Looking beyond the mammogram to assess mammographic density: A narrative review

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Abstract. MD – the white areas on a mammogram (also known as breast density), has long been recognised as an indicator of breast cancer (BC) risk and mammographic masking. Recent legislation in 32 American states has mandated the inclusion of mammography density information in reports for women in the higher two MD quartiles, and it is a growing consideration world-wide. While the mammogram is currently the only means of estimating MD, it suffers from a number of limitations. These are related to the accumulation of low dose ionising radiation used in mammography that limits its repeated use, particularly in young women, women with previous radiation exposure, those having undergone prior surgery, or those with radio-sensitising gene mutations. This review compares and contrasts the variety of emerging technologies that can provide a quantitative and true volumetric analysis of breast density, without the use of ionising radiation.

Keywords: Mammographic density, breast cancer risk factor, magnetic resonance imaging, fibroglandular tissue, ultrasound, ionising radiation

Abbreviations

ADC Apparent diffusion coefficient
AGD Average glandular dose
BC Breast cancer
BI-RADs Breast Imaging-Reporting and Data System
BMI Body mass index

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MD, also known as breast density, refers to the degree of radio-opaque appearance of the mammogram, the whiter the mammogram the higher the density [80]. It is an indicator of tissue composition, and has important consequences for BC risk and mammographic efficacy in detecting signs of malignancy. An Australian woman’s lifetime risk of BC is ~1 in 8 (12.5%) [3], which is comparable to the UK (12.5%) and America (12%) [20,83]. There are ~500,000 deaths annually from BC worldwide from ~14 million BCs detected, indicating the severity of BC (World Health Organisation [WHO]; www.who.int/cancer/detection/breastcancer/en/index1.html). Recent studies have shown that MD can also directly impact the progression and dissemination of BC cells [2,25,36,37,91].
Risk factors for BC include increasing age, high post-menopausal BMI, a family history of the disease, menarche at an early age (<11) and high MD [16,27,115]. In terms of predicting which women will develop BC on a population basis, MD adjusted for age and BMI is as strong a risk factor as all the genetic risk factors identified in the last two decades, including mutations in the BRCA1 and BRCA2 genes [53]. An accurate estimation of an individual’s MD is therefore an important determinant of BC risk and prognosis. This review summarises the current understanding of MD and MD-associated BC risk and progression, and evaluates current and emerging alternative technologies to accurately determine MD and analogous – MD measures.

This narrative review used a PubMed search of original and review articles from 1970 to 2017 with the following terms (Title/Abstract search of: mammographic density; MD; mammography ± alternative measure or volumetric or fibroglandular or MRI or BC risk or background parenchymal enhancement [BPE] or estrogen) to formulate an evidence-based overview of current and experimental approaches to determine MD. 143 articles were retrieved and based on analysis of abstracts and text, 128 were used as a basis for this review.

2. Composition of dense breast tissue, it’s association with increased BC risk, and factors influencing amount of dense tissue in the breast

On a mammogram, radio-dense regions, or regions of high MD, correlate to FGT or collagenous stroma and appear white, whilst radio-lucent regions, or regions of low MD, are rich in adipose tissue and appear dark (Fig. 1). Histological studies from our laboratory and others has revealed that high MD areas have increased dense connective tissue, lower adipose content, and modest but significantly increased proportions of epithelial tissue, which show less complex glandular structures [18,40,47,56]. These findings strongly support the hypothesis that the glandular and/or stromal compartments, and corresponding extracellular matrix (ECM) such as collagens and proteoglycans [56,99], are major determinants of MD.

MD is an established risk factor for BC in women. Women in the highest MD quartile as determined by BI-RADs have a 4–6 times increased risk of BC compared to those in the lowest quartile [15,116]. Although also associated with increased BC risk [80,128], percent MD (PMD), which is the proportion of MD area as a function of the total breast area, was recently shown to better predict masking of interval cancers [72]. Higher brightness thresholding using the Cumulus software resulted in better risk prediction with successively higher brightness thresholds, dubbed Altocumulus and Cirrocumulus [84–86]. When adjusted for other risk factor interactions using OPERA, the risk associated with MD is similar to, or higher than that seen with known gene mutations and family history [53].

Various factors have been suggested to influence the amount of dense tissue in the breast. MD status has been associated with a range of single nucleotide polymorphisms [105], with estrogen fluctuations (reviewed in [105]) during the menstrual cycle, although this is equivocal [1,124], and with menopause (decrease, [106]). Combined hormone replacement therapy (HRT), which increased the risk of BCs in the Women’s Health Initiative trial [95], causes a dramatic increase in MD [44], and this was recently shown to account for the associated increase in BC risk [19]. Conversely parity, which is known to protect against BC [75] decreases MD [126], with higher numbers of live births correlating with larger decreases. More recently, selective oestrogen receptor modulators such as tamoxifen (TAM) have been shown substantially reduce BC incidence in high risk women [39], and to reduce MD concordantly [17,98]. MD reduction in women treated with TAM correlated with reduced initial BC risk in the preventative
setting [29] as well as reduced risk of BC relapse [29,62,70,73]. Additionally, MD is affected by life choices such as diet [74], alcohol (increases [114]), physical activity (reduces; [114]) or lack of parity (increases; [126]). Importantly, these latter influences, along with the HRT and Tamoxifen data above, suggest that MD is dynamic throughout a woman’s life, and to some extent it is possible that MD-associated BC risk can be deliberately modified. As a result, repeated measurements for the longitudinal monitoring of MD may be necessary to dynamically assess patient specific MD-associated BC risk.

Although less described, MD may also be a risk factor for BC in men. In Australia, less than 1% of all BCs occur in men and most will present at late stage [7]. High circulating estrogen leading to gynecomastia is associated with the development of BC in men, as evidenced in men with Klinefelter’s syndrome (testicular failure shortly after puberty) who have 58-fold higher risk of developing BC than normal males [107]. Screening mammography is not recommended for males, due to the lack of mammary tissues, and mammography in males is restricted to the diagnostic setting [93]. The pathologic classification of diffuse glandular gynecomastia presents as high MD on a mammogram and is also associated with higher levels of circulating hormones [6]. It is possible that MD in this context in men similarly leads to both masking and an increase in BC risk due to the tumour-promoting effects of hormone use on the breast tissue, however implications of MD in men is not well documented.
3. How is MD estimated in the clinic?

Despite the emergence of alternative technologies (reviewed in Section 4), the mammogram is still the quickest and most cost-effective method of screening for BC, and presently the only method for estimating MD, as occurs routinely in many states of the United States. In the UK, in a move to develop risk-stratified approaches to population-based breast screening, a trial was conducted in which MD was included to estimate a woman’s overall BC risk, and for determining whether women would want to know this information [38]. This kind of “Breast Composition” categorical assessment (as opposed to “Assessment” which determines presence and severity of breast atypia) is standardised in the BI-RADS (Breast Imaging-Reporting and Data System) scale. Four categories are distinguished: the breast tissue (I) is almost entirely fatty, (II) contains scattered areas of fibroglandular density, (III) is heterogeneously dense, which may obscure small masses or, (IV) is extremely dense, which lowers the sensitivity of mammography [100].

The interpretation of mammography and assessment of MD into one of the four BI-RADS categories has evolved from subjective and qualitative to objective and quantitative. Inter-observer variability has largely been minimised with the advent of computerised approaches to estimate MD using applications such as the semi-automated, user-set thresholding computer program Cumulus [52], its similar but improved alternative AutoDensity [87], and Volpara (Volpara Solutions, Wellington, New Zealand), which is fully automated and provides volumetric data on the breast [103]. These technologies, which standardise MD assessment, have been successfully applied to compare MD in retrospective cohorts [21,32,117]. Machine learning approaches have also identified X-ray ‘textural’ features that overlap only partially with overall MD, and are also strongly associated with BC risk [54,76,112].

While mammography is currently the cheapest and easiest way to determine MD, there are several reasons to develop alternatives. Mammography is not an option for all women – the use of ionising radiation renders mammography unsuitable for young women, women with previous radiation exposure, or those having undergone a partial mastectomy. Low-dose ionising radiation from a chest X-ray has been shown to increase the risk of BC significantly among BRCA1 and BRCA2 mutation carriers [5] and a strong association (odds ratio (OR) 3.21) between CHEK2*1100delC carrier status, BC risk and a history of chest X-rays has been found [10]. Additionally, the use of ionising radiation sets an upper limit on exposure and measurement frequency. As a result, accruing longitudinal data for assessment of changes in MD due to hormonal or lifestyle changes using mammography is not ideal. Alternative MD assessment modalities, such as those mentioned below, may be very helpful in terms of providing refined information on MD-regulatory scenarios. These alternative methods may also add to the understanding of MD through the structural characteristics that they interrogate.

4. Which alternative technologies to the mammogram have been used to define MD?

How can MD be best defined in a routine manner in the clinic, given the array of new technologies available? It could be argued that the strengths of a mammogram-alternate approach to detect MD would lie in its ability to (i) sensitively detect the equivalent of MD in the chosen modality in a true volumetric (i.e. not 3D-extrapolated) manner, (ii) not expose the patient to ionising radiation, (iii) cause minimal discomfort to the patient, and (iv) satisfy cost benefit criteria. Aspects of portability and simplicity of use would be considered secondary to these important issues.

Several alternative technologies have been developed that exploit the various qualities of mammographically dense versus non-dense breast tissue with their “density” concordance to MD summarised
How non-mammographic methods compare with mammogram in estimating MD. Where possible, the Spearman’s ($r_{\text{Spearman}}$) or Pearson’s ($r_{\text{Pearson}}$) correlation factors are stated; $r$ is used when the specific correlation method is not reported; $R^2$ denotes the coefficient of determination from a univariate linear regression (ULR) between the measure of interest and MD, the corresponding $r_{\text{Pearson}}$ correlation factor (calculated by us as $\sqrt{R^2}$) is shown in brackets. US: ultrasound

<table>
<thead>
<tr>
<th>Approach</th>
<th>Correlation with MD determined by mammogram (MD; automated and/or BI-RADs manual assessment)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital breast tomosynthesis</td>
<td>$r_{\text{Pearson}} = 0.54$; $r_{\text{Pearson}} = 0.97$; $r_{\text{Spearman}} = 0.91$</td>
<td>[8,108]</td>
</tr>
<tr>
<td>Duel energy X-ray absorptiometry</td>
<td>$r_{\text{Spearman}} = 0.76$</td>
<td>[78]</td>
</tr>
<tr>
<td>Transillumination Spectroscopy</td>
<td>$r_{\text{Spearman}} = 0.72$; 80–90% prediction with MD; $r_{\text{Spearman}} = 0.88$</td>
<td>[11,101,102]</td>
</tr>
<tr>
<td>Bioimpedance</td>
<td>$r_{\text{Spearman}} = -0.52$</td>
<td>[79]</td>
</tr>
<tr>
<td>US Tomography, B-Mode US</td>
<td>$r_{\text{Spearman}} = 0.69$; $R^2 = 0.67$ ($r_{\text{Pearson}} = 0.81$)</td>
<td>[42,58]</td>
</tr>
<tr>
<td>US Elastography</td>
<td>$R^2 = 0.44$ ($r_{\text{Pearson}} = 0.66$)</td>
<td>[58]</td>
</tr>
<tr>
<td>Diffusion Weighted MRI</td>
<td>Increased MD strongly associated with increased ADC ($p \leq 0.0001$); $r_{\text{Pearson}} = 0.51$</td>
<td>[81,90]</td>
</tr>
<tr>
<td>$T_1$-weighted MRI</td>
<td>$r = 0.78$; $r = 0.76$; $R^2 = 0.73$ ($r_{\text{Pearson}} = 0.85$); $R^2 = 0.67$ ($r_{\text{Pearson}} = 0.82$); $r_{\text{Pearson}} = 0.89$; ($r_{\text{Pearson}} = 0.91$) – average $r_{\text{Pearson}} = 0.87$</td>
<td>[60,68,81,111,120,127]</td>
</tr>
</tbody>
</table>

Table 1

Advantages (denoted by a tick) and disadvantages (denoted by a cross) of various approaches to estimate MD

<table>
<thead>
<tr>
<th></th>
<th>Volumetric</th>
<th>Low cost</th>
<th>No ionising radiation</th>
<th>No breast compression</th>
<th>Simplicity of use</th>
<th>Portability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital breast tomosynthesis</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Duel energy X-ray absorptiometry</td>
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<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Transillumination Spectroscopy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Bioimpedance</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>B-Mode US</td>
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<tr>
<td>US Elastography</td>
<td>✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Diffusion Weighted MRI</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>$T_1$-weighted MRI</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 2

in Table 1 and the advantages and disadvantages of each of these alternative techniques summarised in Table 2.

4.1. Approaches which employ ionising radiation

Digital breast tomosynthesis (DBT) is an extension of conventional 2D mammography, where ionising radiation is used to acquire multiple 2D projection images of the compressed breast from many angles [109]. Reconstruction algorithms combine these images to provide a tomographic-sectional and 3D volumetric view of the breast, with the aim of reducing artefacts and false readings that occur in 2D mammography. Despite the similarities between the two techniques and the image refinement, MD
measured by DBT has been shown to be underestimated compared to MD measured by conventional mammogram [108]. Correlation between MD measured by DBT and MD measured by mammogram has ranged from moderate ($r_{\text{Pearson}} = 0.54$ [108]) to excellent ($r_{\text{Pearson}} = 0.97$ [108]; $r_{\text{Spearman}} = 0.91$ [8]) across the literature.

Dedicated Breast Computed Tomography (DBCT) uses a cone-beam system to perform a true tomo-graphic scan capable of achieving near isotropic resolution in any plane with less noise than DBT and without breast compression [89], and has been demonstrated to be 21.5% more sensitive than mammography in detecting breast lesions [125]. Still in the innovation stages, current prototypes position the patient prone over a breast aperture enabling exclusion of the thorax and body from radiation exposure. It is able to capture images with high signal-to-noise ratio at a similar Average Glandular Dose (AGD) to two-view mammography [14] and less than DBT [89]. The sensitivity of various DBCT prototypes in detecting malignant features and monitoring response to chemotherapy is an ongoing field of research from which improvement in the technology has been derived [89,118]. Studies comparing volumetric density measures between mammography and DBCT have not been reported. However, a study using DBCT to measure Volumetric Glandular Fraction (VGF) in 137 breasts found statistically significant comparison between BI-RADs score and VGF [119].

Dual energy X-ray absorptiometry (DXA) is a technique characterised by low level doses of ionising radiation compared to mammogram and does not require breast compression. Images of the breast using two different X-ray energies are obtained and the difference in attenuation coefficients for fatty tissue and FGT at those two energies can be used, with the aid of a calibration phantom, to calculate the relative portion of each tissue type in the image voxel. Fibroglandular volume (FGV) measured by DXA has showed relatively good agreement with MD from mammogram measurements ($r_{\text{Spearman}} = 0.76$ by ULR [78]). The procedure is commonly used to calculate bone density in medical care settings (reviewed in [34]) and consequently, shows considerable promise as a screening tool for MD requiring lower levels of ionising radiation.

4.2. Approaches which do not employ ionising radiation – transillumination spectroscopy, bioimpedance and photoacoustics

The inherent disadvantage of methods which rely on ionising radiation is the upper limit set on exposure, and in turn measurement frequency, in accordance with patient safety. Conversely, methods which do not rely on ionising radiation have the potential to be used as frequently as required to determine a baseline density, including systematic fluctuations, and monitor longitudinal changes in breast tissue density.

One such technique is Transillumination Spectroscopy, which measures the transmission (the result of absorption and scattering) of non-ionising, optical wavelength radiation (light) through the breast [12,13]. Absorption and scattering of the light as it passes through the breast tissue provides information on tissue composition. Water, haemoglobin and fat have distinctive absorption peaks in the near infrared (NIR) spectrum; 978, 760 and 930 nm respectively [13]. FGT is therefore distinguished from adipose tissue by increased water- and haemoglobin-associated absorption and decreased fat-associated absorption. Additionally, FGT has increased signal attenuation compared to fatty tissue due of the dense cellular and collagen environment, the result of a higher scattering efficiency. MD estimations using this technique have shown good concordance with that of the mammogram (80–90% prediction with MD, $r_{\text{Spearman}} = 0.88$, $r_{\text{Spearman}} = 0.72$, respectively [11,12,101]).
Bioimpedance is another low-cost technique that measures the electrical impedance of a tissue when placed between two electrodes. Because the impedance of fat is higher than that of stromal tissue, measurements of bioimpedance can be used to estimate breast tissue density [30]. Unlike the other techniques mentioned here, which show positive correlations with MD, impedance-based resistance values are lower in dense breasts, such that quantification may present difficulties. Such measurements have been shown to be somewhat inversely correlated with MD determined by mammogram in young women ($r_{\text{Spearman}} = -0.52$ [79]).

Photoacoustics is a hybrid modality combining optical and US imaging techniques to achieve high-resolution imaging. Similar to transillumination spectroscopy, short laser pulses of determined wavelength are delivered to tissue where molecules, such as fat, water and haemoglobin, have different absorption properties. In contrast to transillumination spectroscopy, the recorded signal is generated by the thermoelastic expansion associated with this optical absorption. This expansion propagates US waves which are then detected by a transducer [77]. Heijblom et al. developed a “Photoacoustic Mammoscope” able to differentiate malignant lesions in 30 (out of 31) breasts but with low specificity [50]. Their study also compared the average photoacoustic contrast value for each breast with its BI-RADs category. Their technique, which only used a single wavelength of pulsed laser, was not sensitive to MD [51], however it is theoretically possible that a multi-wavelength investigation may find a photoacoustic contrast-density dependence [50].

4.3. Ultrasound (US) based approaches

Unlike mammography, the above two techniques are non-imaging and provide limited spatial resolution in terms locating regions of high and low density in the breast. Soft tissue imaging techniques such as US allow for a spatially resolved analysis of breast tissue density without exposure to ionising radiation. US transmission tomography exploits the difference in the speed of sound in tissues of various densities, where the speed of sound in dense FGT is faster than in adipose tissue. In US tomography, images are acquired from many different angles around the breast and, from these images the speed of sound map is generated. A strong, positive but non-linear relationship has been shown between the average speed of sound in the breast and MD measured by mammogram ($r = 0.89$, unspecified correlation coefficient, quadratic least squares fit) [41]. Estimation of MD from US tomography can also be achieved by calculating the percentage of high sound speed regions (corresponding to FGT) in the breast, and has shown to have good concordance with mammogram-determined PMD ($r_{\text{Spearman}} = 0.69$ [42]). While this technique is quantitative, US tomography is not portable. It usually requires a water tank in which to submerge the region of interest and either an array of transducers positioned around the breast, or a pair of transducers which undergo rotation around the submerged tissue [33,61,96]. Conversely, B-Mode US is highly portable and low cost, but generally not quantitative for MD. It is a single-sided, pulse-echo technique that produces an image of the breast where voxel grey-level is related to the relative acoustic impedance of different tissue types. Although the volume of B-Mode-US may be used to obtain a quantitative measure of a breast lesion, B-Mode US cannot measure an analogous-MD quantity, although it has been shown that B-mode US is able to predict MD measured by mammogram based on the distribution of grey-level values in the US image ($R^2 = 0.67$ coefficient of determination from ULR analysis) [58]. The same voxel grey-scale analysis has been performed using US elastogram images, but was shown to be less predictive of MD measured by mammogram ($R^2 = 0.44$ coefficient of determination from ULR analysis) [58]. Elastography maps the elastic properties of the tissue by measuring the displacement of the tissue during compression. This can be manually achieved, as in
through gentle compression/decompression of the tissue with the US transducer. However, this technique is not quantitative; rather the grey-level values of the voxels represent the relative stiffness of the regions in the breast. Quantitative US elastography, where the elastic modulus of the tissue is explicitly calculated, uses shear waves to induce tissue compression. While quantitative US elastography has been used to identify breast lesions [9], to our knowledge it has not been applied to breast tissue density estimation. This is somewhat surprising, given that dense breasts can be expected to have a higher elastic modulus as a result of increased collagen/ECM component, as has been demonstrated in vitro [97].

4.4. MRI

Like US, MRI techniques provide spatially resolved, volumetric analysis of breast tissue density. Several MRI approaches can be taken to determine breast tissue density, with varying agreement with mammography. Perhaps the mostly frequently utilised method of assessing MD is based on the $T_1$-weighted sequence. $T_1$-weighted MR images are able to provide contrast between water (associated with FGT) and fatty components of breast tissue as a result of the differing $T_1$ relaxation times of the two tissue types. Segmentation of the MR image into FGT and fatty tissue can be done via manual thresholding [60,122], or using semi- or fully automated image analysis techniques, generally based on the fuzzy clustering (FC) algorithm [46,67,68,88,127]. From the segmentation, the total amount of water-based signal and in turn the amount of FGT (MRI-FGT) can be calculated. This measure has shown relatively good agreement with MD determined from mammogram ($r = 0.78, R^2 = 0.73$ (ULR), $R^2 = 0.67$ (ULR) and $r_{\text{Pearson}} = 0.89$ to 0.91, respectively [60,68,81,111,120,127]). These methods have been applied to standard $T_1$-weighted images of the breast [60,111] and to fat-suppressed images, which have enhanced contrast between the water and fat signal [67,68,120], though generally at the expense of a lower signal to noise ratio. A comparison between fat suppressed and non-fat suppressed $T_1$-weighted protocols have shown small, but statistically significant, differences between the amounts of FGT measured using FC algorithm from the two imaging protocols [22]. As an extension to fat-suppression $T_1$-weighted imaging techniques, the Dixon imaging sequence has also been used to measure FGT volume in the breast [26,43]. This sequence exploits the differences in precession frequencies of the water and fat protons to produce fat-only and water-only (fat suppressed) images from MR images acquired when the water and fat signals are in-phase and opposed-phase. The amount of FGT calculated from this sequence is highly correlated with that calculated from standard $T_1$-weighted imaging using the FC algorithm ($r_{\text{Spearman}} = 0.93$ [26]), but has not yet been compared to MD measured by mammogram. A recent comparative phantom-based study of automated volumetric quantification of FGT has found that both Dixon and $T_1$-weighted sequences exhibit very good precision and accuracy when compared to the ground truth [123].

Quantitative Diffusion Weighted MRI (DW-MRI) provides unique information relating to the microscopic movement of water molecules in their molecular environment and has been shown to be effective in detecting breast lesions [23]. DW-MRI measures the apparent diffusion coefficient (ADC) of protons as a result of their net displacement during the MRI sequence. Because the protons contributing to the fat signal are relatively stationary, and the water protons within the FGT relatively mobile, the average ADC over the volume of the breast gives an indication of the amount of FGT. Increased MD has been shown to be strongly associated with increased ADC [81]. However, in the application of this technique to BRCA1/2 carriers, the measured ADC showed a relatively weak correlation with MD than other techniques ($r_{\text{Pearson}} = 0.51$ [90]).
MRI-based elastography (MRE) may also have the potential to estimate breast tissue density. Like US elastography, compression (through mechanical and acoustic shear waves) induces tissue displacement. From the amount of displacement, the shear modulus (stiffness) of the tissue can be calculated, with stiffer tissues (like FGT) undergoing less displacement than softer tissue (like fat). This technique has successfully been applied to the identification of breast lesions [104]. Mean stiffness of the breast measured by MRE has been shown to distinguish between fatty (BI-RADs I and II assessed by anatomical MR images) and non-fatty (BI-RADs III and IV) breasts \( (p = 0.03) \) [49], however, as of yet, breast stiffness by MRE has not been compared to MD measured by mammogram.

Finally, our recent work (Tourell et al.) has pioneered application of single-sided portable-NMR techniques to characterisation of MD [113], demonstrating for the first time the ability of the \( T_1 \) relaxation time constants measured using portable NMR to distinguish between HMD and LMD breast tissue. While portable NMR does not provide full 3D spatial resolution in the way MRI does, it does provide topographical selectivity combined with depth resolution. We envisaged that in vivo portable NMR instrumentation could be used to obtain depth profiles of \( T_1 \) (or an alternative proxy MD quantifier) at several “key” locations in the breast (e.g. the upper-lateral quadrant or the area above the nipple), providing a condensed MD “fingerprint” of the MD distribution in the breast. The approach shows the potential to fill the niche where radiation-free, low-cost quantification of MD is required in clinical and research contexts. Further research in this direction, including investigation of other MR quantitative metrics besides \( T_1 \), is underway.

5. BPE as a complementary BC risk indicator

BPE occurs during Dynamic-Contrast Enhanced (DCE) MRI. DCE-MRI is commonly used to detect breast tumours, where enhancement is achieved through the intravenous administration of a gadolinium-based contrast agent. As a result, DCE-MRI can detect kinetic features indicative of BC biology, such as neovascularity and vascular permeability [129]. In addition to enhancement of tumour tissue, FGT can also enhance, a phenomenon known as BPE. BPE appears as diffuse white background signal, similar to high mammographically dense tissue on a mammogram.

Similar to MD, BPE is also affected by the amount of circulating estrogen, as best shown in studies examining the effect of menopausal status on BPE, and BPE estimation following anti-estrogen therapy (Table 3). In this latter context, BPE was reduced after estrogen reduction, as has been previously observed for MD assessed by mammogram [98]. However, in the studies shown in Table 3, BPE was shown to be more sensitive to the changing hormonal environment than MRI-FGT and MD [64–66].

Also similar to MD, moderate or marked BPE, in the absence of malignancy, has been associated in several studies with an increase in BC risk ([4,31,55], detailed in Table 4). The target populations in these studies varied, however a major theme was a MRI scan of normal breast tissue, with approximately 1-year follow-up. Generally, BPE was measured by at least two observers and rated on the BI-RADs scale (BPE: minimal/mild/moderate/marked) and a conclusion on risk was made by considering patient outcome at follow-up. Curiously, one study found higher BPE (along with MRI-FGT and MD) in women at risk of developing BC compared to women with BC, however this study did not take into account menopausal status, weight, and details of hormonal therapies, which could reduce BPE [4].

Interestingly, similar to the ability of high MD regions to obstruct lesion detection by mammogram, BPE also appears to have a confounding effect on the accurate determination of breast lesions by MRI [71,110]. In 2013, MRI measurement of BPE was updated and incorporated into the 5th Edition of the
Table 3

<table>
<thead>
<tr>
<th>Study/ref.</th>
<th>Population studied</th>
<th>Years</th>
<th>Stats</th>
<th>n</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| [64]      | Postmenopausal women with BC, MRI findings of the contralateral unaffected breast, before and during 6–12 months of AI treatment (anastrozole, letrozole, or exemestane) | Aug 1999–Jun 2010 | Sign test | 149 | Anastrazole tx: BPE decreased 33/109 (33.9%) vs FGT only decreased 6/109 (5.5%)
Letrozole tx: BPE decreased 33/109 (46%), FGT decreased 1/33 (3%) | BPE more sensitive than FGT to detect reduction |
| [66]      | Women with BC, breast MRI both before and during adjuvant tamoxifen therapy      | 2002–2008  | Sign test | 88  | BPE + FGT decreased in 68% (60/88), 38% (33/88), and 40% (35/88) (p < 0.001) during tamoxifen treatment; continued tx: FGT continued to rise, BPE was detected early in treatment (<90 days) but did not rise | BPE was more sensitive than FGT in response to tamoxifen treatment, but FGT was more long-lasting |
| [65]      | Women scanned by MRI pre-, then post-menopausal (median interval 49 months)     | July–Nov 2010 | Sign test | 28  | FGT and BPE were reduced, BPE more so: unchanged: 39% women BPE reduced: 61% women | BPE more sensitive than FGT to detect reduction |

Table 4

<table>
<thead>
<tr>
<th>Study/ref.</th>
<th>Population studied</th>
<th>Years</th>
<th>Stats</th>
<th>n</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>Women ≥18 yrs, high risk but no family history of BC</td>
<td>Jan 2006–Dec 2011</td>
<td>Conditional logistic regression analysis to estimate odds-ratio (OR)</td>
<td>23</td>
<td>Mild, moderate, or marked BPE versus minimal BPE (p = 0.007; odds ratio = 9.0; 95% confidence interval: 1.1, 71.0).</td>
<td>Mild-marked BPE = nine times more likely to develop ca in followup interval compared with minimal BPE</td>
</tr>
<tr>
<td>[55]</td>
<td>Women who had undergone MRI (MRI)</td>
<td>Feb 2004–Feb 2014</td>
<td>Conditional logistic regression analysis to estimate odds-ratio (OR)</td>
<td>3027</td>
<td>Moderate: 3.4-fold (95% CI 1.6–7.3), Marked BPE: 4.8-fold (95% CI 2.1–10.8)</td>
<td>Moderate-marked BPE 3.4–4.8 fold increased risk of breast cancer</td>
</tr>
<tr>
<td>[4]</td>
<td>Women who underwent mammography and MRI</td>
<td>2010–2015</td>
<td>Pearson’s Chi Square Test</td>
<td>403 (85% BC, 15% at risk)</td>
<td>BPE (p &lt; 0.0001) was higher in high risk women compared to the BC group</td>
<td>MD, FGT and BPE are higher in women at risk of BC</td>
</tr>
</tbody>
</table>

BI-RADs Lexicon [82]. Assessment using BI-RADs with BPE, as defined in this new edition, is subject to variability [45], however computer derived applications are being developed to minimise this source of error [129].

Triple negative BCs (TNBCs) are defined as being negative for the three common types of receptors known to fuel most breast cancer growth — estrogen receptor, progesterone receptor and HER-2/erbB2/neu. Studying the patterns of BPE in MR images of TNBCs has proved informative and has been
predictive for recurrence of these cancers [92,121]. High BPE prior to neoadjuvant chemotherapy (NAC) for pre-identified lesions has also been significantly associated with a poorer recurrence-free survival, where high BPE on pre-NAC MRI (hazard ratio [HR] = 3.851, \( p = 0.006 \)) and triple-negative cancer (HR = 3.192, \( p = 0.002 \)) were independent factors associated with worse regression free survival [24,94]. Several studies have shown that higher MD status also promoted BC progression [25,35,91], and we have recently provided experimental evidence for this [57].

The appearance of BPE determined by DCE-MRI thus exhibits several parallels to MD: BPE can obscure the detection of breast tumours, it has its own BI-RADs category classification, it is affected by estrogen, and numerous studies support the independent associations of BPE and MD with increased BC risk. MD has been shown to have a correlation with FGT as assessed on MRI however BPE appears to be an independent risk factor for BC. According to the literature, BPE and MD do not generally correlate. One study reports a good correlation between these indices [63], whereas several other studies conclude that no direct correlation can be made [28,48,59,69]. Further research is needed to understand exactly why these measures of breast parenchyma do not correlate. It is likely that such work will uncover aspects of this tissue that contribute to BC growth, and hence BC risk, as will a greater understanding of the tissue environments that are responsible for MD.

6. Conclusion

Characterisation of the biophysical make-up of dense breast tissue is advancing, and studies aimed at understanding the contribution of mammographically dense breast tissue components to issues of BC risk and breast cancer progression will reveal novel lifestyle and chemopreventative targets. As understanding in the field of MD increases, and as targets become identified, so will the need and opportunity to employ better screening tools. The increased sensitivity afforded by MRI based approaches, and the added ability to refine risk assessment with the utilisation of parenchymal enhancement characteristics, may provide a way forward in this area.

Acknowledgement

We thank Ms Gillian Jagger (Division of Radiology, Princess Alexandra Hospital) for her support of our program.

Funding

This work was supported by a SPORE grant from the Translational Research Institute (TRI-SPORE), in addition to a Princess Alexandra Hospital Research Foundation grant (ALH Breast Cancer Project Grant). The Translational Research Institute is supported by a grant from the Australian Government.

Conflict of interest

None.
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