Mammographic Density: Use in Risk Assessment and as a Biomarker in Prevention Trials\textsuperscript{1,2}

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Expanded Abstract

Introduction
Mammographic breast density is positively associated with risk of developing breast cancer for both pre- and postmenopausal women. Breast Imaging Reporting and Data System (BIRADS) or similar semiquantitative pattern analyses are inexpensive and suitable for large epidemiologic studies, but intrareader reliability in interpretation is suboptimal. Continuous, computer-assisted measurements have greater intraobserver reliability and are more suitable for prevention trials. There are many technical and physiologic factors that can affect density readings including film exposure, positioning, compression, change in hormonal milieu, weight, and alcohol intake. If mammographic breast density is to be used as a response biomarker, change in these factors must be minimized over the course of the prevention trial. Although drugs (or other interventions) that result in reduced density are likely to result in reduced risk for breast cancer, it is quite possible that there will be interventions (such as weight loss) that will result in reduced risk of breast cancer but will not reduce proportional breast density or will actually increase it. Furthermore, there is no current evidence that change in breast density alters individual breast cancer risk. More studies are needed that examine the comparative discriminatory ability of mammographic density or nondiagnostic tissue sampling (i.e., random periareolar fine needle aspiration) when added to the Gail or other epidemiologic risk models.

Background
Mammographic breast density is one of the reversible biomarkers used to stratify risk estimates derived from epidemiologic models as well as monitor response to prevention therapy (1,2). Others biomarkers include serum prolactin, sex hormone binding globulin (SHBG), and bioavailable testosterone and estradiol in postmenopausal women (3–5); serum insulin-like growth factor-1 (IGF-1) and its binding protein IGFBP-3 in premenopausal women (6); and intraepithelial neoplasia (7–11) and associated molecular markers such as Ki-67 (12,13) in both pre and postmenopausal women.

Mammographic density, unlike serum hormones and growth factors, is reflective of events occurring in the breast. Unlike intraepithelial neoplasia, it does not require an invasive procedure for assessment. Further, because most women between the ages of 40 and 70 are advised to undergo yearly screening mammography, mammographic density should be obtainable at no additional risk and minimal additional expense.

What accounts for mammographic density?
Mammographic density is reflective of the relative amount of epithelium, stroma, and fluid compared to fat (14). Several investigators have suggested that high mammographic density is often associated with underlying intraepithelial neoplasia including atypical hyperplasia (15–18). However, epithelial proliferation is unlikely to account for the majority of the density (19) and it is increasingly apparent that the stroma plays a major role in visualized density (19,20).

Histologic examination of tissue sections corresponding to high vs. low density in a predominately postmenopausal population showed no significant difference in the frequency of ductal and lobular structures but significantly higher collagen content, extent of fibrosis, and expression of 2 stromal proteoglycans lumican and decorin (21). Expression of these proteoglycans is positively associated with the development of breast cancer (22). As stroma is thought to play a major role in carcinogenesis (23), it makes little difference from the standpoint of risk assessment whether the predominant contributions to mammographic density are stromal or epithelial.

Association of mammographic density with other risk factors
In addition to intraepithelial neoplasia, mammographic density is positively associated with several other known risk factors or risk biomarkers for breast cancer including family history (24–27), serum IGF-1 in premenopausal women (28–30), serum...
prolactin in postmenopausal women (29), and combined estrogen plus progestin hormone replacement therapy (31–34). Mammographic breast density is negatively correlated with several factors associated with reduction in risk for breast cancer such as IGFBP-3, early pregnancy, and multiparity (reviewed in 29). Unfortunately, density is also negatively correlated with 2 important risk factors for breast cancer, namely age and body mass index [reviewed by Boyd et al. (29) and McTiernan et al. (35)], and positively correlated with a protective factor, SHBG (29).

Methods to measure density

Multiple methods have been developed to assess mammographic density, with reasonable correlation between techniques (36–41). Wolfe was among the first to identify certain patterns of density on mammography films that were likely to be associated with increased risk (36). He described a pattern of N1 as composed almost entirely of fat with little to no radiologic density; P1 as scattered density occupying <25% of the breast; P2 as heterogeneous density occupying ≥25% of the breast with ductal prominence; and DY as homogeneous sheetlike density in ≥25% of the breast area with no ductal prominence. The greatest relative risk was associated with the DY pattern (36).

The BIRADS system developed by the American College of Radiology is similar to the Wolfe categories and describes breasts as 1) almost entirely fatty; 2) scattered fibrodenticular tissue; 3) heterogeneously dense; and 4) extremely dense (42). The proportion of women having BIRADS category 3 and 4 dramatically decreases with age. Eighty percent of 40- to 49-y-olds, 54% of 50- to 59-y-olds, and 43% of 60- to 69-y-olds have category 3 or 4 density (43). However, only 20% of 40- to 49-y-olds, 5% of 50- to 59-y-olds, and 2% of 60- to 69-y-olds have extremely dense category 4 breasts (43).

Byrne et al., in a nested case-control study using the mammograms from the Breast Cancer Detection Demonstration Project, compared the Wolfe pattern system to a continuous density measurement system assessed by planimetry. In the continuous measurement system, the area of the breast occupied by increased density was measured relative to the total area of the breast (37). They found continuous measurements divided into 5 categories of relative areas of increased density gave better separation of relative risk than the 4-category Wolfe pattern system (Table 1). They also observed that whereas the area of increased density was a risk factor, total breast area was not.

A computer-assisted methodology was developed to provide continuous density measurements and then applied to a nested case control study from the Canadian National Breast Screening Study. Boyd et al. found a 3% change in relative risk for every 406 mm² of increased breast density and a 2% increase in relative risk for every 1% increase in proportional breast density (areas considered to be at increased density divided by the total breast area) (38). Boyd et al. divided breast density measurements into 6 categories similar to those given by Byrne et al. (Table 1).

Both the Byrne and Boyd studies reported that the approximate 10% of women who had >75% increased breast density had a 4- to 5-fold greater risk than women with no areas of increased breast density when corrections are made for weight and reproductive and family history (2,38). Women with 50–75% area of density have a 2.5- to 3.0-fold increase in risk. Boyd et al. have suggested that the increase in relative risk estimates resulting from a breast density measurement lasts at least a decade (29,44). A semiautomated software system (Cumulus) was developed at the Sunnybrook and Women’s College Hospital in Toronto, Ontario and is available to investigators. A similar computer-assisted analysis system (Madena) was developed at the University of Southern California (45).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Risk of development of breast cancer associated with different patterns of mammographic density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification: Wolfe</td>
<td>N1</td>
</tr>
<tr>
<td>nomenclature, % of breast considered to be at increased density</td>
<td>None</td>
</tr>
<tr>
<td>Proportion of women</td>
<td>12</td>
</tr>
<tr>
<td>exhibiting pattern, %</td>
<td>11</td>
</tr>
<tr>
<td>Adjusted odds ratio</td>
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</tr>
<tr>
<td>1.0</td>
<td>1.57</td>
</tr>
<tr>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>1.0</td>
<td>1.2</td>
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</tbody>
</table>

1 In each cell the value for the Wolfe system is provided first, followed by those for Byrne et al. and Boyd et al.
2 Upper bound excluded.

Does mammographic density stratify risk based on the Gail model?

Although validated for populations, the commonly used Gail model has limited discriminatory accuracy (concordance statistic = 0.58) (46). Using a BIRADS assessment method, Tice et al. found only a minimal improvement in the concordance statistic (0.657 to 0.674) as a result of adding breast density to the Gail model in a large screening population (47). For purposes of comparison, the addition of the risk biomarker of cytologic atypia as detected in specimens obtained by random periareolar fine needle aspiration (RPFNA) of high-risk women improved the concordance statistic from 0.638 with the Gail model alone to 0.790 with the combination (48).

Mammographic density used as a response biomarker in prevention trials

Mammographic density is currently being explored as a biomarker of response in primary and secondary prevention trials. Important considerations for chemoprevention studies include maximizing intrareader reliability and minimizing variance resulting from technical and physiologic factors.

In general there appears to be greater intrareader reliability for the 6-category classification system of Boyd et al. (intraclass correlation coefficient of 0.94) (38) than BIRADS or Wolfe (K value of 0.43–0.59 for BIRADS) (49–51). Use of computer-assisted measurements and reviewing both baseline and follow-up films together in a blinded fashion maximize intrareader reliability (52).

Differences in compression, positioning, film exposure, and the amount of breast tissue captured on the film/image may influence breast density assessments. A step wedge will assist in detecting differences in film exposure, but having the mammogram performed on the same machine with the same technician each time can help minimize technical variance. Minimization of physiologic variance is also important. Changes in amount or type of alcohol consumption can increase or decrease breast density (i.e., changing from white to red wine) [reviewed in Harvey and Bovbjerg (52)]. Change in hormone replacement therapy is an important source of variance in postmenopausal women, and assessing density in different phases of the
menstrual cycle is an important source of variance in premenopausal women (53,54). Breast density can also be expected to decrease with age and/or after menopause.

Administration of several selective estrogen receptor modulators including tamoxifen results in a reduction of breast density (54–56). Cuzick et al. reported twice the reduction in dense area for women treated with 4.5 y of tamoxifen as for women given placebo in a nested case-control study performed for IBIS-1 participants (56). The majority of breast density reduction occurred in the first 18 mo of study. There was a significant interaction with age such that a minimal decrease in area of density was observed for women over 55 treated with tamoxifen, that is, 1% compared to 13% for women younger than 45 (56). Importantly, reduction in breast density predicted only one-third of the reduction in breast cancer incidence seen in prevention trials (56). We observed no change in breast density in a 6-mo study of placebo versus a-difluoromethylornithine, a drug that failed to alter any risk biomarker for breast cancer (57). However, no reduction in the area of density was observed in postmenopausal women in a 2-y trial of a low-fat diet (58) despite observations that such a diet may be associated with a reduction in recurrence of breast cancer (59).

In conclusion, for risk assessment, mammographic breast density provides only modest improvement in discriminatory ability over that provided by the Gail model alone. Moreover, mammographic breast density has limited usefulness in obese and older women. As a biomarker of response over an interval of intervention, there are a number of technical issues that contribute to variance. Despite this, breast density has been shown to be a good response biomarker for SERMs in premenopausal women, even though it is less useful for postmenopausal women. Although there is no current evidence that a change in breast density changes individual breast cancer risk, it is probably safe to assume that interventions associated with reduced mammographic density will probably be associated with reduced breast cancer incidence. However, the reverse is not necessarily true: failure to reduce mammographic density will not necessarily predict an ineffective intervention. Finally, more studies are needed that examine the comparative discriminatory ability of mammographic density or nondiagnostic tissue sampling (i.e., random periareolar fine needle aspiration) when added to the Gail or other epidemiologic risk models.

**Literature Cited**


