Breast Density as an Independent Risk Factor for Cancer

Susann E. Schetter, D.O.
Chief, Division of Breast Imaging, Penn State Milton S. Hershey Medical Center, Hershey, PA

Introduction

In 2009, Connecticut introduced the first state law mandating that women be informed of their breast density when they receive the lay letter results of their screening mammogram. Since then, another 12 states have legislated similar requirements with variable budget support for the increased costs of supplemental screening exams. The impetus behind these legislative changes is the understanding that increased breast density is associated with decreased mammographic sensitivity for the detection of breast cancer. Epidemiologic studies of early screening performance showed that increased breast density had a negative effect on mammographic sensitivity, termed masking bias. For this reason, vocal advocacy groups have pushed the agenda politically.

Although a masking bias does exist in women with dense breasts, there is substantial evidence that increased parenchymal breast density (PBD) is one of the strongest predictors of breast cancer risk. Women with the highest breast density have a risk 2 to 6 times those with lowest breast density. As many as 30% of postmenopausal women have dense breasts, which makes increased breast density the most frequently encountered risk factor for development of breast cancer. Further, it is apparent that PBD can be altered with intervention.

This article reviews historical literature and summarizes recent data addressing breast density and the relationship to breast cancer risk. An overview of biochemical and genetic contributions to cancer development and increased PBD, as well as the contributions of hormones and aging is provided. Understanding the known risks conferred by increased breast density will enhance our ability to educate both patients and clinical colleagues when the inevitable questions arise concerning breast density and breast cancer screening.

Historical Use of Breast Density and Mammographic Reporting

Radiologists are accustomed to observing and describing the appearance of the breast tissue on mammograms. In 1976, prior to the acceptance of widespread mammographic screening, John Wolfe published a seminal article in the American Journal of Roentgenology describing four breast parenchymal patterns: N1, P1, P2, DY (least to most dense). He determined that the cancer rate in the DY population to be 37 times that of the N1 group, and made recommendations for consideration of prophylactic mastectomy for women with a DY assessment. Forty percent of the cancers identified in his cohort were prevalent cancers (cancers present in the first screening round) due to the lack of routine screening available. Subsequently, it was apparent that the use of the Wolfe patterns was widely variable with poor inter- and intra-observer agreement. Fortunately, his conclusions were eventually shown to over-estimate the importance of breast density as a risk factor for breast cancer. Nevertheless, a positive relationship of breast density to the incidence of cancer was established.

The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BIRADS) categories for breast density (primarily fatty, scattered fibroglandular, heterogeneously dense, and extremely dense) were in part developed to address the issue of masking bias associated with increased PBD (Fig. 1). The Mammography Quality Standards Act (MQSA) adopted the ACR BIRADS definition and mandated the categorization of breast density into one of these 4 categories. Moderate inter-observer agreement has been measured, with kappa coefficients of 0.43 – 0.59; these k values are higher for BIRADS 1 and 4 assessments, which are more straightforward than the BIRADS 2 and 3 categories. Although there is known decreasing sensitivity of mammograms as one
proceeds from BIRADS 1 to BIRADS 4, there is no inherent relevance to breast cancer risk conferred by this assessment.\(^9\)

Certainly, high breast density decreases the conspicuity of breast lesions, and delay in the diagnosis of breast cancer remains in the top five errors in radiology malpractice claims. In fact, nearly 70% of these claims refer to women less than 50 years of age, accounting for 78% of all indemnity paid. In contrast, more than 75% of all typical infiltrating ductal carcinoma is seen in women over 50 years of age,\(^10\) paradoxically rising in a population with decreasing breast density and raising questions regarding the process of involution and extracellular factors that contribute to carcinogenesis. Yet, data support mammography as the best, albeit imperfect, screening modality, with a resultant decrease in mortality in all age brackets.

Calculations of Breast Density and Breast Cancer Risk

In 1995, two articles were published in the *Journal of the National Cancer Institute* (JNCI) addressing the importance of breast density as a risk factor for the development of breast cancer. Boyd, et al. published the first computer-assisted, threshold measurement of breast density (Cumulus method), developed at Sunnybrook, Toronto, Ontario, Canada.\(^3\) This method includes the digitization of film/screen mammograms which are then presented for evaluation on a high resolution workstation. The observers select the outline of the breast as the first threshold to separate the structure of the breast from the background, and a second threshold is established by the observer to delineate the dense tissue from the non-dense breast tissue. The breast density was calculated as a percentage of “dense” pixels of the total area of the breast (Fig. 2).\(^3\) Boyd, et al.’s study excluded all prevalent cancers and all women who developed cancer within one year of entry into the study. The researchers found a statistically significant increase in the number of cancers developed in the women with the greatest breast density. This positive correlation was seen in all age groups, and a calculated increased relative risk of 5 – 6 fold was similar for both Radiologist-observed and quantitative threshold determination of the percent breast density.

Using screening and follow-up information from the Breast Cancer Detection Demonstration Project, Byrne, et al. determined a similar positive relationship
between high PBD and breast cancer risk that was independent of age and menopausal status. Baseline density evaluations of 1880 case subjects and 2152 control subjects were recorded by observers using the Wolfe classifications. Patients were followed for 16 years, decisively eliminating the masking bias and allowing for determination of the risk conveyed by breast density 10 years beyond the baseline assessment. Both studies show a 4 – 5 fold increase in breast cancer risk for women with >75% breast density, adjusting for BMI and family history.

Subsequently, quantitative evaluations of larger data sets were published, to advance the understanding of these relationships. Harvey, et al. reviewed twelve breast density studies that used the computerized threshold method. An increased cancer risk was associated with increased breast density in every study, outcomes unaffected by masking bias. Incident breast cancer cases showed no dramatic change in breast density over the course of 2 – 8 years, proving that baseline density was as important as density at the time of diagnosis.

A systematic review of aggregate data representing greater than 14,000 cases and 226,000 non-cases explored sources of conflicting data in 42 articles due to the use of different qualitative and quantitative methods of breast density assessment and variable patient age ranges. A meta-analysis of this data was published by McCormack and Silva in 2006. Breast density was confirmed as the strongest risk for breast cancer, independent of masking effect and not restricted to any particular age bracket. Although both screen detected and interval cancers are more numerous in the women with high PBD, there is no correlation between increased breast density and prognosis at the time of breast cancer diagnosis.

A positive correlation between high PBD and the Gail model was established by Palomeres, et al. The Gail model is a commonly utilized tool for breast cancer risk assessment, stratifying risk with well-understood factors related to personal hormonal and familial cancer histories. The model assigns a percent chance of cancer development at 5 years and over a lifetime. Higher PBD was found in women with greater than 15% lifetime risk compared to those with less
than 15% lifetime risk. Interestingly, the women in the higher risk group had twice the breast density of those with lower risk.\textsuperscript{14}

Current published guidelines for women with a 20% lifetime risk recommend supplemental cancer screening with MRI; however, for those whose risk ranges from 15 – 20%, there are no clear recommendations.\textsuperscript{15}

**Contributions to Breast Density**

Intrinsic factors contributing to breast density include age, genetics, serum and tissue hormone levels, and body mass index (BMI). Extrinsic factors include hormone supplements or replacement, diet, exercise, alcohol, and environmental factors.

**Hormones**

The effect of hormones and aging on breast density has been extensively studied. At mid-menstrual cycle, ovulation is accompanied by a strong luteinizing hormone (LH) peak and concurrent rises in estradiol and follicle-stimulating hormone (FSH) (Fig. 3). Although progesterone levels begin to increase at this time, they peak later in the luteal phase with continued elevation of estradiol. This premenstrual elevation of progesterone and estrogens is responsible for retention of water within the breast tissue and increased cellular proliferation, resulting in higher tissue volumes. Breast imaging studies are ideally performed in the follicular phase of the cycle (week 2), when these effects are least influential.\textsuperscript{16} Timing of examinations to the follicular phase decreases discomfort of mammograms and may increase compliance with mammographic screening. The specificity of ultrasound and MRI also increases in the follicular phase. Accuracy of interpretation can improve when timing is optimized as the parenchymal appearance is dramatically altered in some patients. A recent study in *Radiology* showed variation in the levels of enhancement of normal breast parenchyma and benign lesions in week 2 vs. week 4 of the cycle, favoring imaging in week 2. This effect did not apply to the malignant lesions.\textsuperscript{17}

Hormonal influences contribute to higher breast density and higher levels of breast cancer in nulliparous women, as well as in those who have fewer children and at later ages. For women with larger areas of fibroglandular tissue and increased breast density, perimenopausal hormone effects can be dramatic. These effects arise from shortening of the follicular phase of the cycle and higher pre-ovulatory estradiol levels contributing to increasing size and number of breast cysts. It is reasonable to assume that these changes in breast density are related to proliferative effects of endogenous hormones.

Histologic evaluations have shown that morphologic changes in the tissue received from surgical and core biopsy specimens matched with the phase of the menstrual cycle.\textsuperscript{18} Specimens from women in menstrual days 6 – 15 showed clear distinction between epithelial and myoepithelial layers of the acini and an absence of stromal edema. Mitosis and apoptotic bodies were not present. In contrast, at days 25 – 28, epithelial cells showed prominent nuclei, large nucleoli, frequent mitotic figures, and increased apoptosis. Also present in the immediate pre-menstrual phase were increased inflammatory cells and extensive stromal edema.\textsuperscript{18} These histologic data support the recommendations for timing of imaging studies with the menstrual cycle.

Postmenopausal status and increasing age usually contribute to a progressive decrease in breast density. Unfortunately, this is a general trend that does not uniformly apply to all women.\textsuperscript{19}
Age.

The common decrease in breast density and corresponding histologic change that occurs with age is described as involution.19,20 Sixty-five percent of women in their 20’s have greater than 50% breast density. This drops to 50% of women in their 40’s. For postmenopausal women, approximately 30% of women have greater than 50% density, and this proportion persists into the 70’s. In contrast, 34% of postmenopausal women have predominantly fatty tissue.11

The incidence of breast cancer increases with age. The decrease in PBD with age has been attributed to involution of breast tissue. This paradox contributes to some confusion as to the importance of breast density as a risk factor for malignancy. Involuence of breast tissue occurs first peripherally, with progressive radiolucent changes on the mammogram. There may be some protective effect of involution, although the exact mechanism is unknown. It is clear, however, that postmenopausal women with higher breast density are more likely to develop cancer than those with lower breast density.9,19

Genetics.

Hormone status, parity, and BMI influence mammographic density, but genetics may play the largest role in the determination of an individual’s PBD. Twin studies of sisters in North America and Australia proved a positive correlation for similarity in breast density among monozygotic twins that was twice that of the dizygotic twin group, measuring 60 – 67% when adjusted for age and other covariates.21

Mammographic differences exist across racial lines. In a retrospective review of 15,292 patients, the breast density was greatest for Asian women. There was little difference otherwise among whites, African Americans, or other ethnic groups when adjusted for BMI and age.22

Exogenous Hormones.

The Women’s Health Initiative randomized 16,608 women to combined hormone replacement therapy (HRT), estrogen plus progestin, or placebo. Seventy-five percent of women receiving the hormone therapy showed a mean increase of 6% in breast density after one year, compared to the placebo group who charted a 0.9% decrease in baseline PBD. Baseline variables evaluated included race and ethnicity, socioeconomic status and education, full hormonal history, duration and use of oral contraception, physical activity, and use of tobacco and alcohol. The effects of HRT on breast density persisted for the 2-year duration of the study.4 Additional studies have shown an increase in breast density over controls in the cohort receiving HRT; however, there is no evidence that there is a direct relationship to cancer development.5,23 Both ER positive and ER negative cancers have an increased incidence in women with increased breast density.4

BMI.

Higher BMI correlates with a lower quantitative measurement of breast density and perceived density on mammographic interpretation. In contrast, one observes an increase in apparent mammographic breast density when patients experience significant weight loss, as in individuals following bariatric surgery. Obesity is related to increased cancer incidence in postmenopausal women, creating a paradoxical increase in cancer with decreased breast density. The exact mechanism is unknown but is attributed to an increase in local estradiol levels in fat tissue.24

Aromatase activity is found in fatty breast tissue, and larger areas of body fat serve as a source of estrogens. In postmenopausal women, cancer incidence is independent of serum estrogen levels, suggesting that higher local tissue estrogen levels may be more important in cancer development.25

An alternative consideration is that adipocytokines secreted in the breast fat, leptin, and adiponectin, may
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play a role in cancer risk. Leptin promotes proliferation and enhances cancer cell growth, and adiponectin enhances apoptosis, decreases cell proliferation, and also enables the use of insulin. In obesity, leptin levels are elevated and adiponectin levels are low, possibly explaining the association of higher cancer incidence in this population.\(^{26}\)

An unanswered question is whether cancers preferentially occur in sites of greater PBD. DCIS has been associated with mammographically dense tissue,\(^{27}\) but there is little evidence that this is true for invasive cancers. Most invasive cancers occur in the upper outer quadrant of the breast, the location of the greatest concentration of breast parenchyma.\(^{28}\)

Vachon, et al. studied the location of tumors relative to breast density in 372 incident breast cancer cases and 713 matched controls, and determined that increased breast density represented a “general marker of breast cancer risk, not specific to breast side or location of the eventual cancer.”\(^{29}\) Some of the problems with this and other studies of its kind have been the application of rather crude estimations of regional breast density, lack of correlation with volumetric data, as well as other factors that contribute to radiographic breast density such as compression thickness, exposure factors, beam energy, and breast positioning.

Increasing the Accuracy of Quantitative Measurement

Measurements of breast density have historically been achieved either by visual inspection, or the application of a computer-assisted threshold method, in which the operator determines the distinction between dense and non-dense areas as described above. Although there has been considerably high intra-observer and inter-observer concordance reported, visual setting of a threshold is quite subjective. The two dimensional measurements cannot account for the non-uniform thickness of the periphery of the compressed breast, the 3-D non-uniformity of glandular tissue distribution, and the fact that quantification will always be subject to breast positioning (Fig. 4). In addition, published reports use a variety of measures including absolute and percent area density. Newer volumetric methods incorporate the Digital Imaging and Communications in Medicine (DICOM) data from the full field digital mammography (FFDM) image to quantify the amount of breast tissue, using both absolute and percent (relative) density by volume. These methods incorporate the effect of beam energy for the different target-filter combinations, half-value layer (HVL), kVp, and mAs, as well as compression thickness and degree of compression,\(^{30}\) and are highly reproducible for the data set of each image. Few studies are currently
published to validate this volumetric approach. One comparison of threshold and volumetric methods showed no clear advantage in showing correlation with known breast cancer risk factors in a cohort of 370 screening cases, but a larger body of work is emerging.

Reducing Risk Through Modification of Breast Density

Spurring interest in the quantification of breast density is research aimed at the potential to modify a woman’s risk of breast cancer by altering (decreasing) breast density. Although changes in breast density have not been proven to confer protection or increase risk, the use of breast density as a biomarker for risk remains valid. If histologic changes could be matched to the imaging changes in breast density, the possibility of altering risk and preventing cancers becomes even more compelling.

Other risk reduction strategies have been evaluated with mixed results. Protective effects of physical activity have been proven, with 30 epidemiologic studies showing a 20–40% reduction of cancer risk among pre and postmenopausal patients in various geographic locations, despite variations in the techniques used to evaluate this protection. The risk reduction increases with increasing activity. The results of a study evaluating the association of physical activity on breast density found no statistically significant reduction in the percent or absolute breast density at any level of physical activity. A randomized control trial (ALPHA) looked at the influence of aerobic exercise on breast density and found no correlation with breast density reduction, suggesting that the positive effect of exercise operates through another mechanism. Diets lower in fat, higher in fiber, Mediterranean diets, and lower alcohol consumption are associated with lower PBD and decreased overall cancer rates.

Selective estrogen receptor modulators (SERMs) are approved for the adjuvant treatment of breast cancer. The NSABP P-1 trial evaluated the use of tamoxifen, the first widely used SERM, in the adjuvant treatment of ER+ breast cancer. Patients were followed for 15 years after a 2–5 year course of therapy and showed a 50% reduction in the recurrence and contralateral occurrence of breast cancer that persists for 7–12 years. Limiting the widespread use of tamoxifen are undesired side effects of deep venous thrombosis (DVT), stroke, pulmonary embolus, and endometrial cancer. The subsequent NSABP P-2 (STAR) trial proved raloxifene, an effective SERM therapy with far less risk of endometrial cancer and thromboembolic events,

![Figure 5. Selective Estrogen Receptor Modulators’ Effect on Breast Density. CC views of the same patient before tamoxifen therapy (A) and one year after therapy (B) with some reduction in PBD.](image)
provided 78% of the risk reduction of tamoxifen, which equates to a 38% reduction in breast cancer. Tamoxifen has been shown to have a statistically significant decrease in breast density in both premenopausal and postmenopausal women, irrespective of age. Raloxifene has been shown to have a lesser effect on breast density (Fig. 5).

Eilertsen, et al. employed a fully automated, volumetric breast density assessment method to evaluate changes in breast density following HRT (increased density) and raloxifene therapy (decreased breast density). This confirmed the results of prior studies and offered insights into the potential of this tool to eliminate the subjective nature of human measurements. Volumetric methods have shown high correlation with MRI volumetric quantification of breast density. Positive relationships between dense tissue volumes and breast cancer risk have been proven with 3-D methodology. The mathematical 3-D methods which incorporate bio-physical principles in a reproducible and automated manner should be embraced as a superior method of assessing breast density.

If increased PBD conveys a higher risk for breast cancer, can intervention to diminish breast density be protective? This, in part, depends on defining what contributes to breast density. Ductal and acinar epithelium is the site of breast cancer development, but abundant research suggests that density is not solely related to the presence of greater volumes of epithelium.

Aromatase is an enzyme responsible for converting androgens to estrogens on a local level. Through the study of core biopsy tissue, it has been shown that the stromal cells have higher levels of aromatase immunoreactivity than the epithelial cells in areas of dense breast tissue. As a result, there is enhanced estrogen synthesis and a greater lifetime exposure to locally produced estrogen in the breast, independent of serum estrogen levels.

The contribution of collagen to breast density was studied from random sections of subcutaneous mastectomy specimens at autopsy. Li, et al. measured the radiographic breast density of the tissue samples and correlated this with stained nuclear area of epithelial and non-epithelial cells, collagen, and glandular area. Collagen was responsible for 29% of the density, 4% of the nuclear density, and 7% of the glandular area. Interestingly, the percentage of collagen was decreased with increasing parity and number of live births, commonly cited factors that decrease breast cancer risk.

Microdissection techniques have contributed to the biochemical and genetic understanding of the mechanisms of tumorigenic conversion of epithelial cells. There is a strong body of evidence that the extracellular milieu of the fibroglandular tissue is as important as the epithelium in carcinogenesis. Following microdissection of epithelium from the surrounding tissues, transcriptional profiling can differentiate the effects related to these epithelial cells versus the stroma, consisting of fibroblasts, myoepithelial cells and extracellular matrix. Carcinoma-associated fibroblasts (CAF) are shown to promote tumorigenic conversion of initiated epithelial cells when added to epithelial cell cultures. Fibroblasts and myoepithelial cells from normal tissue are shown to suppress this transition. The transformation of these stromal cells is key in the transition of normal epithelial cells to invasive disease. Stroma and the extracellular milieu are integral to cancer development.

Other biochemical interactions related to breast density involve insulin like growth factor -1 (IGF-1) and the IGF-binding protein 3 (IGFBP-3). IGF-1 influences breast development and higher levels are found in women with dense breast tissue. Interestingly, breast density and IGF-1 decrease with age. Tamoxifen also decreases IGF-1 levels.

IGFBP-3 is responsible for involution of breast tissue, increasing with both age and post-lactation, and promoting apoptosis and decreased breast density. High levels of IGFBP-3 are also associated with lower mammographic density in premenopausal women.
Summary

PBD is a surrogate for breast cancer risk. As an independent marker, it can also be influenced by interventions such as hormone therapy, diet, physical activity, and SERMs. In addition, high breast density decreases the conspicuity of breast lesions, and delay in the diagnosis of breast cancer remains in the top five errors in radiology malpractice claims.

Increased density is present in 30% of postmenopausal women, occurring with greater frequency than other well-recognized risk factors. Cyclic hormone changes influence breast density, but effect is conveyed long-term effect is uncertain. The potential to prevent more cancers through intervention is an attractive subject of much research.

Beyond the action of state legislatures, current trends suggest that the FDA may include this metric for MQSA certification. Commercialization of volumetric technology that provides an objective quantification of breast density is available and its use is becoming widespread. Incorporation of this information in the breast cancer risk assessment should be studied and its value to population health management determined. New data derived from technological advances in bioscience and volumetric measurement should further elucidate the important relationship between PBD and cancer. As a result, cost effective strategies for the stratification of risk and the informed application of supplemental breast cancer screening for women in any given population may be possible.

References


