In this issue of the Journal, Ghosh et al. (1) describe the application of two visual assessments to predict breast cancer risk—lobular involution, a histological observation, and mammographic breast density (MBD), a radiological assessment. Previously, this group has demonstrated that more extensive lobular involution was inversely related to both MBD (2) and breast cancer risk (3) in a cohort of women diagnosed with benign breast disease at the Mayo Clinic. Herein, the authors extend this work by showing that a benign biopsy demonstrating histologic changes consistent with incomplete or no involution or a mammogram classified as high density is independently associated with breast cancer risk, and in combination, they are associated with an even greater risk. These findings suggest that visual representations of the architecture of the breast on both microscopic (ie, involution) and macroscopic (ie, MBD) levels potentially represent clinically useful intermediate endpoints. The assessment of these “phenotypes” holds
promise for improving risk prediction, particularly because they reflect the cumulative interplay of numerous genetic and environmental breast cancer risk factors over time; however, these remain early days.

The authors appropriately acknowledge that subjective assessment of lobular involution and MBD, as performed in their analysis, is a limitation. Paradoxically, the fact that both involution and MBD are probably substantially misclassified by the current techniques of measurement might be interpreted in a hopeful way. Future advances that allow improved characterization of “normal” tissues at the microscopic and molecular level, and by breast imaging, represent promising avenues for breast cancer risk prediction.

The seminal work of Russo et al. (4) has been important in highlighting the role of lobular development, involution, and differentiation in carcinogenesis. However, assessing lobules in women is quite difficult, particularly because aging is associated with replacement of epithelium by fibrous tissue and fat. Unlike animal models, human tissues are limited and often suboptimal for assessment of involution. Specifically, thin histological sections of human breast tissues may include only parts of lobules, provoking misleading interpretations about the size and development of these structures. Quantification of lobular involution, as proposed by the authors (1), is an exciting possibility, but methods are needed to define which lobules are suitable for assessment (both “normal” and adequately represented) and which lobular features should be measured (total area, number of acini, etc.). This group has already initiated work on this topic (5). Optimized methods to quantify these measurements and combine them into an integrated risk score remain to be determined. Computer-assisted morphometric methods may allow more precise measurement of microscopic features. Growing evidence that the microenvironment surrounding epithelium is important in carcinogenesis (6) suggests that molecular assessment of epithelial proliferation, apoptosis and differentiation, fibroblast secretion of growth factors and hormones, and analysis of collagen composition may complement risk assessment by microscopic evaluation of histology.

Dense tissue observed on an x-ray film is roughly a reflection of the amount of stromal and epithelial breast tissue. Little is known about the histological or molecular biological characteristics of dense tissue, or why MBD is related to elevated breast cancer risk. However, with the development of more standardized and quantitative computer-assisted technologies for measuring MBD (7), stronger associations with breast cancer risk have been observed (8). Despite these technological advances, an inherent limitation of MBD is that it is a two-dimensional measurement of a three-dimensional organ of varying thickness. Rapidly evolving techniques that measure density as a volume using density phantoms, magnetic resonance imaging, or ultrasound tomography offer further opportunities to increase accuracy in measurement and identify stronger risk associations (9).

In the end, defining the biology of high MBD may be essential because not all women with dense breasts develop cancer, and many women develop cancer without having dense breasts. The vast majority of breast tissue, particularly in very dense breasts, is composed of stroma (9). The histopathologic appearance of radiologically dense tissue is remarkably heterogeneous, ranging from acellular dense collagen to highly active fibroglandular tissue, and encompassing the full spectrum of diagnostic entities from benign findings to cancer. Therefore, high MBD, as currently defined, likely reflects more than one biological process. One hypothesis to account for the risk related to high MBD is that it represents a feature of the microenvironment that is conducive to carcinogenesis. A competing idea would be that it is simply a surrogate of the number of at-risk cells (ie, stem cells). The latter idea is supported by the observation that density declines with aging, although cancer incidence increases. As suggested by Boyd et al. (10), density at young ages may be a key risk marker because it reflects the number of undifferentiated cells that are vulnerable to carcinogenic insults before age-related involution and the differentiating effects of pregnancy. Density could also affect risk by creating a barrier or a conduit that leads to altered signaling by impeding or favoring the passage of molecules through the tissue and creating morphostatic gradients (11) that shape the breast structure and its “molecular histology.”

Fundamentally, it remains unclear whether incomplete involution and high MBD reflect a stimulatory effect on the breast favoring growth, a greater amount of at-risk tissue, both processes, or other mechanisms. Globally, both lobular involution and MBD might be viewed as updated interpretations of the concept of “breast tissue aging” as proposed by Pike et al. (12) and previously discussed by Ginsburg et al. (13). However, it is unclear how one model of tissue aging could account for the plateau in estrogen receptor (ER)–negative cancer incidence rates at age 50 years and the continued rise in rates for ER-positive cancers at older ages (14). Interestingly, high MBD seems related to risk for both ER-positive and ER-negative types of breast cancer (15,16), giving broad relevance to MBD as a general marker of risk. The relationship between involution and breast cancer molecular subtypes (17) remains unknown. In the end, risk models that target potentially lethal or preventable cancers will have greatest value.

Future studies of larger numbers of patients from diverse racial and/or ethnic backgrounds will be important for assessing the utility of involution and MBD for risk prediction. Understanding the relationships between involution and epidemiological risk factors that were incomplete (eg, body mass index) or not reported (eg, age at first live birth, menopausal hormone therapy formulation) in this study will also be critical for advancing our etiological understanding.

It is notable that neither lobular involution nor MBD is a static marker of risk. Although previous studies by this group suggest that regional measures of involution (2) or MBD (18) are generally representative of the entire breast, this would not explain why cancers develop in one particular region of a breast. Accordingly, studying changes in measurements over time, perhaps with attention to regional outliers, may provide important clues for understanding breast cancer etiology. Improved volumetric imaging of the breast could enable consistent alignment of serial images and facilitate such comparisons, but evaluating temporal changes in lobular involution will be limited by access to sequential tissue samples. Finally, whereas the present report is based on surgical biopsies performed in the era of film mammography, practice in the United States has
moved toward radiologically guided biopsies, which are considerably smaller, and digital mammography, which incorporates a great deal of proprietary image processing. These factors may affect the performance of both involution and MBD as risk predictors.

In summary, the recent work by the Mayo group (1) emphasizes the potential for using visual assessments of tissue architecture as integrated measures of risk. Improving breast cancer risk prediction is critically important given the limitations of currently available models (19) and the desirability of tailoring screening and prevention to levels of risk.

References


Funding

G.L.G., L.A.B., and M.E.S. were supported (in part) by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

Affiliation of authors: Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD (G.L.G, L.A.B, M.E.S).