast cancer within the general population. Ideally, more accurate risk assessment models would be developed that could easily be adopted in clinical routine.

Assessment of breast density has shown some value for estimating breast cancer risk, yet this approach is rather crude and highly subjective to inter- and intrarater variability (6). In contrast, radiomics analysis of mammographic breast data allows a sophisticated characterization of the complexity and morphologic distribution of the breast parenchymal patterns. Radiomics analysis is defined as the conversion of medical images to higher-dimensional mineable data by using computer classification algorithms. Radiomics data can be correlated with variables of interest (eg, patient characteristics, patient outcomes, and other "omics" data) for a noninvasive and cost-effective analysis allowing decision support and enabling precision medicine (7). Initial research shows that radiomics parenchymal features are associated with breast cancer independent of breast density and therefore have the potential to augment breast density in assessing a woman's risk of developing cancer (8,9).

In this issue of *Radiology*, Kontos and colleagues expand on this initial body of evidence, showing that radiomic phenotypes reflect the intrinsic properties of mammographic parenchymal complexity and have an independent association to breast cancer (10). They demonstrate that unlike a simplistic global mammographic breast density assessment, radiomics texture features can capture the subtle spatial distribution of the parenchymal complexity patterns. Therefore, radiomics can provide information beyond mammographic density and established risk factors in association to breast cancer.

Kontos et al measured breast density by using publicly available, fully automated software (LIBRA, version 1.0.3). Radiomics analysis was performed to extract parenchymal texture by using a custom-developed software that uses a lattice-based strategy. The authors used a cross-sectional sample of 2029 women screened with digital mammography. Unsupervised clustering was applied to identify and reproduce phenotypes of parenchymal complexity in a separate training set of 1339 women and a test set of 690 women. Four distinct radiomic phenotypes of mammographic parenchymal complexity were identified: low, low to intermediate, intermediate to high, and high complexity. Each of these had different associations with age, body mass index, breast density, and other established risk factors. Breast density was not strongly correlated with phenotype category (R^2 = 0.24), indicating the radiomics parameters provided unique information. The most intriguing finding was that radiomic phenotypes of mammographic parenchymal complexity showed an independent association with breast cancer, both in unadjusted and in models accounting for breast percent density and body mass index.

The concept of characterizing mammographic parenchymal patterns for breast cancer risk assessment dates to 1976. Initial classification systems incorporated qualitative or quantitative assessment of the distribution and pattern of breast parenchyma in a mammogram. Early pioneering studies showed elevated cancer risk among women with more complex parenchymal tissue patterns (1,2). However, those subjective visual estimates of mammographic breast density had high inter-and intraobserver variability. Advances in medical image analysis coupled with radiomics analysis is reproducible and reliable for clinical application.

Kontos et al extracted texture features from multiple regions covering the entire breast, allowing quantification of the heterogeneity of breast parenchyma. Prior studies mainly used supervised analysis to evaluate parenchymal texture patterns. However, Kontos et al used unsupervised clustering to gain insight into the intrinsic mammographic parenchymal patterns on a population basis. This approach constitutes a substantial advancement, allowing four distinct imaging phenotypes to be defined that reflect the intrinsic complexity of the breast parenchymal tissue in addition to breast density.

Women diagnosed with breast cancer had a higher proportion of low- and low- to intermediate-complexity phenotypes, but also higher body mass index and higher breast percent density. The addition of these radiomic phenotypes of mammographic parenchymal complexity to a model with breast density and body mass index resulted in an improved discriminatory capacity for breast cancer risk (area under the curve, 0.84 vs 0.80; P = .03 for comparison). This highlights the potential of radiomic phenotypes of mammographic parenchymal complexity for risk prediction and stratification. Also, the combined assessment of breast density and parenchymal complexity might become a valuable tool in determining the best screening plan for each woman and to guide supplemental screening methods.

In addition, the authors demonstrated that both qualitative and quantitative breast density measures varied across complexity phenotypes. Breast density was primarily different for the low- to intermediate-complexity phenotype (19%, 390 of 2029) but similar across the other phenotype clusters. The low- to intermediate-complexity phenotype had the lowest proportion of women with high breast density (2%, eight of 390), whereas the lowest-complexity phenotype had the highest proportion of women with high density. These findings are not totally unexpected. Whereas women with extremely dense breasts may have low overall complexity as their entire breast is predominantly dense with a homogeneous parenchymal pattern, women with scattered fibroglandular breast densities can have a complex parenchymal pattern due to the presence of a higher degree of inherent heterogeneity in their parenchymal tissue. These results emphasize the complementary aspects of the parenchymal pattern captured by the complexity phenotypes and the potential to provide additional information for risk assessment beyond breast density.

A limitation of the Kontos et al study is that the patient population was restricted to white women to avoid any unknown feature differences due to ethnicity. In addition, no information on menopausal status or hormone replacement therapy, which might have influenced breast density, was available. Also, radiomics analysis was performed by using a previously validated fixed feature set, and no deep learning approaches were used. Nevertheless, this study constitutes an important step toward the realization of risk-adapted screening to validate these phenotypes in association with breast cancer risk and screening outcomes. Further studies with larger multiethnic cohorts, and with more comprehensive feature sets and complementary approaches such as deep learning, will be necessary.

In conclusion, radiomic phenotypes can assess mammographic parenchymal complexity and may provide additional information for risk assessment beyond breast density. Radiomic phenotypes of breast complexity have the potential to improve models of breast cancer risk prediction. We can expect that these advances will help to tailor breast cancer screening strategies to an individual woman's risk, values, and preferences while also accounting for cost, potential harms, and patient-important outcomes.

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