Women are becoming more aware of breast density, its implications on their risk for developing breast cancer, and its influence on detecting cancer.

Imaging Management of Breast Density, a Controversial Risk Factor for Breast Cancer

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Background: Breast density is well recognized as an independent risk factor for the development of breast cancer. However, the magnitude of risk is controversial. As the public becomes increasingly aware of breast density as a risk factor, legislation and notification laws in relation to breast density have become common throughout the United States. Awareness of breast density as a risk factor for breast cancer presents new challenges for the clinician in the approach to the management and screening of women with dense breasts.

Methods: The evidence and controversy surrounding breast density as a risk factor for the development of breast cancer are discussed. Common supplemental screening modalities for breast cancer are also discussed, including tomosynthesis, ultrasonography, and magnetic resonance imaging. A management strategy for screening women with dense breasts is also presented.

Results: The American College of Radiology recognizes breast density as a controversial risk factor for breast cancer, whereas the American Congress of Obstetricians and Gynecologists recognizes breast density as a modest risk factor. Neither organization recommends the routine use of supplemental screening in women with dense breasts without considering additional patient-related risk factors.

Conclusions: Breast density is a poorly understood and controversial risk factor for the development of breast cancer. Mammography is a screening modality proven to reduce breast cancer–related mortality rates and is the single most appropriate tool for population-based screening. Use of supplemental screening modalities should be tailored to individual risk assessment.

Introduction

Breast density is an independent risk factor for the development of breast cancer, although the magnitude of this risk is controversial. Breast density is a visual assessment of the ratio of parenchyma to fat as seen on mammography. Fibroglandular tissue is radiodense or white on mammography, whereas fat is radiolucent or black. Four categories of breast density have been defined by the criteria of the American College of Radiology’s (ACR) Breast Imaging Reporting and Data System, 5th ed. (BI-RADS; Fig 1):

- Almost entirely fatty
- Scattered fibroglandular densities
- Heterogeneously dense
- Extremely dense

The sensitivity of mammography for noncalcified lesions decreases as breast density increases due to a “masking” of the lesion by overlying normal tissue. Approximately 50% of women have breast tissue clas-
sified as either heterogeneously dense or extremely dense, thus reducing the sensitivity rate of mammography. However, almost entirely fatty breasts may have coalescent areas of dense tissue that can obscure lesions. Therefore, the BI-RADS criteria allow for the overall assessment of breast density to convey the likelihood of having an obscured lesion or “masking” effect. Dense tissue is most often seen in the breasts of younger premenopausal women, but it has also been observed in older postmenopausal women.

Reduced sensitivity rates of mammography due to masking alone do not explain the increased risk of breast cancer associated with increased breast density. First described in 1976, Wolfe identified breast density as a risk factor for breast cancer, qualitatively evaluating the mammographic appearance of the breast. A direct relationship was reported between progressively dense breast tissue and increasing risk of breast cancer. McCormack et al performed a meta-analysis of 42 studies and found that increased breast density was a strong risk factor for breast cancer independent of other known risk factors but was confounded by age and body mass index. The risk of breast malignancy associated with dense breasts has been reported to be 4- to 6-fold, making it second only to age and BRCA carrier status for highest risk. However, critics argue that this assessment of risk is an overestimation. The studies compared extremes (ie, dense breasts to fatty breasts) rather than comparing dense breasts to average-density breasts (between scattered fibroglandular and heterogeneously dense tissue). When the risk for breast cancer is expressed relative to average breast density, the risk decreases to 1.2 to 2.1 times higher than the average for heterogeneously dense or extremely dense breasts, respectively. Thus, breast density may more accurately represent a modest risk factor similar to that for a woman with 1 first-degree relative with unilateral postmenopausal breast cancer.

Awareness is increasing among public and medical communities alike regarding breast density as a risk factor for breast cancer as well as the limitations of mammography in women with dense breasts. Thus, in 2009, Connecticut became the first state to mandate patient and referring physician notification of dense breasts, as determined by the interpreting radiologist. Since then, 26 states have enacted similar notification laws, and legislation has been introduced in several other states. Controversy surrounds these notification laws, particularly with regard to how notification relates to additional imaging and reimbursement.

Price et al identified the efficacy, benefits, and
harms of supplemental screening tests as key issues. Although notification increases patient awareness, it also increases patient anxiety. Conversely, notification may give a false sense of security to women with fatty breasts who receive a negative finding on mammography. Critics also raise concerns that notification will increase demand for additional screening beyond mammography, which could result in additional false-positive findings and increased health care costs. Five states have mandatory insurance coverage for supplemental screening, suggesting that disparities could develop between women who can afford additional screening and those who cannot. In a study performed in New Jersey after the implementation of legislation directed at notifying women of their breast density — which also mandated health insurance coverage — an increase was seen in patients utilizing screening ultrasonography, thus resulting in an expansion of the ultrasonography department at the New Jersey institution as well as increasing the direct cost for health care insurers of approximately $4.9 million to $9.8 million for a given month.

Thus, as notification laws gain momentum, clinicians may be faced with new challenges in their approach to breast cancer screening in women with dense breasts. In this review, we address the available types of supplemental screening studies, the risks and benefits of each modality, and suggest an imaging approach to managing the imaging of dense breasts.

**Screening Mammography and Tomosynthesis**

Mammography has long been the mainstay of detecting breast cancer and is the only screening test proven to reduce breast cancer–related mortality. Early detection by mammography has reduced breast cancer–related mortality by up to 50% — a rate based on several large, randomized controlled trials with 10 to 20 years of follow-up time. The overall sensitivity rate of digital mammography is between 81% and 87% for the detection of breast cancer in women aged 40 to 79 years; the detection rate of cancer via mammography is 4 to 5 per 1,000 people in the average population.

However, mammography is an imperfect screening tool. Although it remains the gold standard for breast cancer screening, awareness is increasing that mammography has reduced sensitivity in certain subpopulations of women. In particular, among women with dense breasts, tissue superimposition can occur to a greater degree, and 50% of cancers will be visible in extremely dense breast tissue. Among women with heterogeneously dense or extremely dense breast parenchyma, full-field digital mammography (FFDM) has been shown to be more sensitive than film-screen mammography. The sensitivity rates of both digital and analog mammography remain low in women with dense breast parenchyma, thus limiting its usefulness in younger women at high risk.

Digital breast tomosynthesis is an emerging technology utilized by many breast imaging centers, both domestically and internationally. Digital breast tomosynthesis was approved in February 2011 as an adjunct screening tool. It is an FFDM system capable of producing standard 2-dimensional (2D) and 3-dimensional (3D) tomosynthesis imaging. Digital breast tomosynthesis can help improve the detection and characterization of lesions by minimizing the influence of tissue overlap in women with nonfatty breasts. To acquire the image, the tube moves in an arc across the breast, and a series of low-dose scans are obtained from different angles. Typically, the imaging is then reconstructed into thin, 1-mm slices that can be scrolled through slice by slice — similar to that seen in computed tomography. Thin-slice imaging allows the clinician to better detect lesions, particularly masses, architectural distortions, and asymmetries (Fig 2). Increased lesion conspicuity is beneficial when imaging dense breast tissue because it can be difficult for the clinician to detect lesions in extremely dense breast tissue.

The addition of tomosynthesis to digital mammography has been shown to reduce recall rates and increase cancer-detection rates in the general population. Several studies have reported a 40% rate increase or more in invasive cancer detection when compared with digital mammography alone and a simultaneous 15% reduction in the rate of false-positive results. Two prospective European studies evaluated the efficacy of FFDM in combination with digital breast tomosynthesis for breast cancer screening. Skaane et al reported a 40% increase in the detection rate of invasive cancers with a simultaneous 15% rate reduction in false-positive results in 12,621 screening examinations when using FFDM in combination with digital breast tomosynthesis compared with FFDM alone. In an analysis of 7,292 screening examinations, Ciatto et al demonstrated an increased cancer-detection rate from 5.3 to 8.1 cancers per 1,000 women screened, with a simultaneous 17% reduction in recall rate. Two single-site observational studies performed by Rose et al and Haas et al also demonstrated statistically significant reductions in recall rates of 37% and 30%, respectively, although both groups demonstrated an increase in cancer detection, and neither reached statistical significance — possibly due to small sample sizes.

In a retrospective, multisite study evaluating the use of digital breast tomosynthesis in combination with FFDM among 173,663 patients, Friedewald et al demonstrated an increase in the rate of invasive cancer detection from 2.9 to 4.1 per 1,000 cases after add-
ing digital breast tomosynthesis to FFDM. This was a relative increase of 41%.21 Although an increase was also observed in the rate of biopsy among patients screened with FFDM in combination with digital breast tomosynthesis (19.3 vs 18.1 per 1,000 cases for the digital mammography cohort), a concomitant 21% relative increase was seen in positive predictive values for biopsy, thus reflecting the higher yield of malignancy in women undergoing biopsy from the group undergoing FFDM in combination with digital breast tomosynthesis.21 The association with fewer unnecessary tests and biopsies, with a simultaneous increase in cancer-detection rates, would support the potential benefits of tomosynthesis as a tool for screening.21 This would, in theory, be particularly useful as an adjunct to FFDM screening in women with dense breasts by eliminating confounding, overlapping breast tissue, thereby helping to better detect masses and decrease recall rates.

In a study by Lee et al,26 simulation models of breast cancer were utilized. Compared with biennial FFDM alone, the researchers showed that combined biennial FFDM and digital breast tomosynthesis for US women aged 50 to 74 years with dense breasts would avert 1 additional breast cancer–related death per 2,000 women screened as well as 405 false-positive findings on screening examinations per 1,000 women.26 They concluded that adding tomosynthesis to biennial FFDM for women aged 50 to 74 years with dense breasts was likely to improve health outcomes at a reasonable cost.26

Thus, the evidence supports the finding that digital breast tomosynthesis improves detection rates of breast cancer with both increased sensitivity and specificity. However, its potential drawbacks include increased interpretation time and higher doses of radiation. Thus, further studies are needed to demonstrate whether screening with digital breast tomosynthesis in combination with FFDM results in a greater decrease in breast cancer–related mortality rates compared with FFDM alone.

**Ultrasonography**

The reduced sensitivity rate of mammography in women with dense breasts prompted the search for a widely available, reproducible, and cost-effective adjunct screening tool. Ultrasonography offers an affordable option for the detection of small masses without additional ionizing radiation or intravenous contrast. Robust support for ultrasonography as a supplementary imaging modality for the screening of dense breasts
comes from data collected by Berg et al. Their multicenter, randomized trial included 2,809 women with dense breasts who were at increased risk for breast cancer. The authors compared the performance of 2-view mammography alone to 2-view mammography combined with hand-held survey ultrasonography performed by a radiologist. Mammography in combination with ultrasonography yielded 11.8 breast cancers per 1,000 women compared with 7.6 breast cancers per 1,000 women screened with mammography alone. In a sub-study of the data from Berg et al., 3 annual screening examinations or incident rounds were analyzed from 2,659 eligible women. The data revealed an increase in the rate of cancer detection each year when supplemental ultrasonography was utilized. A total of 32 additional cancers were detected by ultrasonography alone, 30 of which were invasive cancers. The median size of the invasive tumors was 10 mm, and 96% of these had node-negative disease. Overall, the data for the second and third years revealed greater rates of sensitivity for cancer detection when supplemental screening ultrasonography was combined with mammography. Thus, data from these incremental studies suggest a possible benefit in continuing annual screening with supplemental ultrasonography in conjunction with mammography.

A retrospective study was performed by Hool et al. in Connecticut after implementation of the Connecticut Public Act 09-41, which requires that increased breast density be directly communicated to the patient. Hand-held, whole-breast ultrasonography was performed by technologists in 935 women with dense breasts in both the diagnostic and screening populations. An additional 3.2 cancers were detected per 1,000 women screened in the first year of implementation. Similarly, Weigert et al. retrospectively evaluated the utility of ultrasonography for screening among women with dense breasts from 6 Connecticut practices by compiling 8,647 screening ultrasonography sessions during the first year of test availability following the legislation. The addition of hand-held ultrasonography performed by certified technologists resulted in an additional 3.25 cancers detected per 1,000 women with dense breast and normal findings on mammography. The data from these studies support that hand-held ultrasonography — whether performed by a radiologist or trained technologist — could increase the sensitivity rate for detecting breast cancer in women with dense breasts.

A multicenter study by Tagliafico et al. evaluated the cancer-detection rate of tomosynthesis and hand-held screening ultrasonography after a negative finding was obtained on 2D diagnostic mammography among 3,231 self-referred women with heterogeneously dense or extremely dense breasts. Adding tomosynthesis detected an additional 13 breast cancers (12 of which were also identified on ultrasonography, whereas 1 was seen on tomosynthesis alone). Hand-held screening ultrasonography performed by a dedicated breast imaging radiologist detected an additional 23 breast cancers. These cancers were detected with low false-positive recall and biopsy rates. The false-positive recall rates for tomosynthesis and ultrasonography were 1.7% and 2.0%, respectively; the false-positive biopsy rate was 0.7% for both groups. The lower false-positive rate could have contributed to operator experience (ultrasonography was performed by a dedicated breast imaging radiologist) as well as lack of recall for what was likely a benign finding in the clinical practice setting.

Hesitation still exists in implementing routine, supplemental ultrasonography screening despite the data from the aforementioned studies. Using hand-held 2D ultrasonography to detect small masses is labor intensive. Operator variability, shortages of trained personnel, and reductions in radiologist efficiency for image acquisition all contribute to the widespread discouragement for whole-breast surveys. To combat some of these challenges, 3D automated whole-breast ultrasonography has been introduced as an alternative modality. Three-dimensional automated breast ultrasonography received premarket approval by the US Food and Drug Administration (FDA) in September 2012. It is approved for use in combination with mammography for breast cancer screening in women who are asymptomatic who have normal or benign findings on mammography, have had no prior clinical breast intervention, and have dense breast parenchyma (Fig 3). Its automated algorithms give the clinician the ability to obtain reproducible imaging data from volumes of the breast within a short time interval.

Brem et al. conducted a multicenter, prospective study of 15,318 participants with dense breasts, comparing the results of screening mammography combined with automated breast ultrasonography with screening mammography alone. Adding automated breast ultrasonography yielded an additional 1.9 cancers detected per 1,000 women screened. In a study that included data from 6,425 sessions of automated whole-breast ultrasonography and mammography performed in asymptomatic women, Kelly et al. con-
improve rates of cancer detection. However, the limitations of ultrasonography must be considered. Low positive predictive values are generalizable to nearly all of the studies. Results from the trial conducted by Berg et al showed a reasonable recall rate for ultrasonography of 5.4%, but the positive predictive value for recall was 6.5% and the positive predictive value for engendered biopsies was 8.9%. Hooley et al and Weigert et al also reported low positive predictive values of 6.5% and 6.7%, respectively. Brem et al showed a decreased positive predictive value with ultrasonography (performed with automated whole-breast ultrasonography) as compared with mammography alone, which had a specificity rate of 13.4%. As comparison studies become available over years of sequential screening, it has been suggested that the number of biopsies prompted by false-positive findings on ultrasonography may improve.

Ultrasonography is a workhorse for diagnostic breast imaging, but its role in screening remains unclear. Studies utilizing screening ultrasonography demonstrate its capability for detecting invasive malignancies in dense breasts at small sizes and localized stages that could potentiate an increase in breast cancer survival rate; however, more studies are needed to determine the impact on mortality. The best indications for screening ultrasonography in dense breasts may be for women with intermediate risk or in those women at high risk but with a contraindication to magnetic resonance imaging (MRI).

Magnetic Resonance Imaging
MRI is a cross-sectional imaging modality that provides soft-tissue contrast between fat, fibroglandular tissue, and lesions. MRI of the breast was approved by the FDA as an adjunct to mammography for the detection of breast cancer in 1991. Since that time, MRI of the breast has been further refined and is now considered the most sensitive imaging tool available for the diagnosis of invasive breast cancer. Limitations of MRI of the breast must be weighed against the potential benefits when selecting candidates for screening MRI. As such, the role of screening MRI in patients with dense breasts has not been well defined.

Fibroglandular tissue does not mask lesions on MRI, unlike mammography. Administration of intravascular contrast (gadolinium) helps distinguish suspicious lesions from normal breast tissue due to preferential contrast uptake by malignant tumors (Fig 4). However, normal fibroglandular tissue is enhanced to varying degrees, which is an imaging characteristic termed background parenchymal enhancement. Similar to breast density, 4 categories of background parenchymal enhancement are included in the BI-RADS criteria (Fig 5):

- Minimal
- Mild
- Moderate
- Marked

Hypothetically, background parenchymal enhancement may obscure malignancies or yield false-positive results, but studies have shown that background pa-
Parenchymal enhancement does not appear to negatively impact the diagnostic accuracy of MRI\textsuperscript{1,37}. Furthermore, no clear link exists between background parenchymal enhancement and breast density. For example, a woman with extremely dense breasts may have minimal background parenchymal enhancement, whereas a woman with scattered fibroglandular tissue may have marked background parenchymal enhancement\textsuperscript{1}.

Use of screening breast MRI in patients with dense breasts may sound appealing, but data on its efficacy are limited. In 2007, the American Cancer Society released recommendations for screening MRI of the breast as an adjunct to mammography based on evidence and expert opinion\textsuperscript{38}. According to its guidelines for screening MRI, heterogeneously or extremely dense breasts on mammography are considered equivocal, with insufficient evidence to recommend for or against MRI screening (Table)\textsuperscript{38}. Dutch researchers Emaus et al\textsuperscript{39} launched a trial to study dense tissue and early screening for breast neoplasms, which is currently ongoing (NCT01315015), to evaluate the cost and effectiveness of MRI screening in patients with dense breasts and negative findings on mammography. At this time, implementation of MRI screening of patients with dense breasts and no known additional risk factors is not supported by sufficient data\textsuperscript{39}.

The evidence supporting MRI screening of the breast continues to evolve. Many studies have shown benefit in high-risk populations (> 20% lifetime risk)\textsuperscript{28,40-45}. In 2008, Warner et al\textsuperscript{46} performed a meta-analysis of 11 prospective studies that compared the sensitivity rates of annual screening mammography performed in conjunction with MRI and annual screening mammography alone. Their meta-analysis found an increase in sensitivity rate of 94% when mammography was combined with MRI as compared with a rate of 32% for mammography alone.\textsuperscript{46} These findings are similar to other studies, including a multicenter trial by Sardanelli et al\textsuperscript{44}, in which MRI was determined to be more sensitive (91%) than clinical breast examination (18%), mammography (50%), ultrasonography (52%), or mammography plus ultrasonography (63%). In addition, 31% of cancers were detected by MRI alone.\textsuperscript{44} In 2015, Riedl et al\textsuperscript{45} screened a high-risk patient population with mammography, sonography, and MRI, and they found that a higher percentage of cancer was detected by MRI alone (45%) vs mammography alone (5%) and ultrasonography alone (0%). The authors also found an added cancer detection rate of 1.3% with MRI alone, which translates to 13 additional cancers detected per 1,000 screening MRI examinations performed.\textsuperscript{45} A 2015 report by Raikhlin et al\textsuperscript{47} documented detecting an additional 10 cancers per 1,000 patients screened with MRI and mammography together vs mammography alone.

In addition to studies of high-risk populations, the data from other studies support use of screening MRI of the breast in populations for which ACS guidelines in 2007 suggested insufficient data were presented, including patients with high-risk lesions and those with...
a personal history of breast cancer. For example, in a retrospective study of 1,699 patients with a personal history of breast cancer and no other risk factors, Brennan et al. observed a cancer-detection rate of 12%, of which 59% were detected by MRI alone. MRI screening in this study yielded a positive predictive value of 39%, and the authors concluded that a definite benefit to its use exists in this population.

Benefits of MRI screening should be weighed against risks and limitations such as cost. Saadatmand et al. performed a large, prospective study evaluating use of MRI screening in patients with familial risk factors and an estimated lifetime risk of breast cancer that was higher than 15%. The benefit of including annual screening MRI resulted in an estimated mortality rate reduction of 25% vs 17% in those who did not undergo MRI; however, Saadatmand et al. found that adding MRI to the annual screening regimen was 2.5 times more expensive per life-year gained.

By addressing the costs and time limitations of acquisition, active research in abbreviated protocol screening MRI of the breast shows promising results. In 2014, Kuhl et al. conducted a prospective, observational reader study on an abbreviated protocol screening MRI of the breast based on a maximum intensity projection analysis of early, postcontrast, T1-weighted imaging. Compared with the full protocol, which had an acquisition time of 17 minutes, the abbreviated protocol took 3 minutes to perform and, on average, 28 seconds to interpret; in addition, the abbreviated protocol had equivalent diagnostic accuracy. Since then, additional studies have lent further evidence supporting the abbreviated screening protocols, suggesting that they may replace full protocols in the future without sacrificing diagnostic accuracy.

Another important limitation of MRI is its rate of specificity. The increased sensitivity rate associated with MRI comes at a cost in terms of reduced specificity, thus resulting in increased callback rates and

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**Fig 5A–D.** — Postcontrast, fat-subtracted, axial maximum intensity projection imaging demonstrates the 4 categories of background parenchymal enhancement, as defined by the ACR BI-RADS criteria: (A) minimal, (B) mild, (C) moderate, and (D) marked. ACR = American College of Radiology, BI-RADS = Breast Imaging Reporting and Data System, 5th ed. Data from reference 1.
benign findings on biopsies. When MRI was added to mammography, Warner et al.\(^6\) and Sardanelli et al.\(^4\) found that the specificity rates decreased from 99% to 95% and 96%, respectively. Raikhlin et al.\(^7\) reported a specificity rate of 86% for MRI of the breast with associated callback rates nearly 10 times higher and biopsy rates nearly 5 times higher than with mammography alone. Schwartz et al.\(^8\) concluded that the positive predictive value of 20% and the increased callback rate of 24% may not justify MRI screening in the population they studied for the added cancer detection rate of 2%.

Contraindications to MRI of the breast are generally related to gadolinium contrast, including those with gadolinium allergy, compromised renal function, and those who are pregnant. Other contraindications include the presence of a pacemaker/defibrillator, presence of some types of metallic foreign bodies, and claustrophobia.

Screening MRI of the breast is the most sensitive imaging modality for detecting breast cancer, but the limitations of MRI prevent its use as a population-based screening tool. The results from studies show that the benefits of MRI typically outweigh the limitations among patients with an estimated lifetime risk of breast cancer of higher than 20%.\(^2,6,47\) As new data become available, additional indications may emerge. In the meantime, no clear indication exists for performing screening MRI in patients with dense breasts, and the recommended use of screening MRI in this population should be the same as that for the general population based on personal risk.

### Molecular-Based Imaging

Molecular-based imaging technology uses a physiological approach to identify lesions in the breast and can detect mammographically occult cancers.\(^7,58\) Gamma detectors are used to image the breast after injection of a radiotracer, technetium sestamibi, which has preferential uptake in highly proliferating tumor cells, thereby identifying functional differences in tumors from normal breast tissue.\(^58-60\) Breast-specific \(\gamma\) imaging uses a dedicated, single-head, scintillating sodium iodide detector. Molecular breast imaging is the latest generation of systems and uses cadmium zinc telluride detectors in a dual-head configuration. Although the technologies differ between these 2 systems, the terms are often interchangeably used.\(^58,59\) Compared with breast-specific \(\gamma\) imaging, molecular breast imaging has improved rates of count sensitivity, energy resolution, spatial resolution, and lesion detection. In addition, molecular breast imaging requires fewer amounts of injected radiotracer.\(^60\) Positron emission mammography is another nuclear medicine system in practice; however, radiotracer uptake increases with breast density, resulting in background parenchymal activity that could obscure underlying malignancies.\(^61\)

Rechtman et al.\(^57\) investigated the sensitivity of breast-specific \(\gamma\) imaging for the detection of breast cancer in women with dense vs nondense breasts in 347 biopsy-proven breast cancers, and they determined that the sensitivity rate was similar in women with dense (94.7%) and nondense breasts (96.5%). In addition, mammographically occult breast cancers were equally detected in both groups. The authors concluded that breast-specific \(\gamma\) imaging detected breast cancer regardless of the pathological subtype, nuclear grade, or tumor size.\(^57\)

Shermis et al.\(^59\) retrospectively assessed the clinical performance of molecular breast imaging as a supplementary screening tool for dense breasts in 1,696 women not at high risk and detected 13 mammographically occult malignancies, 11 of which were invasive. The authors reported that the incremental cancer detection rate (7.7%) and positive predictive value for biopsy (19.4%) were higher than that seen with screening ultrasonography.\(^59\) They concluded that molecular breast imaging is an acceptable alternative for supplemental screening in women with dense

### Table. Recommendations From the American Cancer Society for Screening MRI of the Breast as an Adjunct to Mammography

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<tr>
<th>Recommend annual screening MRI</th>
<th>Comment</th>
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<tr>
<td>BRCA mutation</td>
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<td>First-degree relative of BRCA carrier but untested</td>
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<td>Lifetime risk ≥ 20%</td>
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<tr>
<td>Received radiation to the chest aged 10–30 y</td>
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<tr>
<td>Li-Fraumeni syndrome and first-degree relatives</td>
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<td>Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives</td>
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<th>Insufficient evidence to recommend for or against screening MRI</th>
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<tr>
<td>Lifetime risk 15%–20%</td>
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<tr>
<td>Lobular carcinoma in situ</td>
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<tr>
<td>Atypical lobular hyperplasia</td>
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<td>Atypical ductal hyperplasia</td>
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<tr>
<td>Heterogeneously or extremely dense breast on mammography</td>
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<td>Women with a personal history of breast cancer</td>
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| Recommend against screening MRI                              | Women < 15% lifetime risk |

MRI = magnetic resonance imaging.

Data from reference 38.
Breasts. These findings are in line with earlier prospective studies: Data have shown that molecular breast imaging can detect mammographically occult cancers that are primarily invasive and range in size from 2 mm to 5.1 cm.

Although studies have shown that molecular-based imaging has a high rate of sensitivity for detecting cancer in dense breasts, as well as a high positive predictive value, its availability and use as a supplemental imaging tool has been limited secondary to concerns of radiation exposure. The injected radiotracer delivers radiation throughout the body, including radiosensitive organs beyond the breast. The radiation dose for breast-specific $\gamma$ imaging has been reported to be more than 5 times that of standard mammography and twice that of standard mammography plus tomosynthesis. The radiation dose of molecular-based imaging is 2 to 5 times greater than the dose of mammography, but research has shown promising results using lower doses of radiotracer, which may be more acceptable. However, future studies are needed to ensure adequate image quality at this dose.

The total dose of mammography and molecular-based imaging is low (< 10 mSv) compared with the dose associated with adverse-event risk (> 50 mSv), so the benefit may outweigh the risk for some women. The only commercially available, FDA-approved biopsy unit is a breast-specific $\gamma$ imaging system. However, biopsy units guided by molecular breast imaging are in development. Advantages of molecular-based imaging over MRI include its lower cost and fewer contraindications.

**Automated Breast Density**

Reporting of breast density has implications on the assessment of patient care and risk of breast cancer. However, intraobserver and interobserver variability exist in the visual assessment of the BI-RADS density category selected by the clinician on mammography. In response to this challenge, several automated software programs have been developed that measure volumetric breast density. However, quartiles of breast density have been eliminated in the BI-RADS criteria, so the assessment is no longer quantitative and brings into question the utility of quantitative software in the BI-RADS reporting. In a retrospective study of 1,185 mammography examinations, Youk et al compared the visual assessment of breast density based on the BI-RADS criteria with that of 2 commercially available software programs. They found that more findings on mammography were classified as being nondense with one program and as dense with another program when compared with the findings from the visual assessment. By contrast, Ekpo et al evaluated one of the programs previously determined to be underestimating. In their study, they compared automated vs visual breast density assessment in 234 women undergoing digital breast tomosynthesis. The authors found a moderate to substantial agreement in breast density assessment between the BI-RADS criteria and the automated software. Active research is being conducted to incorporate both automated and visual density assessments into patient risk models, and volumetric breast density measurements may prove to be beneficial in developing algorithms for automated risk assessment.

**Conclusions**

Approximately 50% of women have breasts that are at least heterogeneously dense — a figure that amounts to...
27.6 million women aged 40 to 75 years in the United States. The American College of Radiology identifies breast density as a controversial risk factor for breast cancer with no consensus that it confers sufficient risk to warrant supplemental screening. In a position statement from the American Congress of Obstetricians and Gynecologists, dense breasts are identified as a modest risk factor for breast cancer. The organization does not recommend routine use of adjunctive studies to screening mammography in asymptomatic women with dense breasts who are without additional risk factors.

Understanding breast cancer risk conferred by density in the setting of a patient’s history, as well as an appreciation of the imaging tools available, will help aid clinicians in developing the most appropriate screening plan for each of their patients. Mammography remains the most appropriate modality for population-based screening. One suggested approach for screening women with dense breasts is to use tomosynthesis for all levels of risk, supplemental whole-breast ultrasonography for women with average risk, and supplemental magnetic resonance imaging for women with intermediate and high risk (Fig 6). For women who are at high risk and also have a contraindication to magnetic resonance imaging, whole-breast ultrasonography or molecular breast imaging, if available, may be an appropriate alternative. Additional studies are warranted to evaluate optimal supplemental screening strategies, although we suspect that the strategy will likely require a personalized approach based on risk assessment.

References