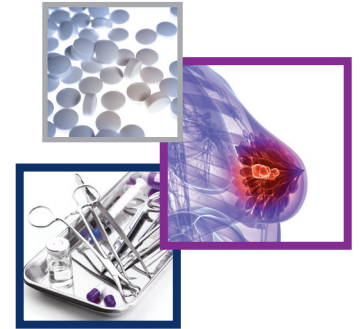


# Current and future methods for measuring breast density: a brief comparative review



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## Practice points

- Breast density is one of the strongest identified breast cancer risk factors; women with the densest breasts are four- to six-times more likely to develop breast cancer.
- Breast density reflects breast tissue composition and its biophysical properties; studies that combine novel density measurements with molecular pathology can inform the relationship between breast density and breast cancer risk.
- The gold standard of breast screening is mammography, but women who present with higher lifetime risk (>20%) are recommended to seek additional screening using MRI or ultrasound.
- Breast density is usually evaluated clinically by qualitative visual assessment of mammograms; however, quantitative approaches that predict risk are frequently employed in research and increasingly, in clinical practice.
- The limitations of mammography may be addressed by the development of other imaging modalities to improve both breast density measurements and breast cancer detection.
- The emerging imaging modality of breast ultrasound tomography shows promise for directly measuring breast tissue density using sound speed imaging, which can be accomplished in 3D without exposure to ionizing radiation.

**SUMMARY** Breast density is one of the strongest predictors of breast cancer risk. Women with the densest breasts are four- to six-times more likely to develop cancer compared with those with the lowest densities. Breast density is generally assessed using mammographic imaging; however, this approach has limitations. Magnetic resonance imaging and ultrasound tomography are some alternative imaging modalities that can aid mammography in patient screening and the measurement of breast density. As breast density becomes more commonly discussed, knowledge of the advantages and limitations of breast density as a marker of risk will become more critical. This review article discusses the relationship between breast density and breast cancer risk, lists the benefits and drawbacks of using multiple different imaging modalities to measure density and briefly discusses how breast density will be applied to aid in breast cancer prevention and treatment.

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KEYWORDS

- breast cancer risk • breast density • mammography • ultrasound tomography

Breast cancer is the most common type of cancer among women in North America, accounting for approximately 1 in 3 cancers diagnosed. Breast cancer death rates began to decrease in the USA in 1990 [1]. This reduction reflects improvements in breast cancer treatment and possibly early detection via mammographic screening, though the role of screening is controversial. Additional effects that could also help explain the reduction include temporal changes in the frequencies of specific tumors types in response to a shift in prevalence of risk factors [2].

Available breast cancer risk prediction models have generally good ability to predict the number of breast cancers that will develop in a specific population (calibration) [3], but assessment of individual risk (discrimination) is limited [4]. Expansion of these models to include additional factors could improve discrimination. Of the many risk factors listed by the American Cancer Society [5], mammographic breast density is one of the strongest predictors of breast cancer risk. Attempts to incorporate breast density into predictive models have shown modest improvements in risk prediction estimates [4,6,7] and efforts to incorporate density in newer risk models are ongoing [8]. Based on age and BMI distribution of US women, approximately 25 million US women have heterogeneously or extremely dense breasts [9], so the inclusion of breast density is an important risk factor to consider when designing a predictive risk model.

The current gold standard for breast cancer screening is digital mammography. Mammography is a low-dose x-ray procedure that produces high quality images that allow visualization of the internal anatomy of the breast. Digital systems may have higher sensitivity than film-based mammography among women under 50 with dense breasts [10,11] and currently account for approximately 90% of mammographic screens in the USA. The American Cancer Society suggests that women receive regular and annual screening mammograms beginning at 40 years of age [12]. Screening has been shown to reduce breast cancer mortality [1,13] and early detection may enable less aggressive surgeries and treatment options.

However, mammographic screening has come under increased scrutiny recently. Mammography suffers from both false-negative and false-positive results. High density has been associated with false negative mammographic screens. Screening also tends to favor

detection of more indolent tumors that develop slowly and which may not have caused harm leading to 'over-diagnosis' [14]. The usefulness of mammographic screening to reduce mortality beyond that of physical self-examination has been called into question, particularly among younger women [15,16].

For women whose lifetime risk of developing breast cancer is greater than 20%, additional forms of screening are recommended in addition to mammography [17]. Among higher risk women, MRI and ultrasound breast screening are recommended in most states as part of a comprehensive cancer screening program. Since breast density is a strong risk factor for breast cancer, knowledge of breast density can greatly affect the assessment of risk. Therefore, screening methods that can stratify breast density for this higher risk cohort would be very useful in risk assessment [18].

Systematic studies have consistently demonstrated that increased mammographic density is related to increased breast cancer risk [19–21]. Boyd *et al.* have investigated this relationship thoroughly over many years [22–26]. It was determined that, when compared with women with lower densities, women with the highest densities showed an increased risk of breast cancer of four to six-fold. Other studies carried out by Byrne *et al.* [27], Byng *et al.* [28,29], Wolfe [30] and Vachon *et al.* [31] further highlight that irrespective of the modality used to measure mammographic breast density, high density is a strong indicator of breast cancer risk. Furthermore, Boyd *et al.* and others have demonstrated that high mammographic density is strongly associated with elevated risk of breast cancer detected by screening or presenting clinically between screening exams (i.e., interval cancers) [24].

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**Molecular mechanisms that mediate the relationship between breast density & breast cancer risk**

Breast density reflects breast tissue composition and its biophysical properties. Compared with nondense, adipose-rich tissue, denser tissues contain a higher proportion of fibroglandular elements, including epithelial and stromal cells, connective tissue and intercellular matrix. Dense tissue impedes the passage of x-rays through the breast, resulting in white opaque regions on a mammogram. Dense tissue corresponds to elevated sound speed in ultrasound tomography (UST) and higher water content of

fibroglandular tissue in MRI. While measurements obtained using different modalities are correlated, differences between measurements among technologies reflect the underlying physics of the modalities [32].

Proposed explanations for the strong positive relationship between breast density and breast cancer risk include:

- Epithelial cell content is greater in denser tissue which might represent a surrogate of cells bearing potentially carcinogenic mutations or stem/progenitor cells with substantial replicative capacity;
- Characteristics of the microenvironment of dense tissue are more conducive to carcinogenesis;
- Dense tissue serves as a biosensor of systemic factors that increase breast cancer risk.

It is unclear which, if any, of these hypotheses about density and risk are correct. However, the first two possibilities suggest that breast density might represent a causal intermediate in carcinogenesis, and therefore, lowering density could reduce breast cancer risk. Studies that combine novel density measurements with molecular pathology can inform this issue.

Denser breasts are associated with a higher content of epithelial cells and/or stromal cells which could reflect a greater number of cells at risk of malignant transformation [23,33–34]. Higher density is also associated with a greater content of terminal duct lobular units, the specific microanatomic structures from which nearly all breast cancers arise [35]. However, epithelial cell numbers may not fully explain density related risk as most data suggest that percentage density is a stronger marker of breast cancer risk than absolute density [21]. Boyd *et al.* suggested that density is most variable in the population at younger ages and converges to a lower more similar value as women age [36]. Given that cellularity and density both decline with age, while breast cancer incidence increases, higher cell numbers alone are likely too simplistic an explanation for the underpinning of density associated risk.

Higher mammographic density is also associated with greater collagen content [33]. Collagen contributes to increased extracellular matrix stiffness [37,38], which may increase cancer development [39,40]. Studies in animal models suggest that tumorigenesis is promoted in the presence

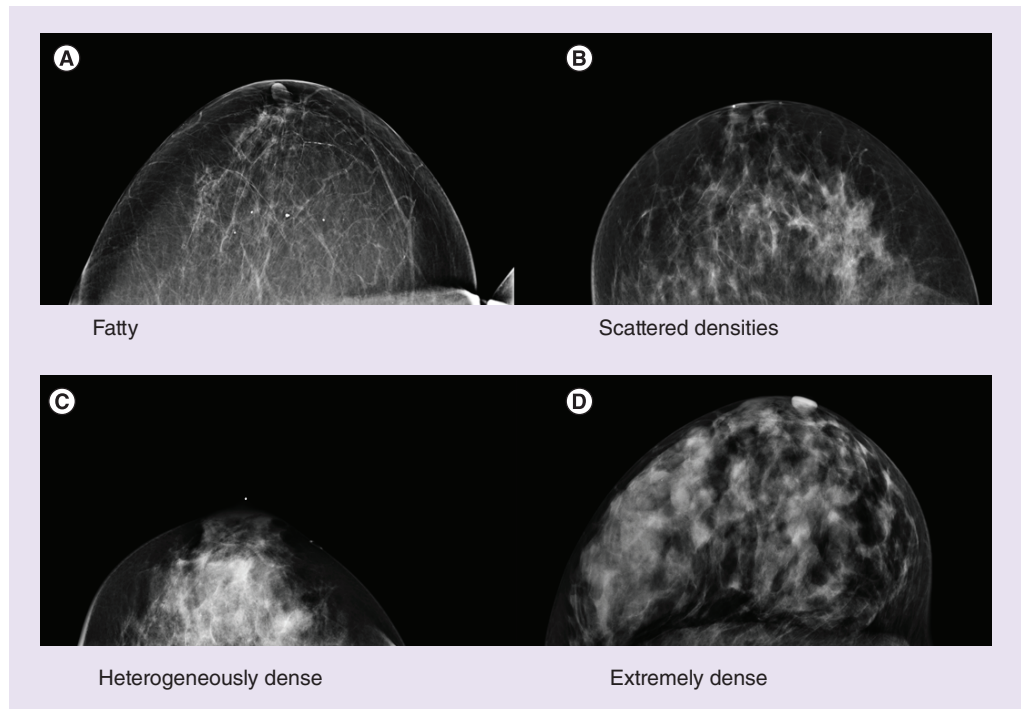
of increased collagen. More recently, Keely and colleagues have demonstrated that altered collagen fiber alignment in tissues may be associated with breast cancer, and particularly, with more clinically aggressive tumors [39,40].

Molecular composition of nondense tissue may also affect associations of density and breast cancer risk. Pettersson and colleagues found an inverse relationship between nondense breast area and breast cancer risk [41], supporting the hypothesis that fat tissue within the breast may be protective against breast cancer development. The molecular relationship between BMI and mammographic breast density is not fully clear. In a recent study, correlations between fibroglandular volume and mammographic dense area were strongest among women that were categorized as lean [42]. However, the strength of the correlations decreased with increasing BMI [42], suggesting that volumetric and area density measurements do not capture nondense tissue in a similar manner. Further, data suggest that density is not associated with risk of breast cancer death in analyses adjusted for prognostic pathologic features (i.e., stage, grade, estrogen receptor status); however, a subset analysis has suggested that obese women with low density may be at elevated risk of death [43].

### Breast density measurements using mammography

John Wolfe, at Wayne State University, was the first to propose a relationship between patterns of breast density on a mammogram and breast cancer risk over 35 years ago [30]. Four classifications were used to separate women into groups according to their relative risk of developing breast cancer. In an effort to standardize mammographic reporting, the American College of Radiology developed an alternate visual assessment method known as the Breast Imaging Reporting and Data System (BI-RADS) [44]. The BI-RADS is a density estimation technique that typically involves a radiologist's visual assessment of the mammogram. It is routinely reported for a large proportion of mammograms in the USA according to four categories: predominately fat (A), scattered densities (B), heterogeneously dense (C) and extremely dense (D) (Figure 1). However, due to the subjective nature of these classifications, considerable inter- and intra-rater variability exists [45].

The relationship of Wolfe's classifications and BI-RADS density score to risk have been



**Figure 1. Examples of the BI-RADS categories for density measurements made on mammography.**

affirmed, and recognition that parenchymal patterns are markers of risk has stimulated the development of more quantitative and objective methods of breast density assessment. Quantitative methods to measure breast density involve the use of computer-assisted programs that are based on interactive or automatic thresholding and segmentation. Examples of such programs include Cumulus [46], Volpara [47] and Quantra [48]. Mammographic percent density (MPD) is determined by finding the ratio of fibroglandular to total breast tissue areas or volumes. MPD can then be treated as either a continuous or categorical variable in subsequent analysis. An example of the Cumulus software [46] being used to measure MPD is shown in **Figure 2**.

**Limitations of density measurements made by mammography**

Despite being the current gold standard for breast imaging, mammography poses the following shortcomings for both cancer detection and breast density measurement:

- MPD more closely reflects the attenuation and absorption characteristics of the breast tissues rather than the physical tissue density;

- Use of ionizing radiation limits its application for density estimates in younger women, creates caution about performing repeated examinations and may increase breast cancer risk [49];
- MPD is derived from 2D projection of 3D volume. It requires compression which can alter density measurements [50]. Attempts to provide an accurate volumetric analysis of the density are limited by the variable breast thickness and assessment of regional density is challenging;
- MPD does not take into account the variability of how images are processed by different mammography manufacturers;
- The measurement does not have an external or absolute scale.

Breast density calculated by the use of mammography is dependent on the variations in breast tissue composition along with x-ray attenuation properties of those tissues and the methods used to generate the images. The image processing that is applied to digital images to maximize contrast helps detect relevant signs of cancers [10], but it can also distort the calculation of density. Digital image processing algorithms

ultimately function to spread the image more uniformly among all the possible gray levels, while film mammography tends to render most of the image toward the black or white levels with few pixels occupying the intermediate gray levels. The differences between manufacturers in the production of the x-ray hardware and processed mammographic images mean that image quality may vary across institutions.

Breast density measurements using mammography are typically based on the 2D projected area of the breast instead of examining the entire 3D volume. For mammographic density measurements, each pixel is simply assumed to represent either completely dense or completely fatty tissue. In reality, each pixel represents the x-ray absorption and attenuation characteristics of both fibroglandular and fatty tissues combined. It is therefore possible that two women may show similar projected areas of dense tissue yet may have different volumes of dense tissue [50]. Efforts have been made to estimate the volume of dense tissue based on these mammographic measurements. These efforts generally involve the use of algorithms or physics models that use the imaging acquisition parameters to convert the mammographic pixel values into estimates of the thickness of the fibroglandular tissue [51].

Although mammographic density estimation using volumetric methods, such as Quantra or Volpara, produces density measurements that correlate strongly with other measures of breast density [47–48,52], improvements in risk prediction when using volumetric as opposed to area density are mixed [25,53–57]. This appears to be counterintuitive as the entire breast volume should logically contain more information than the projected area. Most of the algorithms require knowledge of the breast thickness and the calculated volumes are sensitive to small changes in the measured value. Small errors in the thickness can lead to inaccurate estimations of volume of dense and nondense tissue that can reduce the performance in risk prediction, thereby off-setting theoretical advantages.

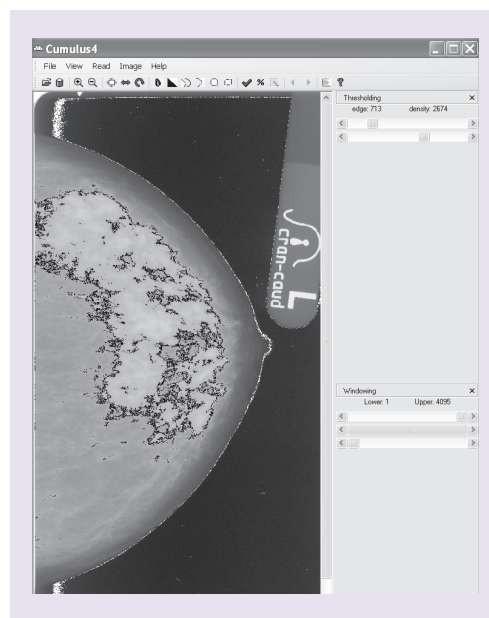
### Alternatives to mammography

Mammography is currently used in routine clinical practice and is the only screening method that has been shown to reduce mortality from breast cancer [1,13]. Therefore, it is likely that mammography will remain as the principal method of breast cancer detection. Digital mammography has largely replaced film mammography in the

USA, based on its reported advantage in detecting breast cancer among younger women with dense breasts [10], yet it is not optimal for the measurement of breast density. Beyond mammography, multiple breast imaging modalities have been developed that could be used to assess breast density, each offering specific advantages and limitations. The major alternatives to mammography are MRI [58–64] and UST [32,65–74]. Additional imaging modalities that can also measure breast density include double x-ray absorption [75–77], digital breast tomosynthesis [78,79], positron emission mammography [80,81], molecular breast imaging [82], breast CT [83,84] and optical imaging [85,86]. Summaries of the advantages and limitations of these different imaging modalities are discussed in [Table 1](#).

### Magnetic resonance imaging

MRI uses nonionizing radio waves to produce 3D images of tissue structures with very good soft tissue contrast. For women with a greater



**Figure 2.** An example of the Cumulus software measuring mammographic percent density in a mammogram. A user selects the edge threshold (white) that separates the breast tissue from the background and the density threshold (black) that separates dense tissue from nondense tissue. MPD can be calculated by taking the number of pixels estimated by the density threshold (dense area) and dividing by the number of pixels estimated by the edge threshold (total breast area) [46].

**Table 1. Benefits and limitations of breast density measurements made with various imaging modalities.**

Imaging modality	Benefits	Limitations
Mammography	<ul style="list-style-type: none"> <li>Widespread access in developed nations</li> <li>Inexpensive and fast</li> <li>Current gold standard for detection of masses</li> <li>Dedicated solely for breast imaging</li> <li>Mammographic density known to correlate strongly with breast cancer risk</li> </ul>	<ul style="list-style-type: none"> <li>Uses ionizing radiation and breast compression</li> <li>Creates 2D images of anatomy</li> <li>Density is measured indirectly, no absolute or external scale</li> <li>Variation in image processing and quality between hardware manufacturers</li> <li>Reduced utility for women with densest breasts, young women; close interval repeated examinations increase radiation exposure</li> </ul>
MRI	<ul style="list-style-type: none"> <li>Useful modality for women with elevated breast cancer risk</li> <li>3D volumetric imaging</li> <li>No ionizing radiation used</li> </ul>	<ul style="list-style-type: none"> <li>Expensive and long exam time limit widespread use</li> <li>Requires special infrastructure to house and technical personnel expertise</li> </ul>
UST	<ul style="list-style-type: none"> <li>3D volumetric images</li> <li>Sound speed is a direct measurement of density</li> <li>Inexpensive, short exam time</li> <li>No ionizing radiation or compression</li> <li>Strong correlations between UST measurements and mammography</li> </ul>	<ul style="list-style-type: none"> <li>Not in widespread use</li> <li>Although expected, no direct link between UST and breast cancer risk yet demonstrated</li> <li>Sensitivity and specificity in screening for invasive cancer not established; currently an adjunct to mammography</li> <li>Not effective in detecting microcalcifications, a marker of ductal carcinoma <i>in situ</i></li> </ul>
Double x-ray absorption	<ul style="list-style-type: none"> <li>Lower dose (relative to mammography)</li> <li>Effective in measuring breast density and soft tissue composition</li> </ul>	<ul style="list-style-type: none"> <li>Uses ionizing radiation</li> <li>No dedicated breast imaging devices</li> </ul>
Breast tomosynthesis	<ul style="list-style-type: none"> <li>3D imaging</li> <li>Possible better sensitivity and specificity relative to mammography</li> </ul>	<ul style="list-style-type: none"> <li>Uses ionizing radiation</li> <li>Density measures are made on 2D projections, not 3D</li> <li>Long-term experience limited</li> </ul>
Positron emission mammography and molecular breast imaging	<ul style="list-style-type: none"> <li>Functional imaging methods provide more than just anatomic information</li> <li>3D volumetric images</li> <li>Radioactive uptake corresponds well with mammography</li> </ul>	<ul style="list-style-type: none"> <li>Not widespread, requires preparation and injection of radioactive probes</li> <li>Long exam time</li> <li>Limited spatial resolution</li> </ul>
Breast CT	<ul style="list-style-type: none"> <li>3D imaging</li> <li>Superior image quality for visualization of masses compared with mammography</li> <li>Density measures correlated well with mammography</li> </ul>	<ul style="list-style-type: none"> <li>Uses ionizing radiation</li> <li>Limited and costly machinery limits widespread implementation</li> </ul>
Optical imaging methods	<ul style="list-style-type: none"> <li>Do not use ionizing radiation</li> <li>Portable devices can be used at bed side</li> <li>Measurements of spectroscopic features or tissue components are made which can potentially provide additional information for risk assessment</li> </ul>	<ul style="list-style-type: none"> <li>Direct measurements of tissue density not made</li> <li>Not in widespread use</li> <li>Can only penetrate up to several centimeters of tissue</li> </ul>

UST: Ultrasound tomography.

than 20% lifetime risk of developing breast cancer, MRI is recommended as an additional form of screening [17], and MRI has been used to measure breast density as well. Breast density using MRI involves creating images where dense tissue

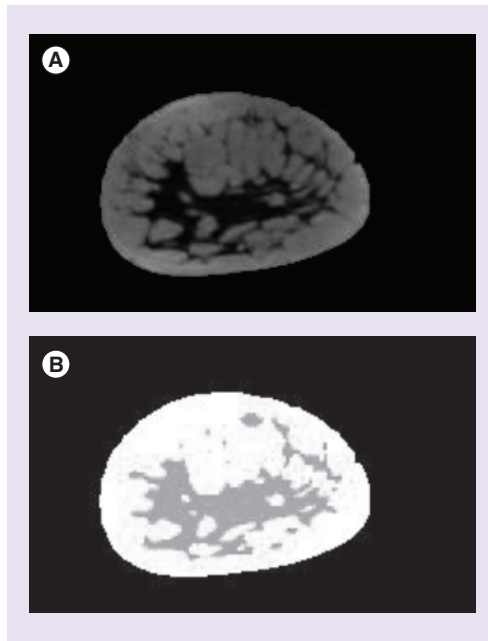
can be segmented from nondense tissue (Figure 3). Many different sequences have been used to create images. A commonly used protocol involves  $T_2$ -weighted MRI scans [61], however correlations between MPD and  $T_2$  relaxation time have been

measured [58]. Furthermore, sequences known as Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation (IDEAL) are believed to directly assess the biochemical features and composition of breast tissue but are still considered a surrogate for the real histological references standard [64]. All of these techniques have shown strong correlations with mammographic density [58–63]. Despite the fact that different sequences have been used to measure breast density on MRI, no definite consensus has been reached about the optimal technical method [59]. In addition, MRI is also associated with false-positive results, has lower specificity compared with mammography and has not yet shown to decrease mortality. Due to the absence of ionizing radiation, MRI may represent a useful screening tool for younger women. However, MRI requires special infrastructure and technical expertise to operate which increases its expense and makes widespread use for density measurement impractical. Current screening sequences also require intravenous contrast injections.

### Ultrasound & ultrasound tomography

Ultrasound imaging, like MRI, is recommended as an additional form of screening for women with increased risk of developing breast cancer [17]. When using automated breast ultrasound (ABUS) in combination with mammography, cancer detection increases compared with mammography alone [87]. Efforts to measure breast density using ABUS have been attempted [88], but it is still a relatively new area of research. Using ABUS to measure density is a labor-intensive process that suffers from problems with accurate segmentation of the breast.

In 1976, Greenleaf *et al.* observed that acoustic measurements made with transmission ultrasound (US) could characterize breast tissue [89] and that differentiation between benign masses and cancers was possible based on plots of sound speed and attenuation. This result led to the development of US transmission scanners in an attempt to measure the transmission parameters *in vivo*. UST is one example of this type of ultrasound scanner. UST does not require ionizing radiation or breast compression. UST examinations are not time intensive and costs of ultrasound technology generally compare favorably with other breast imaging modalities. Therefore, UST may be used for risk assessment in conjunction with mammographic screening for breast cancer.



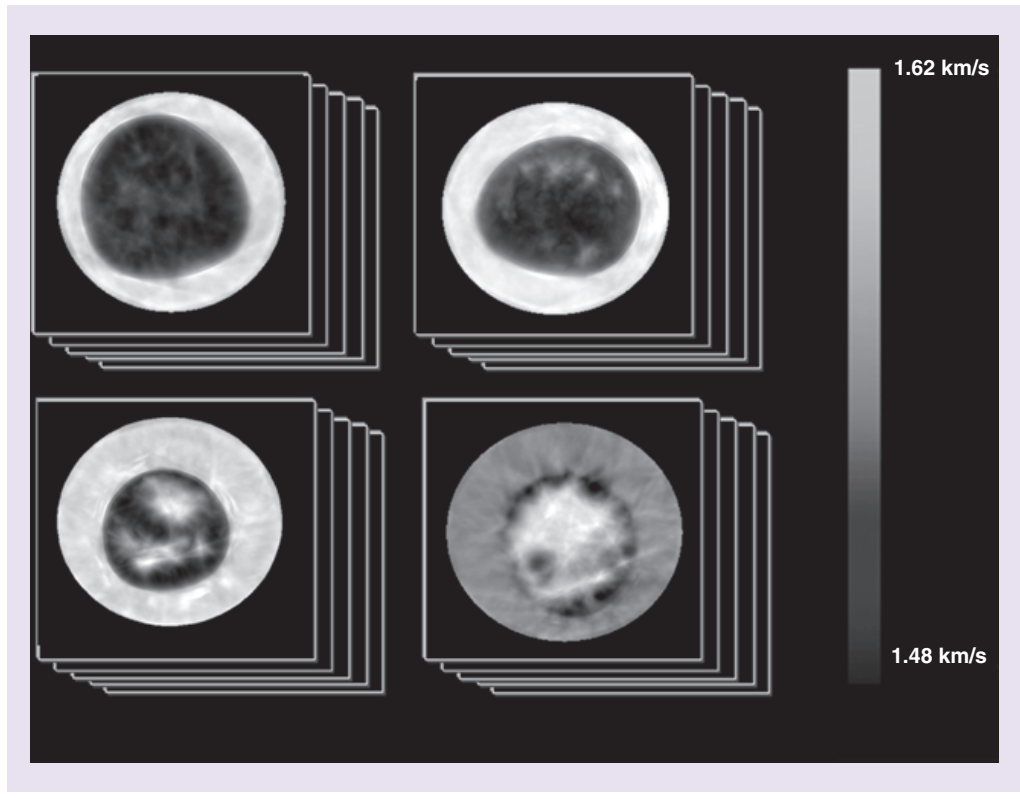
**Figure 3.** (A) Example of a precontrast  $T_1$ -weighted coronal MRI image. (B) The same image with a user-defined threshold used to separate dense tissue (dark) from fatty tissue (white).

UST uses whole-breast sound speed as an indicator of breast density. In breast tissue, the speed of sound ( $v$ ) has the following relationship to the elastic constant ( $c$ ) and material density ( $\rho$ ):

$$v = \sqrt{\frac{c}{\rho}}$$

Studies have shown that in human tissues, the elastic constant scales proportionally to the cube of density ( $c \propto \rho^3$ ) [90–92]. Substitution into this equation reveals that in human breast tissue, sound speed is directly proportional to density. Therefore, the average density of the breast can be measured by calculating the volume averaged sound speed of the breast. This measurement represents an absolute scale that can easily be replicated between current and future machines without the need for phantom calibrations. Examples of the sound speed images produced by UST are shown in **Figure 4**.

Previous work done by Glide *et al.* [70,71] was the first to examine the relationship between UST density measurements and mammography density measurements. It was found that sound speed correlated strongly with the known mass densities and CT numbers of the different regions in an anthropomorphic breast phantom.



**Figure 4. Examples of sound speed images created from an Ultrasound Tomography device.** Each image represents one slice in a stack of images corresponding to a single breast. Image slices are obtained moving from the chest wall to past the nipple to image the entire volume of the breast. The images are roughly organized according to the Breast Imaging Reporting and Data System (BI-RADS) mammographic density categories. Top left is a fatty breast (BI-RADS) category (A), top right is a breast with scattered densities (B), bottom left is a heterogeneously dense breast (C) and bottom right is a dense breast (D).

*In vivo* comparisons of the breast volume averaged sound speed (from UST) to film MPD measurements also gave strong correlations. A volumetric estimation of US percent density (USPD) also showed strong correlations with MPD.

More recent studies carried out by Duric *et al.* [32] using a larger data set support the results by Glide *et al.* They showed that the average UST breast density correlates strongly with both film and digital mammographic density measurements. UST density measurements are positively associated with the amount of dense tissue on a mammogram and negatively associated with the amount of nondense tissue. UST density is higher in premenopausal than in postmenopausal women and shows expected inverse associations with age and weight. Since sound speed is more directly linked to the physical density of the breast tissue than mammography, it has the potential to be a more accurate marker of

breast tissue density than mammographic density measures. However, these results do not link UST density measurements with breast cancer risk.

#### Applications of breast density with CAD

Computer-aided detection (CADe) and computer-aided diagnosis (CADx) are techniques that are designed to assist in the interpretation of medical images [93,94]. CAD systems are designed to improve interpretation of the abundant visual data presented in radiologic images and highlight specific questionable areas for greater scrutiny. CAD techniques have been applied to mammography to aid radiologists in the detection of masses, microcalcifications and architectural distortions. CAD may be viewed as a second reader that assists the radiologist by identifying areas that could have been missed. The impact of breast density on CAD systems has been investigated [95]. Microcalcification



sensitivity is independent of mammographic breast density but density decreases mass sensitivity [96]. The false-positive rate of mammographic screening is lower in nondense breasts versus dense breasts. When using CAD, breast cancer detection was not affected by breast density [97]. This suggests that CAD may be advantageous for patients with dense breasts. As mammographic CAD techniques continue to improve, women with dense breasts may see improvements in early detection and decreased masking bias that currently disproportionately affects them. In the future, extension of CADe and/or CADx to UST-based screening in women with dense breasts appears feasible, as well as helping to automate the monitoring of subtle density changes during chemoprevention and treatment monitoring.

### Conclusion & future perspective

The link between mammographic breast density and breast cancer risk is well-documented. However, the link between other measures of breast density, such as UST sound speed measurements, and breast cancer risk has yet to be investigated. Since the other measures of breast density correlate strongly with mammographic density, it is expected that breast cancer risk would also correlate with the nonmammographic density measures. However, this must be formally validated in future studies.

Breast density can also potentially be used as a marker to observe changes in breast tissue in response to preventive and therapeutic strategies. Several studies have shown that approximately one-third to one-half of women receiving tamoxifen experience a decrease in mammographic density within about a year and that these density declines could predict favorable responses in both the treatment and preventive settings [98–100]. Preliminary work using UST density measurements shows that, among some women, changes in density among those treated with tamoxifen are detectable within a few months of initiating treatment. These results show potential to rapidly provide encouragement to responders to adhere to therapy, while redirecting nonresponders to alternative treatment options [74]. UST density has also been used to assess response to neoadjuvant chemotherapy [101].

In future studies, integrating imaging characteristics with tissue analysis of cellular composition, biophysical properties of tissues and

molecular markers in tissues and blood, may reveal mechanisms that account for density associated risk. Understanding such mechanisms would provide directions for future research aimed at refining risk estimates and developing means to lower density, which could improve radiologic screening, and perhaps, prevent breast cancer.

Breast density is becoming an important topic in the discussion of women's health. Although breast density is one of the strongest risk factors in determining breast cancer risk, work by Manning *et al.* [102] shows that women in Detroit, Michigan were generally unaware that increased breast density is associated with increased risk. Furthermore, they found that approximately one third of women in the study knew their own breast density. In an effort to increase awareness of breast density among women undergoing screening, a growing number of states have passed legislation requiring the reporting of breast density to patients [103]. As more states begin mandating the reporting of breast density information to patients, general knowledge of the link between breast density and breast cancer risk will increase. These interests will converge to place greater demands for improved methods of accurately and reproducibly measuring breast density, assessing its role in risk prediction and guiding screening recommendations. Given the potentially substantial cost implications of these concerns, future research on breast density is needed.

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