MAYO CLINIC

Breast Density and Breast Cancer Risk: A Practical Review

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Abstract

New legislation in several states requiring breast density notification in all mammogram reports has increased awareness of breast density. Estimates indicate that up to 50% of women undergoing mammography will have high breast density; thus, with increased attention and high prevalence of increased breast density, it is crucial that primary care clinicians understand the implications of dense breasts and are able to provide appropriate counseling. This review provides an overview of breast density, specifically by defining breast density, exploring the association between breast density and breast cancer risk, both from masking and as an independent risk factor, and reviewing supplemental screening options as part of a larger framework for counseling patients with dense breasts.

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Over the past few years, breast density has gone from an obscure medical term to break room conversation, which is in part due to the increased media attention after the efforts of Nancy Cappello, who had received a diagnosis of breast cancer without knowing that her previous mammograms had reported dense breasts. In 2009, with Ms Cappello's advocacy, Connecticut became the first state to require that women who have undergone mammography are informed of their breast density. A total of 14 states including Pennsylvania, Texas, California, and New York have followed suit,[1] though the content of laws varies by state. Currently, a statement of breast density is required only in states with a breast density law. A federal bill requiring that every mammography report inform women of their breast density was re-introduced in Congress in October 2013.[2] The Food and Drug

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Administration (FDA) is considering an amendment to the Mammography Quality Standards Act that would require breast density notification. With the increasing awareness of breast density by the public and medical community, it is essential that primary care professionals have a practical understanding of breast density and its implications for clinical practice.

MAMMOGRAPHIC BREAST DENSITY: DEFINITION AND TERMINOLOGY

Breast density refers to the mammographic appearance of the breast. Mammographic breast density reflects varying amounts of fat (dark areas on mammograms) and stromal and epithelial tissues (white areas on mammograms) in the breast. Breast density is measured as the absolute amount of dense or white areas in the breast (dense area) or a proportion of the mammogram that is composed of dense tissue (percent density). There are several tools to assess breast density. The most commonly used tool in clinical practice is the Breast Imaging Reporting and Data System (BI-RADS), which is used by radiologists at the time of mammography; it divides breast density into 4 categories as depicted in the Table and Figure 1. These categories are not to be confused with BI-RADS categories 0 to 6, which are used for standardized reporting of mammographic findings and follow-up recommendations.[3] In some clinical centers, D1, D2, D3, and D4 classifications are used to represent the respective BI-RADS 1 to 4 density categories to minimize confusion with the BI-RADS 0 to 6 scale for mammographic findings. For simplicity, we use the D1 to D4 classification system in this article.

One of the density phrases or values may be present on the screening mammogram reports. Population-based data have revealed that approximately 10% of women have almost entirely fatty breasts (D1), 40% of women have scattered fibroglandular densities (D2), another 40% have heterogeneously dense breasts (D3), and 10% have extremely dense breasts (D4).[4,5] Dense breasts are defined as either heterogeneously dense (D3) or extremely dense (D4). Thus, approximately 50% of the population undergoing mammography would be categorized as having dense breasts. The most common measure used in research is percent density, a semi-automated quantitative measure providing the ratio of dense tissue area to total breast area and is calculated by a trained expert with a computer algorithm.[6] Although widely used, these measures have limitations, including subjective assessment, 2-dimensional measure, and, for BI-RADS density, moderate interobserver agreement.[7,8] Automated density measures including volumetric density are now being studied.[9-11] Two automated volumetric density measures for full field digital mammography are now commercially available: Volpara (Mātakina, Wellington, New Zealand) and Quantra (Hologic, Inc., Bedford, MA, USA). Although these commercial systems have established correlation with BI-RADS density categories, these have not been directly studied in relation to breast cancer risk, to date.[12,13]

BREAST DENSITY: RELEVANCE IN CLINICAL PRACTICE

Masking of Breast Cancer

Increased breast density can make it more difficult to detect smaller cancers with mammography because cancers have the same X-ray attenuation as fibroglandular breast tissue[14-17](Figure 2). As expected, the sensitivity of mammography decreases with increasing breast density. The sensitivity of mammography for women with almost entirely fatty breasts (D1) is 88% as compared with 82% for women with scattered fibroglandular densities (D2), 69% for women with heterogeneously dense breasts (D3), and 62% for women with extremely dense breasts (D4).[15,18] Boyd et al[14] found that compared with women with breast density of less than 10%, women with breast density of 75% or more were 17.8 (95% CI, 4.8-65.9) times more likely to have a breast cancer detected within 12 months of the last screening examination. This markedly increased risk of breast cancer within 12 months of a screening mammogram

TABLE. BI-RADS Categories for Breast Density[3]

Density	Description	Glandular tissue
1 (lowest density)	Almost entirely fat	<25%
2	Scattered fibroglandular densities	Approximately 25%-50%
3	Heterogeneously dense, which could obscure detection of small masses	Approximately 51%-75%
4 (highest density)	Extremely dense, which may lower the sensitivity of mammography	>75%

BI-RADS = Breast Imaging Reporting and Data System.

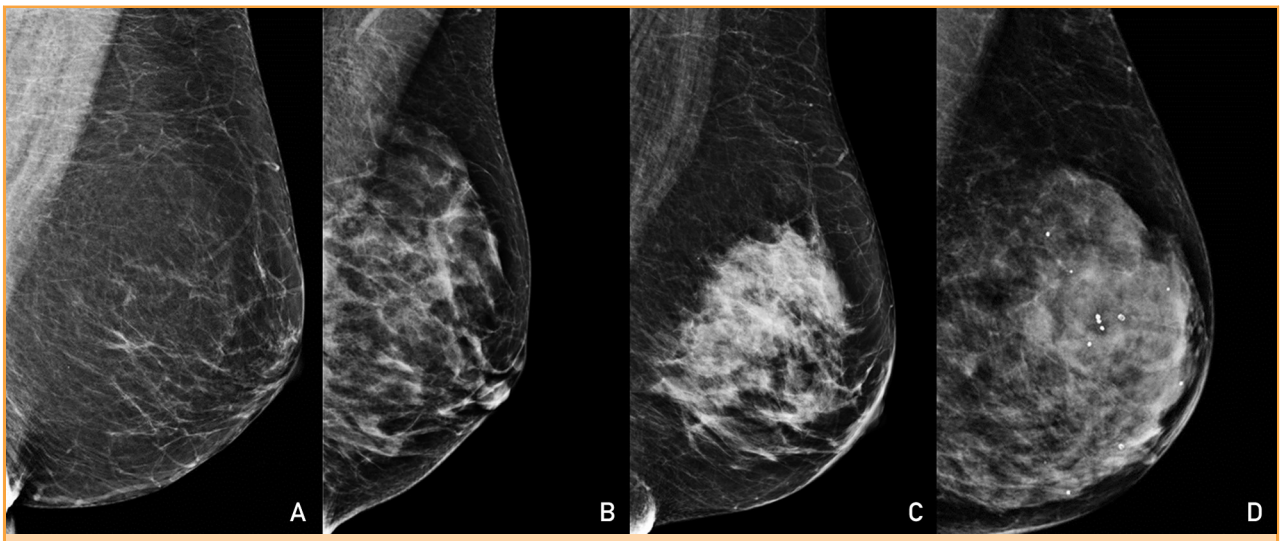

FIGURE 1. Mediolateral oblique mammographic views depicting the 4 BI-RADS density categories: (A) almost entirely fat (BI-RADS 1 density); (B) scattered fibroglandular densities (BI-RADS 2 density); (C) heterogeneously dense (BI-RADS 3 density); (D) extremely dense (BI-RADS 4 density). BI-RADS = Breast Imaging Reporting and Data System.

showing no abnormalities is likely related to the effect of density masking breast cancers.[14] Although masking of tumors by dense breasts is important, it is essential to recognize that the association between breast density and risk for breast cancer is more than just masking bias and cannot be explained by the reduced sensitivity of mammography alone.[19]

High Breast Density Increases Breast Cancer Risk

To eliminate the effect of masking, studies examined mammograms obtained many years before a breast cancer diagnosis. In 1 study, women with a breast density of greater than 75% (assessed on a screening mammogram at least 5 years earlier) had a 3.25-fold risk of breast cancer compared with women with breast density less than 5%.[20] The consistent association between increased density and cancer risk across time emphasizes the potential for risk prediction.[14,21] Density has consistently been found to be a major risk factor for breast cancer in scores of studies regardless of age at mammography[22] or ethnic background of the study population.[20,23,24] Breast density is a stronger predictor for breast cancer than most known risk factors for breast cancer, including family history.[25] However, it is important to recognize that these estimates may be artificially high because investigators often compare the 10% of women with extremely dense breasts with the 10% of women with almost entirely fatty breasts.[26] When comparing women with dense breasts with women with scattered fibroglandular densities (D2), the relative risk is 1.2 to 1.5 for heterogeneously dense breasts (D3) and 2.1 to 2.3 for extremely dense breasts (D4).[14,21,24,27-29] Breast density has also been associated with an increased risk of local and locoregional recurrence of breast cancer but not distant metastasis or survival.[30,31] This finding is consistent with 2 recent large studies that found that breast density was not associated with increased breast cancer mortality or all-cause mortality rates[32,33]; however, additional research is needed because of the limited studies on this topic.

Breast density decreases with advancing age; a large study found that 74% of women in their 40s had dense breasts (D3 or D4) as compared with 36% of women in their 70s.[34] One study of 1900 women aged 49 to 69 years found that breast density decreased by an average of 11% over a 10-year period.[35] Nevertheless, high breast density increases breast cancer risk across all age groups, but the association is strongest in premenopausal women and women receiving postmenopausal hormone therapy (HT).[22] In postmenopausal women with the highest breast density, HT use was associated with a higher risk

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of breast cancer than was no HT use (hazard ratio, 1.38; 95% CI, 1.25-1.50).[22] Hormone therapy not only is associated with increased breast cancer risk among increased density categories but also increases breast density. The Women's Health Initiative study[36] found that HT users on a combination of estrogen and progestin had a 6% increase in mammographic breast density after 1 year compared with a 0.9% decrease in the placebo group. Similar to the relationship between breast density and age, breast density also decreases with increasing body mass index (BMI), though breast density and BMI are independent risk factors for breast cancer.[37-39]

Breast Density as a Potential Surrogate Marker of Treatment Response

Breast density is a potential indicator of treatment response for certain types of breast cancer prevention and treatment. Tamoxifen is efficacious in both breast cancer treatment and prevention, and it has been suggested that some of its therapeutic effect may be mediated through reductions in breast density. In the primary prevention International Breast Cancer Intervention Study-1 trial, 46% of high-risk women randomized to tamoxifen experienced a more than 10% reduction in breast density compared with 25% of those taking placebo. Women treated with tamoxifen with more than 10% reduction in breast density experienced a 63% decrease in breast cancer risk compared with no change in risk in women in the placebo group and women treated with tamoxifen with no change in breast density.[40,41] Reductions in breast density have also been associated with a reduced risk of recurrence in patients with breast cancer treated with tamoxifen as adjuvant therapy.[42] A recent Swedish study with 15 years of follow-up found that women with breast cancer treated with tamoxifen as adjuvant therapy who experienced a reduction of more than 20% in breast density had a 50% reduced risk of breast cancer mortality compared with women treated with tamoxifen with no reduction in breast density.[43] Thus, breast density may be an important marker of response to tamoxifen therapy for chemoprevention and adjuvant therapy for breast cancer.

Conversely, this finding has not been consistently found in studies of aromatase inhibitors (AIs). Multiple studies have examined the effect of AIs on breast density with largely negative results,[44-46] though 1 recent study of a cohort of Korean women with breast cancer found small reductions in breast density with AI use (−3.1%±6.3% with either anastrozole or letrozole).[42] However, women in this Korean cohort were younger and had a much higher baseline breast density than in other studies and more than 75% of the cohort received adjuvant chemotherapy, which may also cause breast density reduction through ablative effects on ovarian function in premenopausal women.[42,47] Other studies that found reductions in breast density with AI use did not have comparison groups,[48,49] which clouds the findings, because breast density is known to decrease with increasing age. Vachon et al[46] performed the largest study of AI use and breast density in postmenopausal patients with breast cancer receiving AIs as adjuvant therapy and found that 14% of women had a 55% or greater reduction in breast density, but this did not differ from reductions experienced over the same time period in age- and BMI-matched healthy postmenopausal women. It is important to note that this lack of breast density reduction with AI use does not purport lack of therapeutic efficacy; in fact, AIs have been found to be more effective than tamoxifen in reducing breast cancer recurrence in postmenopausal women.[50] In

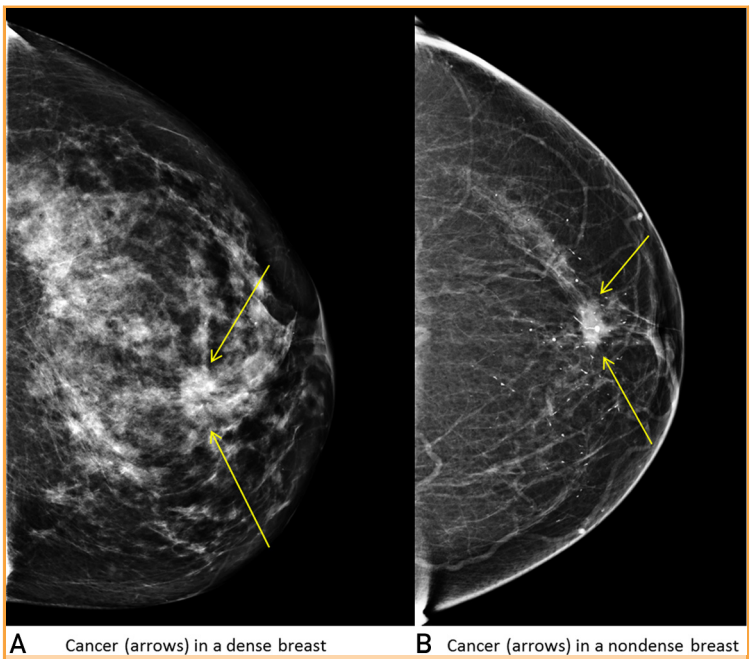
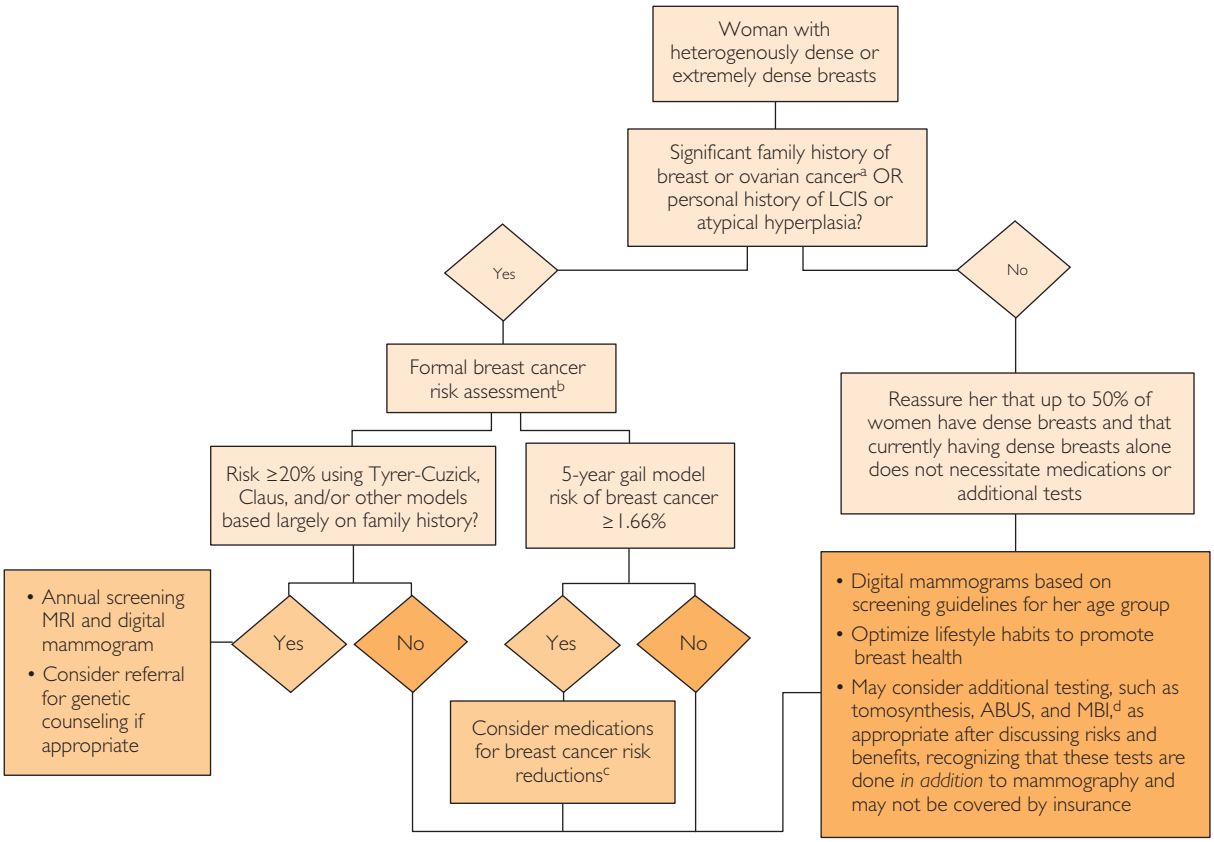


FIGURE 2. Craniocaudal mammographic views of a breast cancer in a BI-RADS 4 density breast (A) and a breast cancer in a BI-RADS 1 density breast (B).



Abbreviations: ABUS = automated whole-breast ultrasound; LCIS = lobular carcinoma in situ; MBI = molecular based imaging; MRI = magnetic resonance imaging.
[a] Significant family history includes a first-degree relative with breast or ovarian cancer, multiple relatives with breast or ovarian cancer on one side of the family, especialy premenopausal or in male relatives.
[b] Risk assessments should be done by clinicians with expertise in using breast cancer risk prediction models.
[c] Breast cancer risk reduction medications include tamoxifen, raloxifene, and exemestane.
[d] MBI is not available at many centers. Currently there is little consensus as to when or which additional screening test should be used.

FIGURE 3. Approach to a woman with dense breasts (clinical algorithm).

contrast to tamoxifen, AIs may not substantially affect breast density, and even if there are minor reductions in breast density with AI use, it is questionable whether breast density will be a useful marker in this context.

RECOMMENDATIONS FOR WOMEN WITH DENSE BREASTS

Counsel your patient regarding her risk factors for breast cancer and what risk reduction strategies she can undertake (Figure 3).

Discuss the mammographic breast density description on the mammogram report with your patient, if available, and inform her that up to 50% of women have dense breasts (D3 or D4). Consider sharing details of magnitude of risk of breast cancer associated with dense breasts. The relative risk is 1.2 to 1.5 in women with heterogeneously dense breasts (D3) and 2.1 to 2.3 in women with extremely dense breasts (D4) as compared with women with scattered fibroglandular densities (D2). Explain that though there is a higher chance of missing a cancer on a mammogram in a woman with dense breasts than in a woman without dense breasts, mammography is still valuable and the test of choice for breast cancer screening for women ages 40 and older. Encourage her to be breast self-aware and to seek prompt medical attention if she detects a breast change, even if she has had a recent screening mammogram showing no abnormalities. If she is otherwise at average risk,

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explain that high breast density alone does not automatically necessitate risk-reducing medications (eg, tamoxifen, raloxifene, and exemestane) or additional imaging. Additional screening options are available, but there is little consensus on when or which additional measures should be used; this requires a thorough discussion of risks and benefits (discussed below).

As you would do for any woman, assess her risk factors for breast cancer. Evaluate her family history of breast and ovarian cancer and any personal history of benign breast disease, including atypical hyperplasia and lobular carcinoma in situ, because these are also independent risk factors for breast cancer. If either of these is present, she may benefit from more formal breast cancer risk assessment by a clinician with expertise in using and interpreting models such as Claus and Tyrer-Cuzick as well as other models based on family history. Risk estimates using these models vary; therefore, the use of more than 1 model is recommended.[51] Currently none of these risk models incorporate a density measure, but the models are under development.[52,53] If these models generate a lifetime risk of breast cancer of 20% or greater, the patient qualifies for annual screening magnetic resonance imaging (MRI) in addition to routine screening mammograms, according to American Cancer Society guidelines.[51] If family history is suggestive of a *BRCA* mutation, refer her for genetic counseling. If her lifetime risk is less than 20%, she should undergo routine screening mammography and counseling regarding the risk and benefits of potential additional imaging tests.

Optimize the patient's modifiable risk factors: encourage all women to exercise regularly and maintain a healthy weight. Make informed choices regarding the use of postmenopausal HT and limit alcohol intake to no more than 1 drink per day, because these factors are independently associated with both breast density and breast cancer.[22,37,54,55] One alcoholic drink (0.6 ounces of pure alcohol) is equivalent to 12 oz of regular beer, 8 oz of malt liquor, 5 oz of wine, and 1.5 oz of 80-proof distilled spirits or liquor (eg, vodka, whiskey, rum, and liqueurs).[56]

Ensure That Your Patient Is Undergoing Digital Mammography

In women with dense breasts, digital mammography has been reported to be significantly more accurate than film mammography (sensitivity of 70% with digital mammography compared with 55% with film mammography).[57] It is therefore preferable that women with dense breasts undergo digital rather than film screen mammography. Most current mammography centers use digital mammography.

Be Familiar With Additional Screening Measures That May Be Considered for Women With Dense Breasts

Several imaging tools that are not limited by breast density are being investigated as supplemental tests, in addition to mammography, for breast cancer screening in women with dense breasts. These tools include tests that assess anatomical information such as tomosynthesis and whole-breast ultrasound (US) and those that assess functional differences in tissue such as MRI and molecular breast imaging (MBI).

Breast tomosynthesis, or 3-dimensional (3D) mammography, uses multiple low-dose digital images of the breast and a computer algorithm to reconstruct thin slices that cover the entire breast, similar to a computed tomography scan. With tomosynthesis, overlapping dense tissue is less likely to obscure or simulate a meaningful finding. Tomosynthesis detects an additional 0.5 to 2.5 cancers per 1000 examinations and reduces the screening recall rate for noncancerous findings by 40% to 60% in women with dense breasts when performed in conjunction with standard 2D mammography.[58,59] A potential limitation of current screening tomosynthesis is that it is performed in conjunction with a standard 2D mammography and, although still under the FDA-approved dose, doubles the radiation exposure. However, a new technology has recently been approved by the FDA that allows synthesis of the 2D mammogram from the 3D (tomosynthesis) data set, thus decreasing the radiation dose for both sets of images to that of a standard 2D mammogram.[60,61] This new technology appears promising, but how it performs in clinical practice is yet to be determined. Cost is another limitation of tomosynthesis because multiple factors make it more expensive than standard mammography, including cost of the machine, increased reading time by radiologists, costlier viewing workstations, and increased image storage cost. It is anticipated that at least some of the additional cost will be offset by cost savings in the reduction of screening recalls.[62] Practices that offer screening tomosynthesis do

so at no, or minimal, additional cost to the patient.

Whole-breast US has gained popularity as an adjunctive screening test for women with dense breasts because it is noninvasive, widely available, relatively inexpensive and does not involve radiation exposure. By assessing the addition of whole-breast US to mammography in high-risk patients with dense breasts (of which >50% had a history of breast cancer), an additional 4.2 cancers were detected per 1000 women screened.[63,64] This result is similar to published data collected after the enactment of Connecticut's breast density law, which found 3.2 additional cancers per 1000 women with dense breasts.[65,66] The major limitation with US is low specificity. There is considerable overlap in the appearance of cancers and benign breast lesions detected by US. Approximately 5% of women undergoing whole-breast US should expect to have a biopsy, with a cancer yield of 8.9%.[63] This result is compared with a 1% to 1.5% biopsy rate for screening mammography, with a cancer yield of 3 to 6 per 1000 screening mammograms.[67] The newest US technology is automated whole-breast ultrasonography (ABUS), in which the US transducer is placed on the breast by a technologist and the images are acquired automatically and then stored for later interpretation. Abnormal findings obtained on an ABUS examination require the patient to be recalled for a standard US examination. There is little published data on ABUS, but preliminary studies have found an increase in breast cancer detection and decreased specificity when added to mammography as compared with mammography alone.[68]

Magnetic resonance imaging has the highest sensitivity for detecting breast cancer. A study using breast MRI in women at the highest risk of breast cancer (*BRCA1* and *BRCA2* mutation carriers) has reported up to 30 additional cancers detected per 1000 screening examinations.[69] Cancer detection in other high-risk populations ranges around 18 additional cancers detected per 1000 screening examinations.[64] Like US, specificity is also a limitation of breast MRI. Ten to 20% of those undergoing screening MRI will be recommended for further work-up; approximately 8% will undergo a biopsy, of which the cancer yield is approximately 20%.[64] Magnetic resonance imaging is also expensive and requires an intravenous injection of gadolinium. Screening MRI is currently recommended by the American Cancer Society as an adjunct to mammography for women who are at high risk for breast cancer, specifically women who have *BRCA* mutations, are untested first-degree relatives of BRCA carriers, or have greater than 20% estimated lifetime risk of breast cancer using one of the risk prediction models that are based on family history.[51] Gadolinium is excreted by the kidneys and contraindicated in pregnant women and those with compromised renal function. It is considered safe for women to continue breast-feeding after gadolinium because less than 0.01% of the systemic dose is expected to be absorbed by the infant from breast milk; women who remain concerned can make an informed decision to express and discard milk for 24 hours.[70]

Molecular breast imaging is a promising screening tool because it identifies functional differences in tumor and normal breast tissue. Screening MBI systems use dual-headed, high-resolution, CZT gamma detectors to image the breast after an intravenous injection of sestamibi, a radiotracer with preferential uptake in highly proliferating cells.[71] There are commercially available lower-resolution, single-detector systems, sometimes also referred to as MBI or breast-specific gamma imaging, that are not appropriate for screening. In a study of 936 asymptomatic women with dense breasts and at least one additional breast cancer risk factor, the use of a dose of 20 mCi of technetium-99m sestamibi in dual-headed, high-resolution MBI with mammography detected an additional 7.5 cancers per 1000 examinations as compared with mammography alone.[71] Similar, but unpublished, results have been reported at lower radiation doses of 8 mCi of technetium-99m sestamibi,[72] which is less radiation exposure than annual background radiation. Molecular breast imaging may have higher specificity than do other supplemental screening tests; Rhodes et al[71] report a biopsy rate of 3% with a cancer yield of 28% in dense breasts. However, MBI is not yet widely available and requires a radiotracer injection; MBI-guided biopsy systems are still in the development phase.

Although tomosynthesis, whole-breast US, MRI, and MBI are screening options that may be considered in addition to mammography for women with dense breasts, patients must be informed of the potential risks of additional

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testing.[63,64,71] Finding a false-positive result can lead to further testing including biopsies, increased patient anxiety, inconvenience, and additional cost. Many of these tests are not currently covered by insurance and may result in out-of-pocket cost to the patient. Furthermore, it is important to recognize that this is a rapidly evolving field and consensus on which additional modality is best has not yet been reached. Patients also need to be informed that the long-term effect on morbidity and mortality related to these supplemental screening tests is unclear.

CONCLUSION

As increasing legislation mandates that women be informed of their breast density as part of their mammography results, clinicians will be contacted with questions regarding breast density and supplemental screening examinations in addition to mammography. Thus, clinicians need to be aware of the clinical implications of breast density, including both the masking effect and the increased breast cancer risk. Familiarity with additional screening measures is also necessary to enable a discussion of risks and benefits of these modalities with an individual patient. The future of breast cancer risk prediction is bright, with the development of risk prediction models incorporating new breast density measures and discoveries of more than 75 common genetic loci associated with breast cancer risk.[73] These advances will help women and their clinicians tailor breast cancer screening strategies on the basis of an individual woman's risk, values, and preferences while also accounting for cost, potential harms, and patient-important outcomes.

Abbreviations and Acronyms: **3D** = 3-dimensional; **ABUS** = automated whole-breast ultrasonography; **AI** = aromatase inhibitor; **BI-RADS** = Breast Imaging Reporting and Data System; **BMI** = body mass index; **HT** = hormone therapy; **MBI** = molecular breast imaging; **MRI** = magnetic resonance imaging; **US** = ultrasound

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