Mammographic Breast Density: Impact on Breast Cancer Risk and Implications for Screening

Phoebe E. Freer, MD

Abbreviations: BCSC = Breast Cancer Surveillance Consortium, BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, ICER = Institute for Clinical and Economic Review, NCCN = National Comprehensive Cancer Network, PPV = positive predictive value for malignancy of biopsied lesions detected at screening


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1From the Department of Radiology, MGH Imaging, Massachusetts General Hospital, 15 Parkman St, Wang Building, ACC-240, Boston, MA 02114. Presented as an education exhibit at the 2013 RSNA Annual Meeting. Received March 23, 2014; revision requested July 15 and received August 15; accepted August 19. For this journal-based SA-CME activity, the author, editor, and reviewers have disclosed no relevant relationships. Address correspondence to the author (e-mail: pfreer@partners.org).

See also the article by Winkler et al (pp 316–324) and the discussion by Butler (pp 324–326) in this issue.

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ Describe the effects of breast density on mammographic screening.
■ Discuss the evidence regarding supplemental screening of women with dense breasts.
■ Summarize current expert guidelines on when to use supplemental screening.

See www.rsna.org/education/search/RG.

Introduction

Mammographic breast density is rapidly becoming a hot topic in both the medical literature and the lay press. In the United States, recent legislative changes in 19 states (38%) now require radiologists to notify patients regarding breast density as well as the possible need for supplemental screening. Federal legislation regarding breast density notification has been introduced, and its passage is likely on the horizon. An understanding of the context, scientific evidence, and controversies surrounding the topic of breast density as a risk factor for breast cancer is critical for radiologists. The current state of evidence is presented regarding supplemental screening for women with dense breasts, including the use of digital breast tomosynthesis, whole-breast ultrasonography, and gadolinium-enhanced magnetic resonance imaging. A review of current practice guidelines and additional sources of information will improve radiologists’ understanding of the relevant subject of breast density and enable them to respond appropriately to questions from patients, clinicians, and the media.

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The relative risk for cancer in women with heterogeneously dense breasts compared with the average woman is approximately 1.2, and the relative risk for cancer in women with extremely dense breasts compared with the average woman is approximately 2.1.

Data suggest that the masking effect of dense breasts on cancer detection is greatly reduced with the use of digital mammography versus film-screen mammography.

Supplemental screening of women with dense breasts who are of average or low risk is not currently recommended by most major medical societies or evidence-based review studies.

The importance of the radiologist in reinforcing evidence-based best practices and counseling and educating patients, clinicians, and, in some cases, the media or legislators regarding these best practices cannot be overemphasized.

**TEACHING POINTS**

- As breast density legislation continues to be implemented, it is important to stress to providers and patients that a woman’s breast density is not a fixed entity but may vary over time because of interpreter variability and physiologic changes that may affect breast density and breast positioning.

- When discussing breast density, researchers combine the classifications of “heterogeneously dense” and “extremely dense” and categorize them as “dense,” whereas the patterns of “fatty” and “scattered areas of fibroglandular density” are labeled as “nondense.” Some researchers report that as relatively low as 31%–43% of the general screening population have dense breasts.

- Regardless of the classification system used, there is considerable inter- and intraobserver variability in the subjective classification of breast density. Even with the attempts in the fourth edition of the BI-RADS lexicon to quantify tissue density according to the amount of dense tissue relative to fatty tissue, substantial variability and lack of reproducibility remain.

- For this reason, automated quantitative tissue-density software has been developed. Although the objective measurements provided can help reduce interpreter error, they are still fraught with the error of attempting to measure the three-dimensional properties of the breast with two-dimensional projections. Objective measurements also vary according to breast positioning; a greater amount of retroglandular fat included in the image will automatically decrease the density measurement.
Figure 1. (a) Photomicrograph (original magnification, ×50; hematoxylin-eosin [H-E] stain) of a breast biopsy specimen shows normal mature adipocytes, which account for radiolucent areas seen at mammography (not shown). (b) Photomicrograph (original magnification, ×100; H-E stain) of a breast biopsy specimen in a different patient shows normal ducts, with ductal epithelium and stromal elements that account for radiopaque areas seen at mammography (not shown).

Figure 2. (a) Left craniocaudal normal screening mammogram obtained in a premenopausal 46-year-old woman shows findings that could be interpreted as scattered areas of fibroglandular density or as heterogeneously dense tissue. (b) Left craniocaudal normal screening mammogram obtained 8 years later, after the patient experienced menopause and gained weight, shows an appreciable decrease in breast density.

Consequently, three-dimensional, volumetric, quantitative automated programs are being developed; however, none are currently widely used in the United States in the general mammographic screening population (11–13).

As breast density legislation continues to be implemented, it is important to stress to providers and patients that a woman’s breast density is not a fixed entity but may vary over time because of interpreter variability and physiologic changes that may affect breast density and breast positioning. For example, breast density decreases with an increasing body mass index and decreases with age (paradoxically, two factors that otherwise increase breast cancer risk). Other factors such as tamoxifen therapy, hormone replacement therapy, weight changes, and changes in dietary intake may also affect tissue density (Fig 2) (14). These changes may cause a woman to have mammographic findings that are interpreted as dense one year and nondense the subsequent year, a situation that, without proper education of the patient and referring clinician, may provoke confusion (Fig 3). Because study results remain unclear regarding how these changes in tissue density may affect a woman’s cancer risk, the radiologist plays a vital...
role in educating clinicians and patients regarding the inherent uncertainty and lack of objectivity of the current breast density assessments used clinically in the United States.

Breast Density and the Risk for Breast Cancer
Breast density affects mammographic screening in two primary ways: breast density has a masking effect on underlying cancers and also is an independent risk factor for breast cancer.

Masking Effect
It is well established that mammographic sensitivity decreases with increasing density, largely as a function of the superimposition of overlapping radiopaque dense breast tissue on an underlying cancer when the three-dimensional breast is imaged in a two-dimensional plane. The language of the BI-RADS lexicon accounts for this by wording the dense tissue patterns as “the breasts are heterogeneously dense, which may obscure small masses” and “the breasts are extremely dense, which lowers the sensitivity of mammography” (5). The decrease in mammographic sensitivity with increasing tissue density was established by using film-screen mammography. In two separate BCSC reports of film-screen mammography, mammographic sensitivity decreased from a level of 85.7%–88.8% in patients with almost entirely fatty tissue to 62.2%–68.1% in patients with extremely dense breast tissue (15,16).

The masking effect of breast density leads to an increased percentage of interval cancers (cancers that manifest within 1 year of a normal mammogram) in women with dense breasts. In one meta-analysis of three Canadian studies of breast density, it was found that in patients with more than 75% tissue density, the overall odds ratio of breast cancer was 4.74 when compared with women with less than 10% tissue density. However, in women who were diagnosed with interval cancers, the odds ratio of the risk for breast cancer in women with greater than 75% dense tissue skyrocketed to 17.81 (17). For cancers that were detected more than 12 months after a negative mammogram, the odds ratio of the risk for being diagnosed with an interval cancer in women with dense breasts when compared with women with fatty breasts is a direct demonstration of the masking effect of breast density on the detection of underlying radiopaque malignancies concealed by radiopaque normal dense tissue.

The results of a meta-analysis by McCormack and dos Santos (18) confirm the masking effect of breast density. It has been suggested that because dense breasts may make a woman more likely to be diagnosed with an interval cancer, women with dense breasts might benefit from shorter screening intervals (18). In a recently published retrospective review of 335 breast cancers detected at screening US, 263 (78%) were occult at mammographic review because they were obscured by overlapping dense breast tissue, a finding that confirms the masking effect of dense tissue on breast cancer detection (19).

Density as an Independent Risk Factor
Breast density itself is an independent risk factor for breast cancer, although the degree to which it is an independent risk factor is debated among experts and is highly controversial. Breast density as a risk factor seems intuitive because
density refers to the **amount of epithelial** and stromal elements of the breast, and breast cancers most commonly arise in epithelial cells. A greater amount of epithelial tissue in the breast indicates a greater chance that cancer may arise in one of the epithelial cells. Some researchers propose that breast density may increase the risk for breast cancer by up to **six times**, and breast density is often reported to cause a **fourfold** increase in the risk for breast cancer in women with dense breasts (17,18,20). In a meta-analysis of studies that evaluated breast density as an independent risk factor for breast cancer, the relative risk associated with dense breasts was 2.92 for breasts that were 50%–74% dense and 4.64 for breasts that were 75% or more dense (18). A linear increasing trend in the relative risk for breast cancer with respect to increasing tissue density has been noted when density is measured quantitatively (18). In a summary of studies that evaluated breast cancer risk with respect to quantitatively measured tissue density, the odds ratio of the risk for breast cancer ranged from 3.6 to 6.0 (17).

The **relative risk of breast density is much smaller than** that of other major risk factors for breast cancer, such as **age**, **family history**, **reproductive history**, and **genetic mutations**. However, because mammographically dense breasts are relatively common (approximately 50% of the screening population), some authors have proposed that the risk factor of density alone contributes far more cancer risk to the population than other much stronger but less common risk factors, such as a significant family history or known deleterious genetic mutations such as **BRCA** mutations (17,18).

Many of the studies of breast density and the risk for breast cancer have not used the BI-RADS density classification but have used either a percentage classification or the Wolfe classification instead. Use of the BI-RADS classification has been shown to result in a similar but milder association of risk with respect to breast density (18). In one study of the Vermont population from the BCSC registry that used the BI-RADS classifications of breast density, the relative risk for being diagnosed with breast cancer in women with **extremely dense breasts** was 4.6 (95% confidence interval: 1.7–12.6) in premenopausal women and 3.9 (95% confidence interval: 2.6–5.8) in postmenopausal women (21).

However, the relative risks reported in these studies have been calculated for the population of women with dense breasts when compared with the small population of women with breasts that are almost entirely fat. Because fewer than 10% of women actually have either extremely dense breasts or almost entirely fatty breasts, it may mislead clinicians and patients and cause needless anxiety to compare the risk for breast cancer in women with the highest breast density to that in women with the lowest breast density. Instead, given that nearly half of the population has dense breasts, it makes more sense to compare the risk for cancer in women with dense breasts to the risk in the average patient (who will have a tissue density approximately halfway between the two middle categories of scattered areas of fibroglandular density and heterogeneously dense breasts). When such a comparison is made, the relative risk for cancer in women with **heterogeneously dense breasts** compared with the average woman is approximately 1.2, and the relative risk for cancer in women with **extremely dense breasts** compared with the average woman is approximately 2.1 (22).

Some researchers have argued that the majority of the association of breast cancer with dense breasts is attributable to the masking effect of dense tissue. However, the association of breast cancer with increasing mammographic density does not decrease over time, even up to 10 years after screening, which suggests that the association is due to more than just the masking of interval cancers by overlapping normal dense tissue at the time of initial mammography and is instead a real effect that lasts for at least a decade (20,23,24). Furthermore, the findings of a randomized case-control study conducted as part of the International Breast Cancer Intervention Study (IBIS) suggest that women whose breast tissue density decreased while undergoing tamoxifen therapy had a greater reduction in breast cancer risk than women whose breast density did not decrease to the same degree (25). Similarly, in postmenopausal women undergoing adjuvant tamoxifen therapy after a diagnosis of breast cancer, a decrease in mammographic density has been associated with a survival advantage compared with women who did not have a breast density change (26).

Therefore, although a masking effect is definitely present in women with breast cancer, there is at least some element of breast density as a risk factor for breast cancer that is independent of other risk factors. In addition, although breast density measurements are inherently inaccurate (especially in the majority of studies that have reported on density [10]), breast density remains an independent risk factor to at least a small degree.

**Current State of Legislation Regarding Breast Density Notification**

Stemming from grassroots organizations and patient advocacy groups, breast density legisla-
tion was first passed in Connecticut in 2009. The Connecticut law mandates notification of breast density to patients and suggests that patients with dense breasts may benefit from supplemental screening. The law requires the following:

Each mammography report provided to a patient shall include information about breast density, based on the Breast Imaging Reporting and Data System established by the American College of Radiology. Where applicable, such report shall include the following notice: “If your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician’s office and you should contact your physician if you have any questions or concerns about this report” (27).

At the time of this article, 19 states (38%) have passed laws that require some sort of breast density notification to patients after screening mammography, and additional states are working on legislation (Table 1). Only a small fraction of these states also have legislation that mandates insurance coverage for supplemental screenings that are indicated by the results of screening mammography (Table 1). The lack of insurance coverage for supplemental screening in most states may lead to an inappropriate stratification of health care according to income because many of the tests requested will not be covered by insurance.

The various state laws are inconsistent in their wording and mandates, and there is now a push for standard federal legislation. Federal legislation requiring breast density notification was first introduced in 2011, was most recently reintroduced in the fall of 2013 (led by Congresswoman Rosa DeLauro of Connecticut), and is currently referred to the U.S. House of Representatives Subcommittee on Health (28). The purpose of the legislation is to create an amendment to the Public Health Service Act (commonly known as the Mammography Quality Standards Act of 1992 [MQSA]) that would require notification to patients regarding their breast density and informing them that they may benefit from supplemental screening tests. In addition, the U.S. Food and Drug Administration has considered adding a breast density reporting amendment to the MQSA.
Evidence for Supplemental Screening

Digital Mammography

Most of the evidence suggesting that breast density is a risk factor for breast cancer stems from studies that were performed using film-screen mammography. Digital mammography, likely as a function of its improved contrast resolution, has been shown in the Digital Mammographic Imaging Screening Trial (DMIST) to have an improved sensitivity and accuracy for cancer detection relative to those of film-screen mammography in women with dense breasts (29). Similarly, data from the BCSC have demonstrated that digital mammography has an improved sensitivity for cancer detection in women with dense breasts compared with that of film-screen mammography (83.6% vs 68.1%, \( P = .051 \)) and approaches the sensitivity of film-screen mammography in women with fatty breasts (83.6% vs 85.7%) (16). The trend for increased sensitivity of digital mammography compared with film-screen mammography is especially true in younger women aged 40–49 years with extremely dense breasts (86.8% sensitivity of digital mammography vs 62.3% sensitivity of film-screen mammography), whereas for older women aged 65–79 years with fatty breasts, digital mammography has a similar sensitivity to that of film-screen mammography (83.7% vs 89.1%) (16).

In a recent modeling study, Stout et al (30) proposed that tailored mammography performed on the basis of breast density is effective in reducing mortality from breast cancer; however, it is expensive and may not be cost effective, especially in light of the increased false-positive results. This study used models and focused on both annual and biennial screening, but the results demonstrate that the true clinical benefit of switching to digital mammography remains unclear. Nevertheless, over 90% of mammography facilities in the United States now use digital mammography (31).

Further, data suggest that the masking effect of dense breasts on cancer detection is greatly reduced with the use of digital mammography versus film-screen mammography. Kerliwoske et al (16) note that the use of digital mammography significantly improves the detection of hormone-negative breast cancers, which usually are higher grade and have a poorer prognosis than estrogen receptor–positive breast cancers (78.5% vs 65.8% sensitivity of digital vs film-screen mammography, respectively, \( P = .016 \), in women aged 40–79 years; 95.2% vs 54.9% sensitivity, \( P = .007 \), in women aged 40–49 years). These are the types of cancers that often manifest as interval cancers and likely make up some proportion of the cancers masked at film-screen mammographic screening in women with dense breasts (32,33). Unfortunately, many of the clinical studies that have evaluated supplemental screening methods, including the majority of studies of whole-breast screening US, have primarily used film-screen rather than digital mammography for their analysis, which may falsely elevate the incremental cancer detection rate for supplemental screening modalities. It remains to be seen, with large amounts of evidence, what the incremental cancer detection rate for many of the supplemental screening tests would be if repeated with digital mammography in the population of women with dense breasts. In addition, many of the investigations of supplemental screening modalities have grouped women with heterogeneously dense and extremely dense breasts together in their investigation, and it remains to be seen what differential effect there may be in pursuing supplemental screening in the minority of patients with extremely dense breasts only.

Digital Breast Tomosynthesis

DBT is rapidly being implemented in the screening and diagnostic settings for breast cancer since its approval by the U.S. Food and Drug Administration in 2011. DBT uses a series of low-dose mammograms acquired over an arc to reconstruct the breast in thin tissue planes that reduce the superimposition of overlapping radiopaque dense breast tissue (34). Large-scale studies of screening DBT in the real-world clinical setting (two international studies [35,36] and three U.S. studies [37–39]) have repeatedly shown an increase in cancer detection and a significant reduction in recall rates compared with the use of traditional two-dimensional digital mammography at first examination, likely as a direct result of a decreased masking effect.

However, there are limited data regarding the effects of DBT related to breast density. Initial data from reader studies conducted before the clinical implementation of DBT suggest that DBT improves the accuracy of interpretation in patients with fatty or dense breasts; however, the gain in the area under the receiver operating curve is two to three times higher in women with dense breasts than in those with fatty breasts with use of combined DBT and digital mammography compared with use of two-dimensional digital mammography alone (40). The prospective clinical STORM trial by Ciatto et al (35) noted that the incremental cancer detection rate beyond that of two-dimensional digital mammography in women screened with combined DBT and mammography was similar for dense and nondense breasts (2.5 per 1000 vs 2.8 per 1000, respectively).
The two international studies of screening DBT may not be generalizable to the U.S population because the countries studied have an inherently lower callback rate and screen biennially in a slightly older patient population than in the United States. Evaluation of the true impact of DBT is limited because all of the researchers published their data shortly after the initial implementation of DBT, so there is no long-term follow-up, no ability to calculate interval cancers in the studies published, and no data from incidence screens rather than prevalence screens. However, the results of these initial studies remain quite promising. Further, although these studies implemented DBT combined with two-dimensional mammography, therefore increasing the radiation dose relative to that of standard two-dimensional mammography, synthesized mammograms reconstructed from DBT data are now available. Early studies show that the use of DBT with a synthesized mammogram is similar to the use of DBT with an actual acquired mammogram and involves nearly the same radiation dose as mammography alone (41,42).

The question remains whether the improved rate of cancer detection and decreased rate of false-positive results with DBT will help equalize the decreased sensitivity of mammography secondary to tissue density and perhaps obviate any additional screening tests in women with dense breasts and otherwise average or intermediate risk (Table 2). However, current data remain insufficient to recommend DBT screening. The National Comprehensive Cancer Network (NCCN) guidelines acknowledge that “early studies show promise” for DBT but state that there is “insufficient evidence” to date to recommend its routine use for screening or diagnosis (44). Furthermore, the incremental benefit of supplemental screening with whole-breast US or MR imaging beyond that of screening DBT remains unknown, with large prospective studies yet to be published.

### Whole-Breast US

No randomized controlled trials have evaluated the use of supplemental screening with whole-breast US for breast cancer detection in women with mammographically dense breasts. A recent, comprehensive, evidence-based 2013 review conducted by the ICER (43) tabulated the results of 15 large studies of whole-breast US screening in women with mammographically dense breasts, although many of these studies were retrospective or used film-screen mammography rather than digital mammography (Table 3). In addition, many of the studies were performed in countries with different screening guidelines than those used in the United States, and, therefore, the conclusions may not be applicable to a population screened with annual mammography. Even with the large variation in study design, including how breast density was defined in each study (many of the studies regarded women with scattered fibroglandular tissue density as having dense breasts), there is a consistent incremental cancer detection rate with whole-breast US beyond that of mammography; however this comes with the cost of a high false-positive result rate. The PPV, is reported to be as low as 3.2% for whole-breast US. The ICER report surmises from the results of these studies, along with those of the ACRIN 6666 study (60), that an appropriate estimate for the incremental cancer detection rate with supplemental screening whole-breast US is two to three per 1000, although the PPV, is markedly low (6%–7%) (Table 2). The report also estimates that the

### Table 2: ICER Summary Estimates of the Effects of Supplemental Screening on Incremental Breast Cancer Detection Rates

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Incremental Cancer Detection Rate (per 1000 Patients) beyond Mammography</th>
<th>PPV, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital mammography</td>
<td>4.2*</td>
<td>24</td>
</tr>
<tr>
<td>DBT†</td>
<td>1–3</td>
<td>25</td>
</tr>
<tr>
<td>Whole-breast US</td>
<td>2–3</td>
<td>6–7</td>
</tr>
<tr>
<td>MR imaging</td>
<td>8</td>
<td>22–48</td>
</tr>
</tbody>
</table>

Source.—Reference 43.

Note.—ICER = Institute for Clinical and Economic Review, PPV, = positive predictive value for malignancy of biopsied lesions detected at screening.

*For digital mammography, this is the screening examination baseline cancer detection rate and not the incremental cancer detection rate.

†The ICER review evaluated DBT as a supplemental screening modality rather than as a replacement for mammography. Because most sites that implement DBT for screening use it as a primary (not supplemental) screening modality, the true effect is unknown.
Table 3: Incremental Cancer Detection Rate and PPV of Whole-Breast US in Asymptomatic Women with Dense Breasts in 15 Large Screening Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>PPV, (%)</th>
<th>Incremental Cancer Detection Rate (per 1000)</th>
<th>No. of Women</th>
<th>Comments</th>
<th>Country and Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parris et al* (45)</td>
<td>5.5</td>
<td>1.8</td>
<td>5519</td>
<td>. . .</td>
<td>U.S., 2013</td>
</tr>
<tr>
<td>Hooley et al* (47)</td>
<td>6.5</td>
<td>3.2</td>
<td>935</td>
<td>20% of patients were placed in short-term follow-up; 9% of those opted for biopsy instead</td>
<td>U.S., 2012</td>
</tr>
<tr>
<td>Kolb et al (48)</td>
<td>10.3</td>
<td>2.5</td>
<td>4897; total of 12,193 examinations</td>
<td>Included breasts with scattered fibroglandular tissue</td>
<td>U.S., 2012</td>
</tr>
<tr>
<td>Kaplan (49)</td>
<td>11.8</td>
<td>2.7</td>
<td>1862</td>
<td>10.2% underwent follow-up imaging or biopsy</td>
<td>U.S., 2002</td>
</tr>
<tr>
<td>Girardi et al (50)</td>
<td>Unable to be calculated from data given</td>
<td>2.2</td>
<td>9960</td>
<td>Incremental cancer detection rate did not differ significantly for dense vs fatty breasts or breasts with scattered fibroglandular tissue</td>
<td>Italy, 2013</td>
</tr>
<tr>
<td>Corsetti et al (52)</td>
<td>7.5</td>
<td>4.4</td>
<td>3356; total of 7224 examinations</td>
<td>. . .</td>
<td>Italy, 2011</td>
</tr>
<tr>
<td>Corsetti et al (53)</td>
<td>5.7</td>
<td>4.0</td>
<td>9157</td>
<td>24% of cancers were detected at mammography in a retrospective blind review of the quality of the initial mammographic interpretations</td>
<td>Italy, 2008</td>
</tr>
<tr>
<td>De Felice et al (54)</td>
<td>6.4</td>
<td>6.8</td>
<td>1754</td>
<td>Demonstrated increased costs</td>
<td>Italy, 2007</td>
</tr>
<tr>
<td>Brancato et al (55)</td>
<td>3.2</td>
<td>0.4</td>
<td>5227</td>
<td>Demonstrated increased costs</td>
<td>Italy, 2007</td>
</tr>
<tr>
<td>Leconte et al (56)</td>
<td>Unable to be calculated from data given</td>
<td>3.8</td>
<td>4236 (included diagnostic examinations but excluded palpable lesions)</td>
<td>Included breasts with scattered fibroglandular tissue</td>
<td>Belgium, 2003</td>
</tr>
<tr>
<td>Crystal et al (57)</td>
<td>18.4</td>
<td>4.6 (in women with dense breasts and normal risk, the cancer detection rate fell to 2.7)</td>
<td>1517</td>
<td>Included breasts with scattered fibroglandular tissue</td>
<td>Israel, 2003</td>
</tr>
<tr>
<td>Buchberger et al (58)</td>
<td>8.8</td>
<td>3.9</td>
<td>8103</td>
<td>Included breasts with scattered fibroglandular tissue</td>
<td>Austria, 2000</td>
</tr>
<tr>
<td>Maestro et al (59)</td>
<td>13.3</td>
<td>5.7</td>
<td>350</td>
<td>14% of patients had an incidentally detected solid mass</td>
<td>France, 1998</td>
</tr>
</tbody>
</table>

Source.—Reference 43.

*Published studies of the Connecticut experience with supplemental screening whole-breast US after implementation of breast density notification legislation.
recall rate is likely at least twice as high as that for mammography, and the biopsy rate is likely about three times higher (43).

The most relevant data on the benefit of whole-breast US comes from the large, prospective, multi-institutional ACRIN 6666 trial, in which the incremental cancer detection rate above that of mammography was three to four per 1000. However, this benefit comes with a high rate of false-positive results and a low PPV, (6.8%) (60). In addition, the ACRIN 6666 population was higher risk because the inclusion criteria mandated that women have breast density in at least one quadrant and also have an additional high-risk marker (eg, prior personal history, strong family history, known BRCA gene mutation, or prior biopsy demonstrating lobular carcinoma in situ or atypical ductal hyperplasia); therefore, the cancer detection rate is likely elevated in this population given a likely higher prevalence of disease relative to the population of women with dense breasts alone.

Real-world implementation of whole-breast US supplemental screening in the population of women with dense breasts and a negative mammogram has been documented in three Connecticut studies conducted after the implementation of breast density legislation in 2009 (45–47). Hooley et al (47) demonstrated the early feasibility of implementing a whole-breast US screening program and successfully used technologists trained in whole-breast US rather than physicians to perform the examination, with an incremental cancer detection rate and a PPV, similar to those in the ACRIN 6666 study and other published studies. However, in the subset of patients with dense breasts who were otherwise low risk, the incremental cancer detection rate was approximately half that reported in other studies. In addition, approximately 25% of women who underwent screening whole-breast US had a BI-RADS diagnosis of 3, 4, or 5 that necessitated follow-up or biopsy. Interestingly, the researchers estimate that only 16% of their eligible population of women with dense breasts and a negative mammogram underwent screening whole-breast US. Furthermore, they note that whether patients underwent whole-breast US was dependent on the referring physician, with some clinicians referring a majority of their eligible patients and others referring no patients. This discrepancy highlights the need for an improved understanding of the issues related to breast density on the part of referring clinicians and patients and the need for radiologists to lead the way in educating referring physicians and patients. In the Hooley et al (47) study, only 40% of patients returned for repeat annual whole-breast US, but 80% returned for annual mammography.

In another study that evaluated the implementation of whole-breast US after the Connecticut legislation, the incremental cancer detection rate was 1.8 per 1000, or approximately half that expected on the basis of the ACRIN 6666 results and the ICER estimate (45). The authors of this study hypothesize that perhaps their detection rate was low secondary to operator error (they used newly trained technologists), although it should be emphasized that the majority of their population were of average risk, and therefore the cancer prevalence would be expected to be lower. Their estimates may closer approximate the effect of screening whole-breast US in women with dense breasts who are otherwise low risk.

The issue of the feasibility of implementing screening whole-breast US is relevant if it is to be considered for women with dense breasts and low or intermediate risk (about 50% of the screening mammography population). In the ACRIN 6666 study, the average time of handheld screening US was 19 minutes (60). The examination is inherently operator dependent. Given these limitations, much interest is now being turned toward automated whole-breast US. This technology, approved by the U.S. Food and Drug Administration in 2012, reduces operator error because imaging is performed automatically after the technologist places the patient’s breast in light compression, and it has a faster interpretation time (7–10 minutes) (61). The actual data on automated whole-breast US remain limited to date. Three studies have been published (61–63); however, the findings are not generalizable to the question of the effect in women with dense breasts when used as a supplemental screening tool after a negative mammogram. Many high-risk patients were included in the studies, some of the comparison mammograms were obtained with film-screen instead of digital mammography, and, in one of the studies, the majority of patients included did not have dense breasts. However, if the results of automated whole-breast US mimic those of traditional whole-breast US, the examination is likely to be more cost effective and more readily implementable for a larger volume of patients than traditional whole-breast US.

**MR Imaging**

No studies have evaluated the benefit of adjunctive screening MR imaging in women with dense breasts and negative mammograms. Researchers with the Dutch DENSE trial are currently enrolling patients and hope to better define the role of screening breast MR imaging in women aged 50–75 years with a negative mammogram and extremely dense breast tissue. The researchers plan to randomize 7237 women to receive supplemental
screening MR imaging and 28,948 women to undergo routine care without MR imaging (64). Although the results of this study will improve our understanding of the effect of supplemental screening MR imaging in women with extremely dense breasts, the expected completion date is not until December 2019, and the study will screen only biennially; therefore, the findings will not be directly translatable to annual screening in the United States. In addition, the question of whether supplemental screening MR imaging is beneficial in women with heterogeneously dense breasts as the highest risk factor will remain unanswered.

The current American Cancer Society (ACS) guidelines suggest that screening MR imaging is neither recommended for or against in women with the risk factor of dense breasts (65). It has been widely established that in certain high-risk women (higher risk than simply having dense breasts), MR imaging has an increased sensitivity for cancer detection and will depict more cancers than mammography alone (65–69). In two large summary studies that evaluated the incremental benefit of screening MR imaging compared with mammography in high-risk women (a meta-analysis of 11 studies by Warner et al [70] and the recent comprehensive ICER review that identified a different but overlapping group of 11 large prospective studies [43]), the sensitivity of MR imaging for cancer detection was consistently increased; however, it was accompanied by a decrease in specificity and a high false-positive rate. The incremental cancer detection rate was 8–36 per 1000, which is notably higher than the standard three to six per 1000 reported for mammography (43). Although the recall rate of MR imaging is approximately four times higher than that of mammography, the PPV of MR imaging is at least as high, if not higher, than that of mammography (22%–48% versus 24%, respectively) (Table 2) (43). In the ACRIN 6666 study, Berg et al (71) showed that use of MR imaging plus mammography will have a higher cancer yield and a lower false-positive rate than use of whole-breast US plus mammography, thus confirming that it is preferable to perform MR imaging rather than whole-breast US in women with sufficient risk. However, MR imaging is costly, requires intravenous gadolinium contrast agent administration, has a risk for contrast agent reactions, and is not well tolerated by all patients (72).

Because no studies have evaluated the use of screening MR imaging in average- or low-risk women, the true value of supplemental screening with breast MR imaging for women with dense breasts remains unclear, and currently no evidence supports its use.

**Expert Guidelines on Supplemental Screening**

Supplemental screening is meant as an adjunct to mammography and should never serve as a replacement for annual mammography. Screening mammography remains the only imaging test that has been shown in randomized controlled trials to reduce the mortality from breast cancer (73,74). In addition, neither US nor MR imaging screening will depict all cancers that are seen at mammography (71,75).

The NCCN and expert public health review panels such as the California Technology Assessment Forum (CTAF) and the New England Comparative Effectiveness Public Advisory Council (CEPAC) agree that there is sufficient evidence to suggest that digital mammography is preferred over film-screen mammography in women with dense breasts and will help reduce the masking effect. There are no current guidelines that recommend routine screening with DBT, although many societies and panels note that the results of early studies look promising. It is likely that as more studies of DBT emerge, a similar reduction in the masking effect will occur with DBT screening.

In women with a sufficiently high risk (lifetime risk >20% or 5-year risk >1.7%), experts agree regarding the use of supplemental screening independent of mammographic breast density. Multiple national and international societies, including the ACS, the NCCN, the American College of Radiology/Society of Breast Imaging (ACR/SBI), the American Society of Breast Surgeons, and the European Society of Breast Imaging, recommend annual screening with breast MR imaging as an adjunct to annual screening mammography in women who are high risk (63,44,76,77). As noted in the ACRIN 6666 data (71), there is no additional value of whole-breast US screening in women who can undergo mammography and breast MR imaging. If a woman cannot undergo MR imaging (secondary to a contrast agent allergy, a pacemaker, or lack of access), then adjunct screening whole-breast US with annual mammography is indicated per the ACR/SBI practice guidelines.

Supplemental screening in intermediate-risk women is more of a gray zone, regardless of breast density. The ACR/SBI appropriateness criteria state that MR imaging of intermediate-risk women (ie, women with a personal history of breast cancer, lobular neoplasia, atypical ductal hyperplasia, or a 15%–20% lifetime risk for breast cancer) is “usually appropriate” and is rated as 7 out of 9 on the appropriateness scale (76). Screening whole-breast US is listed as 5 out of 9 and “may be appropriate.” If having dense breasts in the setting of other risk factors would elevate a patient’s risk
to the 15%–20% level, then supplemental screening could be considered, after discussion with the clinician and patient regarding the risks of false-positive results incumbent in this group. According to the ACR/SBI guidelines, “supplemental screening with US for women with intermediate risk and dense breasts is an option to increase cancer detection” (76).

Supplemental screening of women with dense breasts who are of average or low risk is not currently recommended by most major medical societies or evidence-based review studies, including a large comprehensive Cochrane review, the CTAF review panel, the CEPAC review panel, the U. S. Preventive Services Task Force (US-PSTF), the NCCN, the American College of Obstetricians and Gynecologists (ACOG), the ACR/SBI, and the ACS (44,78–81). The NCCN states that “there is insufficient evidence to support routine supplemental screening in women with dense breasts and no other risk factors” (44).

The ACOG recommends annual screening mammography and does not recommend the routine use of alternative or adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional risk factors” (78). A 2013 Cochrane review concludes that there is no evidence to support the routine use of adjunct whole-breast US in women at average risk for breast cancer and that, in women with dense breasts, the evidence supporting its use is “limited and has to be interpreted cautiously” (79). A website for the public developed by the California Breast Density Information Group includes the following information:

There is no formal recommendation from the radiology community at this point regarding screening ultrasound. Some radiologists are opposed to it, while some believe that it has a role. The results of screening breast ultrasound may be more favorable in centers with a dedicated program. Whichever supplemental screening test is being considered, it is important to keep in mind that for patients who are not high risk, the a priori probability of breast cancer is low. Therefore, the benefit of additional screening is diminished, whereas the potential harms remain the same (82).

The Information

Age and Evidence-based Medicine

In the Information Age, we are moving to a world of increased patient knowledge as patients take more control of their health (83). Patients desire expanded information regarding their health options and are more engaged in decision making. Breast density legislation is due, in large part, to patient-driven advocacy and the desire to seek more information. For radiologists, this brings a wonderful opportunity to enhance patient health and increase the number of beneficial discussions with the patient and her health care provider. The benefit of increased information will be realized, however, only if a patient is guided appropriately and understands the risks, benefits, and supporting medical evidence (or lack of evidence) regarding her options. In a recent article, Ho et al (84) argue that “advocacy may harm rather than help” and remind us that “legislating medical practice is a bold step, and even those who feel that it is occasionally warranted must hold themselves to a rational guiding principle.”

The power of the breast density advocacy movement is admirable and may in many ways prove beneficial, but in the interest of primum non nocere, radiologists must take responsibility for educating themselves and their communities regarding breast density, the benefits and limitations of mammographic screening, and the evidence (or lack thereof) for supplemental screening in various subgroups. A recent editorial notes, “Research suggests that letters [explaining breast density] alone are insufficient, and there is no guarantee that simply adding breast density notification language to result letters will enhance a woman’s understanding and empower her to choose a course of action that is sensitive to her personal preferences” (85). The importance of the radiologist in reinforcing evidence-based best practices and counseling and educating patients, clinicians, and, in some cases, the media or legislators regarding these best practices cannot be overemphasized.

Conclusion

Breast density legislation is rapidly being implemented around the United States and is affecting patient decision making. Although breast density is known to decrease the sensitivity of mammography, especially film-screen mammography, the evidence supporting supplemental screening tests (eg, whole-breast US or MR imaging) in women with dense breasts as a sole risk factor remains markedly limited. As breast density legislation becomes more widespread and perhaps national, it is critical that radiologists continue to practice evidence-based medicine and ensure that the benefits of any additional testing offered outweigh the risks. Further, breast imagers must take the lead in advancing current knowledge with evidence-based studies that help guide decision making in tailored screening and in establishing evidence-based standards. Radiologists must take responsibility for educating referring clinicians as well as patients in order for women to continue to receive the most benefit from breast cancer screening.
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References
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