Studying Mammographic Density: Implications for Understanding Breast Cancer

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Several epidemiologic studies (1-3) have reported the magnitude of the risk associated with increased mammographic density to be between fourfold and sixfold, exceeding that of most other predictors of breast cancer. In these studies, this increased breast cancer risk was not explained by other traditional breast cancer risk factors. Despite the level of evidence of an independent association with breast cancer and the large number of women who are having routine mammographic screening, mammographic density is perhaps the most undervalued and underutilized risk factor in studies investigating the causes of breast cancer. Many studies of breast cancer risk have not included measures of mammographic density either because of practical reasons, such as difficulty in obtaining mammographic images and in assessing features in a systematic manner, or because of misconceptions stemming from the interpretation of early studies of mammographic features. The fact that this strong predictor of risk has been overlooked in many studies of breast cancer seems particularly unfortunate because of the profound implications to both cancer screening and etiology that attention to these factors may have. Thus, to fully comprehend the causes of breast cancer, we need to understand the role of breast density in the disease process and to identify the determinants of mammographic density. To avoid some of the methodologic problems inherent in the early studies, investigators incorporating mammographic density in their research must pay close attention to the potential for bias inherent in their study design, in their assessment and quantification of mammographic features, and in their interpretation of findings (4-6).

Since first reported by Wolfe (7) in 1976, interest in mammographic features as a predictor of breast cancer has fluctuated. In Wolfe’s early studies, mammographic features were assessed primarily from xeromammographic images and classified into four categories based on the visual interpretation of the relative amount of dense tissue and the characteristic appearance of the breast tissue. In response to Wolfe’s initial reports of very high breast cancer risk that was associated with the high breast density patterns, many others have also evaluated the associations between mammographic features and breast cancer risk (4,5). Since these other studies did not all confirm the initially reported association, many were willing to dismiss any possible association. Many of the nonconfirmatory studies, however, did not consider the potential bias from the use of lower contrast film-screen images, not blinding the radiologist reading the mammogram to case status, use of diagnostic images for assessment, and inadequate training of the radiologist (6,8-10). The assessment of “parenchymal patterns,” even by trained radiologists, was highly variable in many of these studies, although the differences in assessment decreased after specific training in the recognition of mammographic features (9,10). The studies that were designed to minimize these potential sources for bias consistently reported the association between mammographic features and breast cancer risk (4,5).

Subsequent studies (2,11) evaluating the components of the parenchymal patterns reported that visual estimation of the percentage of the breast with dense tissue into five or six categories predicted breast cancer risk. To improve upon the visual assessment, Wolfe et al. (12) first reported marking and measuring, with a manual planimeter, the area of the breast with dense appearance and the total breast area on the mammogram. From these measurements, one could calculate the percentage of the breast area with any mammographically dense tissue, a measure now known as “breast density” (12). This measurement technique minimized both the variation due to the subjective measure of mammographic features and the difficulty of visually assessing relative area from an irregularly shaped image. The percentage of breast density was thus measured reliably on a continuous scale. The measurement of breast density has been adapted in several subsequent studies, using either a computerized planimeter or an interactive software system, where the radiologist reading the mammogram determines the gray-scale threshold for a digitized image to identify dense tissue (2,3).

These studies that measured mammographic breast density reported that women whose breast tissue is predominantly dense (>75% of total breast area) were at a greater than fourfold increased risk of developing breast cancer than women with little or no breast density (1-3).

In this issue of the Journal, Pankow et al. (13) report their findings from a segregation analysis of cross-sectional, multi-generation information evaluating whether the transmission of a major gene influences mammographic density. Incorporating the assessment of mammographic features into this epidemiologic and genetic study of breast cancer families enabled these researchers to evaluate predictors of mammographic density at this time and to determine the role of mammographic density in the

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See “Notes” following “References.”
Breast density changes throughout a woman's life. Adjustment years, the mammograms of mothers and daughters reflect the in the magnitude of the correlations. In this regard, the authors assessed that the smaller number of mother–daughter pairs and the nonsignificant correlations in mother–daughter pairs and lower nonsignificant correlations in sister–sister pairs were more similar than the area of mammographic density that are easily performed should be considered. Individuals assessing breast density should demonstrate that they are identifying the features of breast density that are associated with breast cancer risk, either by comparison with others who have reported this measured risk or in a pilot assessment study. Many well-qualified individuals may be consistent in their assessment, but they may not be measuring the appropriate aspect of breast density. Previous studies (9,10) have reported that the gradient in breast cancer risk generally increased after training was given in assessment techniques. Although it is not possible to assess the impact of such misclassification in the study by Pankow et al., these two study aspects—training the reader and measuring the breast density—should be considered in future studies.

A proposed epidemiologic study of the cause of breast cancer that did not intend to assess menopausal status, use of postmenopausal hormones, parity, or age at first birth would be considered incomplete even though each of these factors is associated with only a moderate change in breast cancer risk. However, increased breast density, which is associated with a much greater increase in risk, is typically overlooked. Pankow et al. (13) are to be credited for the inclusion of mammographic assessment in the baseline measures in their epidemiologic and genetic follow-up study of breast cancer families. Their analysis is consistent with a genetic component being one of the factors influencing mammographic density. Perhaps the most notable result of their analysis, however, is the implication that a large number of the factors that may influence mammographic density are unknown at this time. Since more than 46% of breast cancers in some studies are attributable to having any measurable breast density (3), a better understanding of what is measured by mammographic density, what factors predict mammographic density, and what happens to breast cancer risk if mammographic density changes are three areas particularly in need of further research. So as not to repeat past problems, studies of mammographic features must make an extensive effort to conduct a standardized assessment of measured breast density, which would include assessment of both the validity and the reliability of the measures used.

References

Cell Transformation, Invasion, and Angiogenesis: a Regulatory Role for Ornithine Decarboxylase and Polyamines?

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In this issue of the Journal, Kubota et al. (1) report that overexpression of ornithine decarboxylase (ODC) triggers mitogen-activated protein (MAP) kinase activity, which in turn implies a proportional increase in invasiveness. They demonstrate that transfection of mouse 10T1/2 fibroblasts with rat ODC complementary DNA (cDNA) elicited morphologic transformation; the ODC transformants formed colonies in monolayer tissue culture and proliferated in semisolid soft agar. Kubota et al. suggest that the ODC-induced cell transformation mechanism can be explained, at least in part, by activation of the MAP kinase pathway, since the ODC transformants that they studied displayed increased protein kinase activity against myelin basic protein used as an MAP kinase substrate in in-gel assays. In addition, they postulate that deregulated ODC activity may influence invasion of a cancer cell. This was evidenced by migration of ODC transformants through a reconstituted basement membrane-coated filter in Boyden chambers in vitro. Furthermore, Kubota et al. show increased secretion of matrix metalloproteinase (MMP)-2, a 72-kd progelatinase considered to be one of the key players in extracellular matrix degradation. The results obtained by these investigators provide strong evidence that ODC activity and polyamines may affect a number of processes that have an impact on tumor development, including abnormal cell proliferation and invasion.

Polyamines—putrescine, spermidine, and spermine—are small cationic organic molecules that are indispensable for cell proliferation and differentiation. All eukaryotic cells contain one or more of the polyamines. Their concentrations vary during the cell cycle, and one of the first events in proliferating cells is induction of polyamine synthesis, preceding both nucleic acid and protein synthesis. Beyond that, however, it is hard to elucidate the specific biologic functions of polyamines.

The key enzyme in the polyamine biosynthetic pathway is ODC. In its active form, ODC is a dimer of two identical subunits of 51 kd. It is one of the most strictly regulated enzymes known. ODC has a turnover rate ranging from a few minutes to 1 hour. In contrast, the average life of mammalian enzymes is counted in days. This rapid turnover is essential for fast and dramatic changes in ODC levels in response to many kinds of growth stimuli that affect the rate of enzyme synthesis, preceding both nuclear acid and protein synthesis. Beyond that, however, it is hard to elucidate the specific biologic functions of polyamines.

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