Comparing Mammographic Measures Across Populations

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Mammography reveals wide variation among women in the composition and structure of the breast, reflecting the cumulative effects of genetic and environmental exposures that may also play roles in breast carcinogenesis (1,2). Mammographic density (MD), one measure of the characteristics of the image, reflects the relative representation of radiodense epithelial and stromal tissues and radiolucent adipose and has been studied as a biomarker of breast cancer risk for more than three decades (3–5).

This phenotype has been of great interest to researchers, clinicians, and women because it has consistently been found to be associated with higher breast cancer risk and, simultaneously, with reduced sensitivity of mammographic screening. Although the distribution of mammographic features varies by age and menopausal status (6) and between high- and low-risk populations (7), MD remains a strong risk predictor in all subpopulations. In addition, MD is a risk factor that seems to be applicable across the intrinsic subtypes of breast cancer (8).

Percentage density, defined as the proportion of the area of the breast image considered dense, has been measured in numerous epidemiologic studies of screened populations using a widely adopted, computer-based, semiautomated method (3). This method is highly reproducible and valid when carried out by a trained and competent reader; however, the distributions of measured dense areas and nondense areas vary across research studies, perhaps because of differences in reading technique, measurement system, or population (7,9).

Pettersson and colleagues have carried out a meta-analysis on the association of percentage density and its component measures with breast cancer risk, combining estimates from 13 case–control studies analyzed in a standardized fashion (10). The combination of data from multiple studies allows estimation of risk associations in larger and more diverse study samples but also poses a challenge when the original measures are not made on a standard scale (11). In this analysis, the investigators calculated summary odds ratios, combining study-specific odds ratios calculated per standard deviation of the normalized distributions of each MD measure in each study.

Included studies are part of a consortial project aimed at identifying genetic markers of MD or other studies led by the same investigators. In addition, all of the case–control studies had digitized, prediagnostic film mammograms; assessed MD using a semiautomated thresholding technique; and included relevant covariable data measured within a few years of mammographic assessment.

Their summary results suggest that breast cancer risk is increased in pre- and postmenopausal strata after adjustment for age, body mass index, and parity by factors of 1.52 and 1.53, respectively, for each standard deviation of percentage density, increased by factors of 1.37 and 1.38, respectively, for each standard deviation of dense area, and reduced by factors of 0.78 and 0.79 for each standard deviation of nondense area.

Pettersson and colleagues observed heterogeneity across study-specific risk estimates for nondense area and percentage density; in premenopausal women, heterogeneity was observed by study, ethnicity, and age, and in postmenopausal women, by study and mammogram view. In contrast, there was no indication of heterogeneity of effect across risk estimates associated with dense area in either menopausal group. The heterogeneity appeared to be attributable to differences across subgroups in estimates of risk associations for nondense area. Several previous studies of this component of MD have also produced conflicting results on its association with breast cancer risk (12,13).

Although percentage density may perform better as a marker within certain populations, these data suggest that dense area is a better marker for application in studies that include multiple ethnicities, a wide age range, or differences in available mammographic views. Interestingly, this coincides with the results of a previous study by Maskarinec et al. (7), which described MD measures made by a single reader on images from women drawn from populations of diverse ethnicities (Japanese, Latino, Native Hawaiian, and white) and locations (Hawaii, Arizona, Japan, and Norway), covering a wide range of breast cancer risks. In this ecologic study, mean measures of dense area were strongly correlated with breast cancer incidence rates across the ethnic/geographic subgroups under study, whereas mean percentage density was not a statistically significant correlate of breast cancer rates (7).

It would be of particular interest to understand whether the observed heterogeneities of effect remain apparent if individual level data is combined. Analysis of pooled individual level data would allow the opportunity to study this heterogeneity in greater detail but would still be complicated by the challenge of combining measures that are not standardized.

Numerous research groups have worked toward the development, characterization, and application of standardized automated methods for measurement of MD. These include diverse approaches, including area measures (14), volumetric measures (15), and texture-based measures (16,17). It remains to be seen which measure or combination of measures will prove to be the most widely applicable and accurate measures of breast cancer risk. We look forward to future studies that apply standardized measures in diverse populations, which should provide useful information for both clinical and research purposes.


Notes

The views expressed are those of the author(s) and do not necessarily represent those of the Uniformed Services University of the Health Sciences or the Department of Defense.

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