Clinical Radiology 73 (2018) 334–357

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

Breast density: why all the fuss?

S.J. Vinnicombe*

Cancer Research, School of Medicine, Level 7, Mailbox 4, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK

ARTICLE INFORMATION

Article history:
Received 10 September 2017
Accepted 17 November 2017

The term "breast density" or mammographic density (MD) denotes those components of breast parenchyma visualised at mammography that are denser than adipose tissue. MD is composed of a mixture of epithelial and stromal components, notably collagen, in variable proportions. MD is most commonly assessed in clinical practice with the time-honoured method of visual estimation of area-based percent density (PMD) on a mammogram, with categorisation into quartiles. The computerised semi-automated thresholding method, Cumulus, also yielding area-based percent density, is widely used for research purposes; however, the advent of fully automated volumetric methods developed as a consequence of the widespread use of digital mammography (DM) and yielding both absolute and percent dense volumes, has resulted in an explosion of interest in MD recently. Broadly, the importance of MD is twofold: firstly, the presence of marked MD significantly reduces mammographic sensitivity for breast cancer, even with state-of-the-art DM. Recognition of this led to the formation of a powerful lobby group ('Are You Dense') in the US, as a consequence of which 32 states have legislated for mandatory disclosure of MD to women undergoing mammography. Secondly, it is now widely accepted that MD is in itself a risk factor for breast cancer, with a four-to sixfold increased relative risk in women with PMD in the highest quintile compared to those with PMD in the lowest quintile. Consequently, major research efforts are underway to assess whether use of MD could provide a major step forward towards risk-adapted, personalised breast cancer prevention, imaging, and treatment.

Introduction

The adult female breast is composed of variable proportions of adipose tissue and fibroglandular parenchyma. At mammography, fibroglandular parenchyma, being denser than adipose tissue, attenuates X-rays more and appears whiter; hence the term breast density or mammographic density, MD (Fig 1). These terms are often used interchangeably and are effectively synonymous. Breast radiologists have always consciously or subconsciously assessed the amount of MD in relation to the visualised total breast area; breasts with little or no MD are regarded as non-dense, whereas breasts in which MD occupies >50% of the visualised total breast area are regarded as dense.[1]

MD has excited much interest and debate amongst breast clinicians and researchers in the past decade. There are two main reasons for this: firstly, the association of higher levels of MD with reduced mammographic sensitivity,[2–4] and secondly, the positive association of mammographic density

* Guarantor and correspondent: S. J. Vinnicombe, Cancer Research, School of Medicine, Level 7, Mailbox 4, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK. Tel.: +44 01382 383286.
E-mail address: s.vinnicombe@dundee.ac.uk

https://doi.org/10.1016/j.crad.2017.11.018

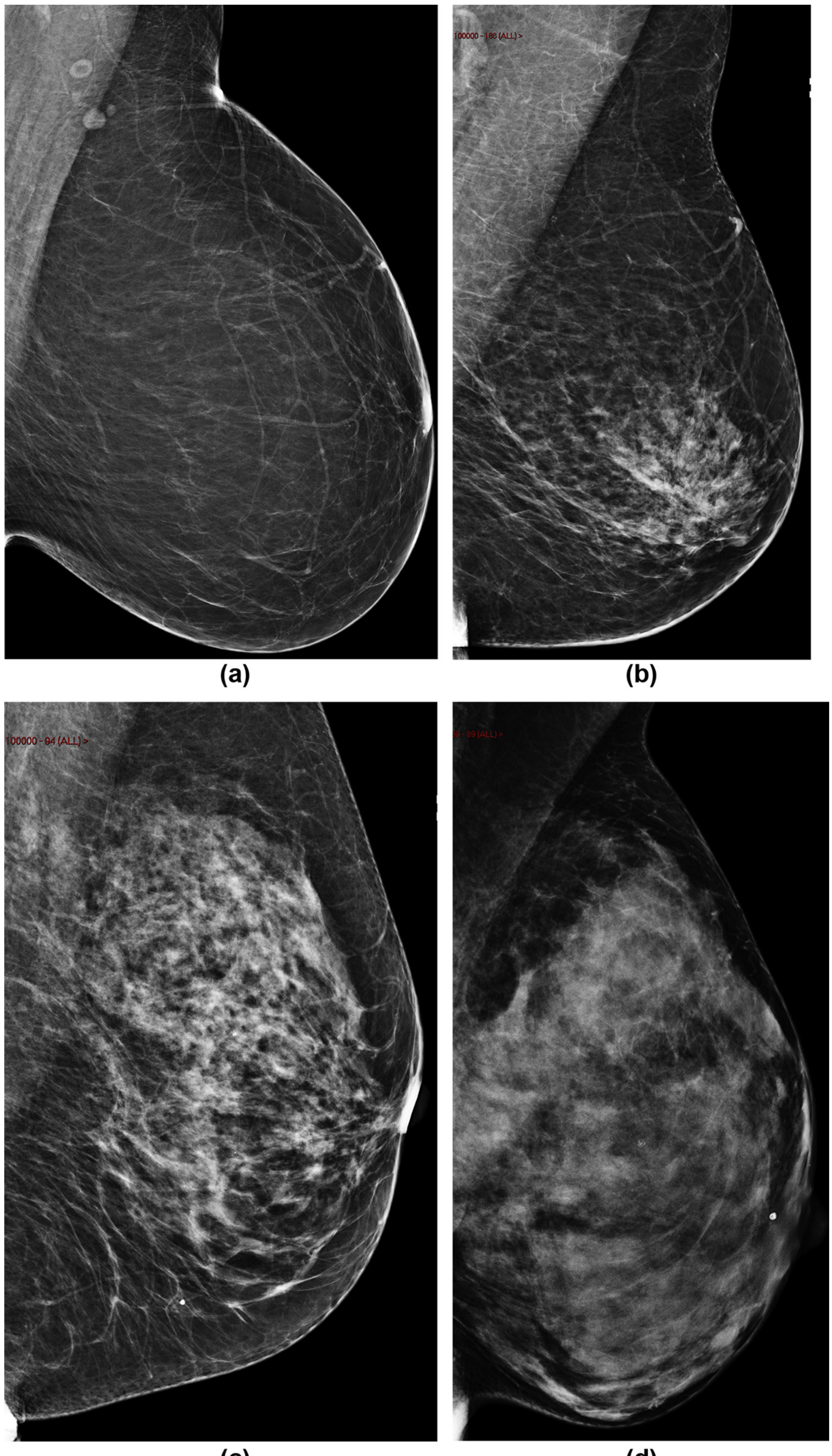


Figure 1 Examples of differing mammographic density. (a) BI-RADS 4th edition 1; 5th edition, a. Wolfe N1, Tabar II. (b) BI-RADS 4th edition 2; 5th edition, b. Wolfe P1, Tabar I, III. (c) BI-RADS 4th edition, 3; 5th edition, c. Wolfe P2, Tabar IV. (d) BI-RADs 4th edition, 4; 5th edition, d. Wolfe DY, Tabar V.

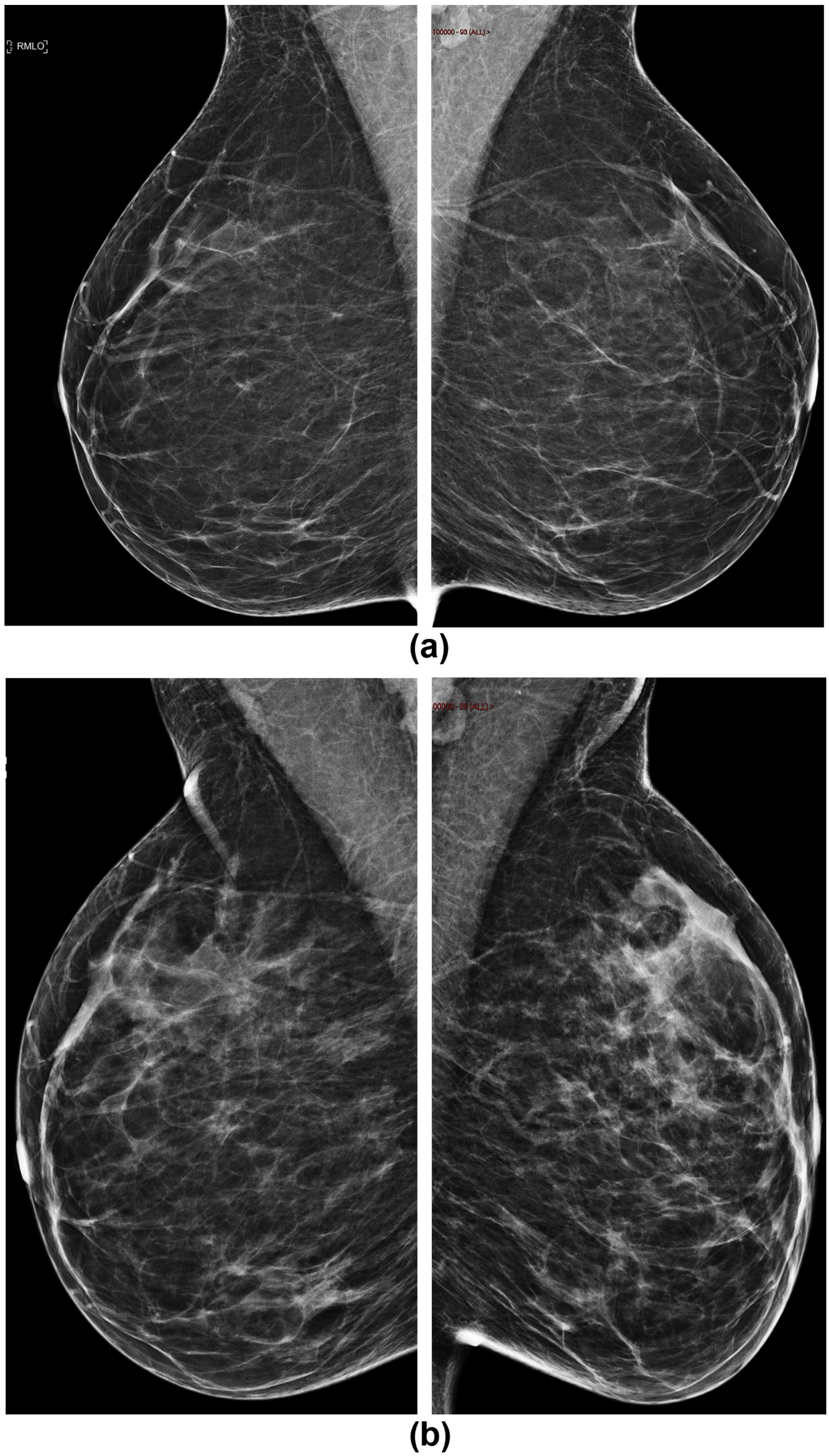


Figure 2 Effect of HRT. Bilateral MLO views (a) before and (b) 1 year after commencement of HRT.

with breast cancer risk.[5] This is particularly important as MD is modifiable.[6–8] A major research effort is underway to elucidate the nature of the risk-conferring components of MD and to understand the underlying genetic, epigenetic, and molecular mechanisms involved. Meanwhile, imaging scientists continue to explore methods of assessing MD in a robust and quantifiable fashion, while breast radiologists and epidemiologists devote much effort into establishing the most efficacious approaches to screening and imaging the dense breast. This review will discuss the nature of density, the risks associated with it and how it can be assessed. Finally, it will discuss how density might be incorporated into routine clinical practice in the near future.

Breast composition

Mammographic density comprises two main components: epithelial or glandular elements and supporting stroma, the latter containing stromal cells, collagen, and extracellular matrix (ECM).[9] Early studies of MD, using tissues obtained from mastectomy, biopsy, or autopsy specimens showed variable increases in the proportions of both epithelial elements (largely reflecting the number of terminal duct lobular units, TDLUs) and stromal components (particularly collagen) and decreases in the proportions of adipose in dense tissues.[9,10] Some studies have shown an increase in nuclear and glandular area, findings confirmed in a study in which image guidance was used to biopsy dense and non-dense areas of the same breast in women with no known history of breast disease[11]; however, increases in the stromal area were greater still, by up to 11-fold. Other studies have shown differences in glandular complexity and the number of acini per TDLU,[12] but these samples were from high-risk women. Part of the discrepancy in the literature regarding the histological nature of MD may be attributable to varying risk profiles of the population studied and failure to control for confounding factors.

Attention has also focused on the composition of the ECM and collagen organisation within breast stroma. Small proteoglycans and stromal matrix regulators such as metalloproteinases are differentially expressed in stroma from high MD breasts,[13,14] and recent research has shown that the organisation of collagen fibrils in periductal stroma differs in areas of high and low MD.[15] McConnell *et al.* used atomic force microscopy and spectroscopy to show an abundance of large, (>80 μm) aligned periductal collagen fibrils in high MD tissues, resulting in locally increased stiffness rather than a diffuse increase in fibrosis.[15] Second harmonic generation imaging has also demonstrated the presence of more organised stromal collagen in areas of high MD.[16] However, the mechanisms behind the altered collagen architecture have yet to be elucidated.

Factors influencing MD

Unlike many factors influencing the breast in health and disease, MD is modifiable. It decreases with age after early adulthood, especially after the menopause.[17] The International Consortium on Mammographic Density (ICMD) recently studied differences in MD by age and menopausal status in over 11,000 women with no history of breast cancer from 40 ethnic groups in 22 countries. They showed that MD decreased with age both pre- and post-menopausally, with a large age-adjusted difference in percent MD (PMD) between pre- and postmenopausal women regardless of ethnicity.[18]

Life-course body size also has a significant effect on breast density. A high body mass index (BMI) and large breast size are associated with reduced MD; a higher BMI at any age during childhood is associated with lower MD in adulthood. The odds of high MD are increased with later menarche, some studies also finding that greater birthweight and adult height are positively associated with high MD.[19] A study from the UK found that first-generation South Asian and Afro-Caribbean women had lower age-adjusted breast density than Caucasians, only partly explained by higher BMI and lifestyle factors.[20] This group later showed that while BMI, parity, and ethnicity were associated with PMD, these factors did not affect the within-woman rate of change of PMD at each age. This high degree of tracking of PMD for a woman with age is important, as it suggests that high PMD could be identified by a single mammographic examination at a young age.[21]

Numerous studies have documented the increase in PMD associated with hormone-replacement therapy (HRT), specifically combined oestrogen/progestogen therapy[7,8,22] (Fig 2). As HRT is also associated with increased breast cancer incidence, the question arises whether causality is mediated via MD. A recent case–control study within the Women's Health Initiative Trial found that for each 1% increase in PMD 1 year after commencement of HRT, breast cancer risk increased by 3%.[23] For women in the highest quintile of PMD change (>19.3% increase), breast cancer risk increased over threefold and after adjusting for change in MD, the effect of HRT on breast cancer risk was removed. The implications of this for counselling of women considering HRT are significant.

Lifestyle and reproductive factors probably only account for approximately 35–40% of the variance in MD; the remaining 60–65% is genetically determined.[24–27] Boyd and colleagues undertook two twin studies in Australia and North America, in which they demonstrated that after controlling for relevant covariates, the correlation coefficient for PMD was over 0.6 for monozygotic pairs. At any given age, heritability was estimated to account for 63% (95% confidence interval [CI]: 59–75%) of the variation in MD in all twins.[24] They later showed that both dense and non-dense areas shared the same high heritability.[25]

A number of genome-wide association studies have investigated associations of single nucleotide polymorphisms (SNPs) and MD. These include polymorphisms of genes involved in epidermal growth factors, EGF (*AREG*), oestrogen receptors (ER; *ESR1*), and insulin-like growth factor signalling, as well as cell proliferation, migration (*LSP1*), and tissue vascularisation.[28–30] Some of these SNPs also influence breast cancer risk, a recent meta-analysis finding that of 77 known breast cancer susceptibility SNPs, 18% were associated with at least one measure of MD (absolute or percent dense area),[31] lending credence to the suggestion that MD is causally linked with breast cancer.

How common is MD?

The prevalence of high MD is highly population-dependent. A study from the US found that around 40% of women aged 40–59 years had >50% area based MD, and the corresponding figure for women aged between 60–80 years was 25%.[32] Data taken from the Breast Cancer Surveillance Consortium (BCSC) in the US demonstrated heterogeneously or extremely dense breasts in 43% of women aged 40–74 years.[33] Conversely, recent data from an urban screening centre in the UK found that 50% of women had predominantly fatty breasts and only 32% had heterogeneously dense breasts (L. Wilkinson, personal communication). Urbanisation and degree of social deprivation can result in quite striking regional differences in incidence of MD, even in small countries.[34]

The clinical importance of breast density

Reduced mammographic sensitivity

The recognition that increased MD can reduce mammographic sensitivity is not new. In 1977, Egan and Mosteller found that many more cancers developed within 6–36 months after a normal study in dense breasts compared with fatty breasts.[35] They suggested that the increased breast cancer risk described by Wolfe[36] in association with certain parenchymal patterns was in fact attributable to masking of breast cancers in the denser breast.

Subsequently many studies have confirmed the relationship between high MD and reduced mammographic sensitivity.[3,4,37–42] This probably accounts for the larger size of screen-detected cancers in dense breasts compared to fatty breasts[43–45] and the excess of interval cancers in dense breasts compared to fatty breasts.[3,37,38,40] In one study of >4,000 women (97% of whom were undergoing screening or surveillance mammography), the sensitivity of mammography for impalpable cancers was 80% in non-dense breasts and 56% in dense breasts.[40] A nested case–control study within the NHS Breast Screening Programme in East Anglia showed a much higher odds ratio (OR) for interval cancers than screen-detected cancers in P2 and DY groups, especially in the first 18 months after the last screening mammogram (ORs 3.8 and 4.1, respectively).[37] Porter *et al.* later found that screen-detected cancers were significantly smaller in fatty breasts and that there was a statistically significant increase in the proportion of dense breasts in women presenting with interval cancers rather than screen-detected cancers.[44]

These early studies all considered screen-film mammography (SFM) but the introduction of full-field digital mammography (DM) has only partly overcome the problem. Although the DMIST study did demonstrate a statistically significantly improved performance for DM over SFM in the dense breast, with areas under the receiver operating characteristic (ROC) curve (AUCs) of 0.78 and 0.68, respectively, sensitivity was still much lower in dense breasts, a finding confirmed in a subsequent cohort study.[2,46]

Data from one Dutch screening unit using DM between 2003 and 2011 showed screening sensitivity to fall progressively with increasing MD, from 85.7% in fatty breasts to 61% in very dense breasts.[47] The authors also found a progressive increase in the number of false-positive recalls from screening to assessment with increasing MD, from 11.2% in predominantly fatty breasts to 23.8% in very dense breasts.[47] In a further study, using volumetric density measures, they demonstrated a strong positive association of volumetric MD with interval cancer rates with a hazard ratio (HR) of 8.37 for extremely dense breasts compared to fatty breasts.[48]

The phenomenon of reduced mammographic sensitivity in the dense breast has received an enormous amount of publicity, particularly in the US. The ‘Are You Dense’ Advocacy group (http://www.areyoudenseadvocacy.org/) was founded by Dr Nancy Capello in 2004, after she was diagnosed with locally advanced breast cancer shortly after a normal screening mammogram. Subsequently, Connecticut became the first US state to pass a law mandating the reporting of breast density at mammography and communication of this to the woman. Since then, a further 31 states have passed similar legislation. In six states, the provision of insurance cover for supplemental screening in women with dense breasts is also mandated. The level of information communicated to the woman varies by state and where dense breasts are defined, it is with BI-RADS categories. Defining the population that might benefit from supplemental screening and the best means of doing this is hotly debated (see below).

The influence of MD on mammographic performance also affects symptomatic populations. Numerous studies have demonstrated lower mammographic sensitivity in younger women with dense breasts.[4,39,41] A recent study of the performance of DM and US in the diagnosis of cancer in women under 40 found that patients with a false-negative mammogram were much more likely to have dense breasts[49] and in a study from 2016 on the predictors of ultrasound-only visible cancers, higher PMD was the strongest predictor for the failure of mammography.[50]

Cancers in dense breasts are associated with higher T stages and greater likelihood of lymph node positivity at diagnosis.[51] Larger tumour size at diagnosis probably accounts for the poorer prognosis of cancers in dense breast.[52,53] In a case–control study of interval and screen-detected cancers, Eriksson *et al.* found that the HRs for breast cancer survival were three-times higher in interval cancers,[53] but after adjustment for tumour size (used as a proxy for time to diagnosis), survival differences in dense breasts disappeared. Interestingly, there was still a statistically significantly increased HR for interval cancers in non-dense breasts (5-year survival HR=2.43, p=0.001), suggesting that interval cancers developing in non-dense breasts are truly biologically more aggressive. This observation has been made elsewhere,[54,55] one study finding that interval cancers in non-dense breasts were more likely to be triple negative or HER2 amplified and lymph node positive.[54]

Increased breast cancer risk

The second reason for the clinical importance of MD is that it is in itself a risk factor for the development of breast cancer. In Wolfe's original paper, he described four xeroradiographic patterns (N1, P1, P2, and DY) where N1 represents the fatty breast, P1 a breast with a nodular pattern of fibroglandular parenchyma involving <25% of the visualised breast area (termed a prominent "duct pattern"), P2 with a more extensive "ductal pattern" and DY, a so-called "dysplastic" breast with uniformly increased MD[36] (Fig 1). Types N1 and P1 are regarded as non-dense and P2 and DY as dense; the latter were both associated with markedly increased breast cancer risk. Subsequently, Wolfe demonstrated a strong correlation between parenchymal patterns and area-based PMD measured with planimetry, finding that the relative risk of breast cancer was even greater for breasts with >25% density than it was for the P2 and DY patterns.[56]

The question as to whether MD was truly a risk factor or whether the increased incidence could be attributed solely to masking[35,57] has been settled.[58] Boyd *et al.* carried out three nested case–control studies in three Canadian screening populations with a total of 1,112 matched case–control pairs.[58] PMD was categorised visually into sextiles and using a computerised semi-automated thresholding method. After adjustment for confounders, the OR for those with 75% or more MD compared to those with <10% was 4.7. Calculation of attributable risk suggested that MD accounted for many breast cancer cases regardless of mode of detection (screen detected or interval). An exceptionally high OR of 17.8 for women with MD ≥75% within 1 year of a normal screen was secondary to masking, but thereafter the OR remained high at 5.7, suggesting causality. It has been estimated that for every 3–6% increase in MD, relative breast cancer risk increases by 10%,[59] and this association has been shown to persist over extended periods.[60,61]

A meta-analysis from 2006 included data from more than 14,000 breast cancer cases and 226,000 non-cases from 42 studies.[5] Higher MD was consistently associated with increased risk despite the great variations in populations studied, method of assessing MD, and whether incident or prevalent cancers were considered. Relative risks were much stronger when PMD was assessed, rather than Wolfe patterns, varying from 4 to 6 comparing the least and most dense breasts. An elegant prospective study of women in the Swedish Kopparberg randomised controlled trial looked at the effect of baseline breast density on breast cancer incidence, stage, mortality, and screening performance.[42] By considering preclinical (screen-detected) and symptomatic (interval) cancers, they were able to confirm higher preclinical incidence rates (indicating causality), but also shorter mean sojourn times (indicating masking) in dense breasts compared with non-dense breasts.

Only age and BRCA carrier status are associated with larger relative risks than extremes of PMD, and as high PMD is common, the population attributable risk is also very high. Boyd estimated that for women under the median age of 56 years, the attributable risk for PMD >50% was 26% for all cancers and similar estimates have been obtained in other cohorts.[58,62] By contrast, the population attributable risk for BRCA mutation carriers is <5%.[63] In a more recent case–control study from the BCSC, MD was the most prevalent risk factor and had the largest effect on the population attributable risk proportion; the authors estimated that roughly 39% of premenopausal and 26% of postmenopausal breast cancers could be averted if all women with heterogeneously or extremely dense breasts shifted to scattered fibroglandular breast density.[64]

Risk-conferring components of MD

Although epidemiological observations suggest a causal relationship between MD and breast cancer risk,[65–68] proof of this requires demonstration that a change in breast cancer risk is mediated through the accompanying change in MD (i.e., that MD is an intermediate phenotype). The extent to which reproductive and lifestyle factors influence breast cancer risk through effects on MD is not totally clear.[69,70] Rice *et al.* recently found that MD mediated much of the association of early life body size and breast cancer risk, and a significant proportion of the risk associated with benign breast disease and HRT usage,[70] but little of the risk associated with a positive family history. It seems paradoxical that MD declines with age whereas breast cancer incidence increases, but cumulative exposure to PMD with increasing age reflects cumulative exposure of breast stroma and epithelium to mitogens and mutagens, whether hormonal, growth factor related, or epigenetic.[69] This is in accord with Pike's model of breast tissue ageing, in which the cumulative rate of breast tissue ageing describes the age-specific incidence of breast cancer in the US[71] and elsewhere.[21,72,73]

The precise nature of the risk-conferring element of MD is unknown. Simplistically, as breast cancers arise from epithelial cells, it is logical to suppose that the greater the MD, the greater the number of epithelial cells and amount of epithelial proliferation. This is consistent with the observation that high MD is associated with increased risk of proliferative lesions and ductal carcinoma in situ (DCIS),[74,75] though one study failed to show any statistically significant association between MD and breast cancer risk in women with atypical hyperplasias.[76] Some studies, although not all, have shown that age-related atrophy of TDLUs is negatively associated with breast cancer risk and that PMD and failure of TDLU involution are independently associated with breast cancer risk.[77–79]

Some groups have found increased stromal expression of ER and epithelial or stromal expression of PR in dense tissue samples from women at population risk or increased risk.[80,81] Laboratory studies using mouse models and human tissue xenografts have shown that tamoxifen treatment promotes remodelling of stroma to a tumour-inhibitory phenotype, with reduced ECM turnover and decreased stromal tissue.[82,83]

Non-epithelial components of the stroma and epithelial–mesenchymal interactions appear to be key in the relationship of MD and breast cancer risk. Collagen remodelling and organisation differs in high and low MD breasts and also in different regions of the normal breast.[15,84] Boyd *et al.* found that tissue stiffness estimated from mammography was significantly associated with breast cancer and that the addition of stiffness improved the performance of a breast cancer risk prediction model that included percent MD.[85] ECM stiffness is known to promote tumorigenesis, and collagen alignment adjacent to breast tumours appears to have a direct impact on invasion and metastasis.[86] In mouse models, increased stromal collagen and collagen reorganisation is significantly tumorigenic,[87] but how exactly aberrant expression of ECM proteins and increased stromal stiffness promotes tumorigenesis in the dense breast is unknown.

Does it predispose to a particular sort of cancer?

A number of studies have evaluated the association of MD with tumour subtypes and ER positivity or negativity. These studies were highly heterogeneous, but most found no association, others showed stronger associations for ER-positive tumours[88–90] and others, stronger associations for ER-negative tumours.[91] No association with HER2 status was shown in a meta-analysis from 2013.[92]

The influence of MD on outcomes

Women with greater MD have a higher risk of dying from breast cancer, largely explained by the increased breast cancer incidence associated with MD[42,91]; however, a number of studies have shown that baseline MD may affect outcomes in patients treated for breast cancer. A couple of groups have demonstrated an adverse effect of high MD on local recurrence rates and breast cancer survival, but only in patients who had not received radiotherapy.[93,94] Another found that high MD predicted for a greater risk of local recurrence even after radiotherapy, with a HR for high MD breasts compared to low MD breasts of 4.30.[95]

Women with high MD diagnosed with DCIS appear to be at greater risk of developing subsequent ipsilateral invasive breast cancer[96] and contralateral DCIS or invasive disease.[97] Two large cohorts examining the effect of high MD on breast cancer survival did not identify any adverse effects[44,52] whereas a third showed a borderline association,[42] but these studies did not specifically address the possible confounding effect of radiotherapy. All these studies provide support for the concept that high MD stroma is able to promote cancer initiation and progression.

Measurement of MD

There are two main methods of assessing MD: qualitatively or quantitatively. The former include the Wolfe,[36] Tabar,[98] and the BI-RADS 5th edition[99] classifications, which assess parenchymal patterns and distributions (Fig 1). Quantitative methods include simple visual methods (the BI-RADS 4th edition,[1] the Boyd six category classification [SCC],[100] and visual analogue scales [VAS][101]), semi-automated methods (Cumulus, Madena or planimetry), and fully automated methods. The latter can be area-based or volumetric.

The BI-RADS 4th edition utilised area-based PMD in quartiles (0–24%; 25–49%; 50–74%, and 75% area-based density); the SCC is similar but divides the first quartile of PMD into 0%, <10%, and 10–<25%. The fully automated area-based methods include AutoDensity, Densitas, ImageJ, iReveal, STRATUS, Libra, and MedDensity, but only iReveal has US Food and Drug Administration (FDA) clearance. The best-known volumetric methods, Quantra and Volpara, are model based and have FDA clearance, as does Spectral Density, developed with the Philips Microdose DM system. Other newer fully automated volumetric methods, such as BD_{SXA} and CumulusV, are used in the research arena. All of the volumetric methods require the raw ("for processing") images from DM units, whereas all the area-based methods, aside from iReveal, function on the processed "for viewing" images.

Qualitative methods are quick, requiring nothing but the observer's eyes. These pattern-based methods appear to add little to visual assessment of area-based PMD[102] and suffer from poor reproducibility yet with the BI-RADS 5th edition, a qualitative element of parenchymal pattern classification has been reintroduced to address the possibility of masking. Thus, BI-RADS a denotes almost entirely fatty breasts; BI-RADS b, the presence of scattered areas of fibroglandular density; BI-RADS c, heterogeneously dense breasts where small masses could be obscured, and BI-RADS d, extremely dense breasts, lowering the sensitivity of mammography. A key difference between the BI-RADS 4th and 5th editions is that a breast with <50% PMD may be classified as BI-RADS c if there is regional MD where small masses could be obscured (Fig 3). Tabar described five patterns. Type IV is predominantly dense (equivalent to BI-RADS 3, c or Wolfe P2) and V is uniformly dense (equivalent to Wolfe DY, BI-RADS 4 or d); like the P2 and DY patterns, Tabar types IV and V are associated with increased breast cancer risk.

Simple visual methods of assessing area-based PMD have stood the test of time and numerous studies have confirmed the association with risk, but the SCC and VAS methods are only used in a research setting.[103,104] VAS, in particular, is useful as, unlike semi-automatic computerised thresholding methods, it is quick, does not require digitisation of mammograms, and does not require specific training; however, as with parenchymal patterns, there are major issues around reproducibility.[105] Data from the PROSPR (Population-Based Research Optimizing Screening through

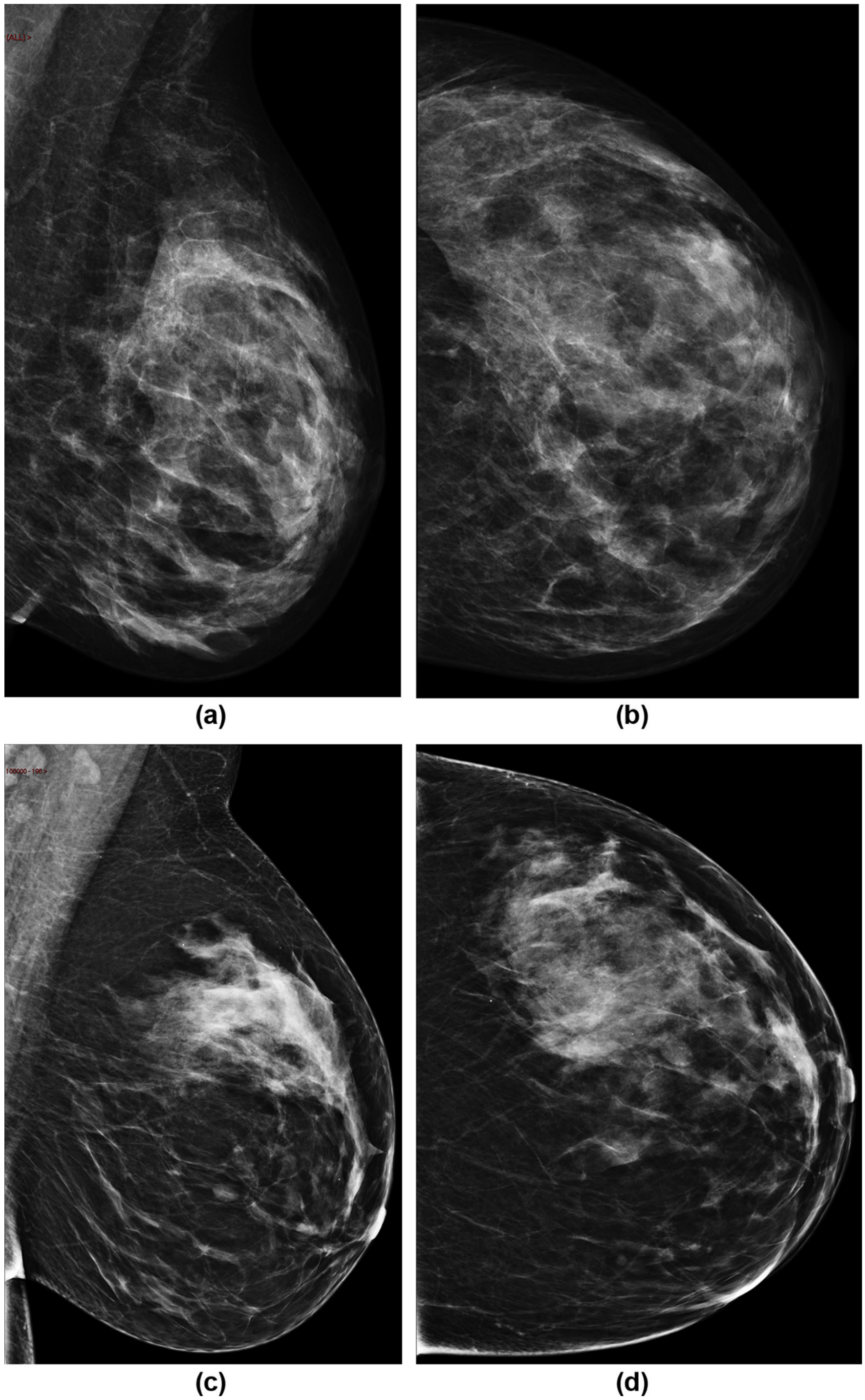


Figure 3 Effect of change from BI-RADS 4th edition to 5th edition. Left MLO and CC views from two different patients, both classified as BI-RADS c; in the 4th edition the first patient would be BI-RADS 3 and the second, BI-RADS 2. 3a, b: BIRADS 3 and c. 3c,d: BI-RADS 2 and c.

Personalized Regimens) consortium indicate that the percentage of mammograms perceived as showing dense breasts (BI-RADS 3 or 4) varies widely across radiologists, from 6.3% to 84.5% (median 38.7%) regardless of patient characteristics. A systematic review of reproducibility of BI-RADS classifications from 2016 found that approximately one-fifth of women would be categorised differently by the same radiologist at consecutive screens, but more alarmingly this figure was around one-third when serial mammograms from one woman were read by a different radiologist. Re-categorisation from dense to non-dense or vice versa occurred in 13–19% of women, a finding that has significant implications in the US.[106] Reader experience is important, but even experience cannot overcome the subjectivity of visual assessment, as shown by Lobbes *et al.*[107]

The effect of the change from BI-RADS 4th to 5th editions was analysed by Ekpo *et al.*,[108] who found better intra- and inter-reader agreement with the 5th edition and near-perfect agreement when a binary classification (dense or non-dense) was used. The findings of Youk *et al.* were similar, but they also showed a significantly greater proportion of breasts classified as dense with the 5th edition.[109] Other groups found significantly poorer intra- and inter-reader agreement with the 5th edition.[110] A major issue with BI-RADS is that, in most developed countries, most screening age women fall into categories 2 and 3 (or b and c), the interquartile range, where most reader disagreement is found. As 2 and 3 or b and c differentiate between dense and non-dense breasts, it is difficult to use BI-RADS for clinical decision-making about an appropriate risk-adapted screening protocol, although training can improve assignment to BI-RADS categories to a certain extent.[111]

Semi-automated assessment

The best known method, Cumulus, was developed by Boyd and Yaffe at the University of Toronto in an attempt to overcome the limitations of visual density assessment.[112] For many years, Cumulus has been regarded as the reference standard of area-based PMD measurement for research purposes. It is a computer-based semi-automated thresholding technique requiring digitisation of SFM, a major drawback. The user first defines the chest wall, masking the pectoral muscle, and segments the entire breast area. An interactive thresholding tool is then used to define the breast parenchyma; the output is PMD (Fig 4). With training, the reproducibility of Cumulus is excellent within and between readers, and there is generally good agreement both between right and left breasts and mediolateral oblique (MLO) and craniocaudal (CC) views.[113,114]

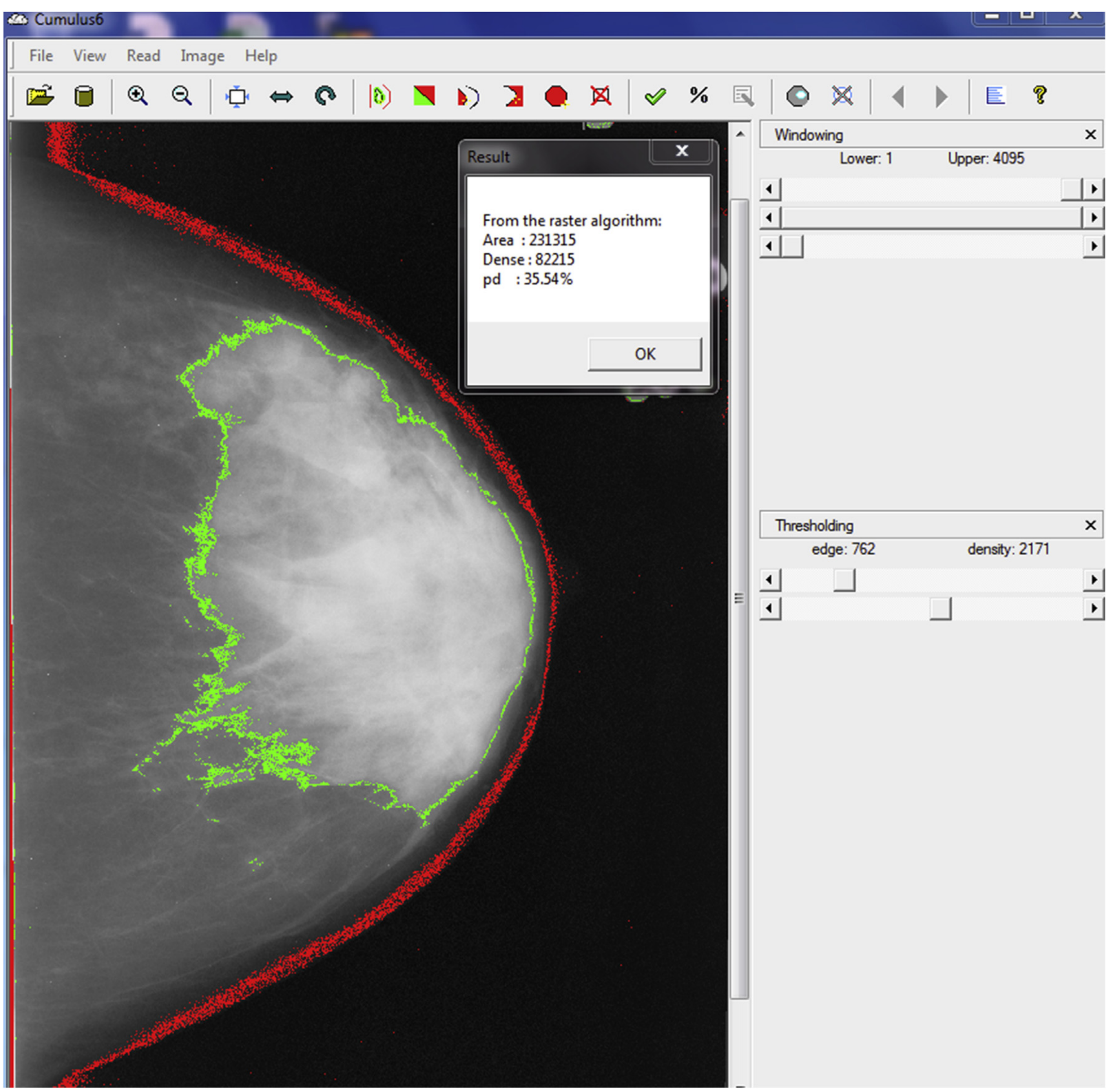


Figure 4 Screen capture of user graphical user interface for Cumulus. Red lines denoted masked chest wall and skin; interactive thresholding tool enables segmentation of MD. (Image reproduced courtesy of Cumulus).

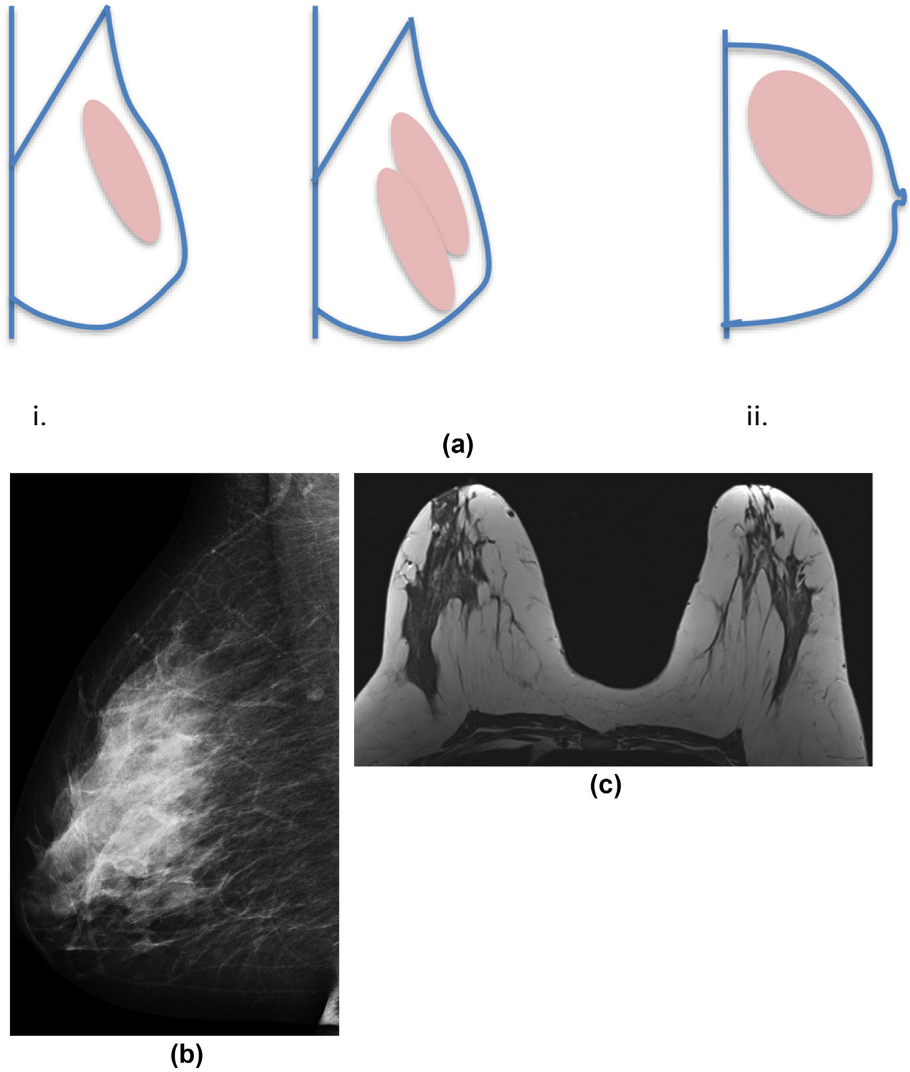


Figure 5 (a) Schema demonstrating difficulty in assessing volumetric MD from a 2D projectional image. (i) The second MLO has double the amount of MD. (ii) On the CC view, area-based percent MD appears the same for both MLOs. (b) Right MLO, BI-RADS categorisation 3 or c. (c) On the corresponding axial T2 weighted MRI, there is well under 50% area-based percent MD.

Cumulus PMD has been validated repeatedly and shown to correlate with breast cancer risk in numerous studies[58,113,115]; however, as a clinical tool it is impractical. The same is true of Madena, which also requires human input for segmentation into dense and non-dense tissue.[113] Later iterations, AltoCumulus and CirroCumulus, work on DM images and one area of active research is into the effect of altering thresholding in DM images, with higher thresholds appearing more predictive of risk.[116]

Automated volumetric methods

Radiographic factors and positioning can have a profound effect on measured PMD (Fig 6) and concerns about the basic relationship between area-based PMD from a two-dimensional (2D) mammographic projection and breast cancer risk persist, as there is no information on breast thickness and therefore volume of dense tissue (Fig 5), which might be expected to be a more relevant metric.[117] Thus there was a pressing need for fully automated volumetric methods of measuring MD and the advent of DM has made this possible. The best known of these methods are Quantra and Volpara, a multi-vendor method. Quantra was the first commercial method, based on research by Highnam and Brady, who continued work on their algorithm to develop Volpara a few years later. Both are model based, but work in slightly different ways to calculate dense volume, total breast volume, and percent volumetric MD (VBD) from individual pixel intensities and known X-ray attenuations. Quantra uses an absolute model and includes the skin; Volpara uses a relative physics model by finding a pixel of pure fat attenuation as an internal reference.[118] As well as yielding dense and total breast volumes, Volpara gives a density grade (VDG) that can be aligned to the 4th or 5th edition of BI-RADS and Quantra gives a similar measure (Fig 7). Both methods have been shown to correlate well with breast cancer risk, particularly Volpara.[115,119]

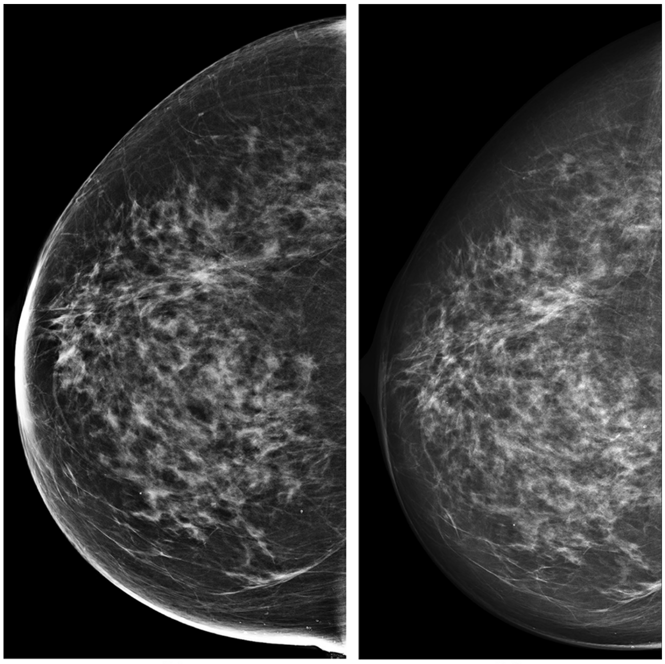


Figure 6 Effect of positioning. Same patient, right CC views I year apart. Positioning is better in (a) than (b) with more of the breast pulled on. Percent MD will be lower in (b). The human eye can appreciate the difference in positioning whereas an automated or semi-automated program may not.

BD_{SXA} uses a phantom step wedge that requires placement on the image receptor and which is compressed to the same degree as the breast so as to provide grey-scale references for each pixel on the mammographic image for calculation of volumetric MD[120]; CumulusV calculates volumetric MD from compressed breast thickness and X-ray attenuation after calibration of the DM unit using breast-equivalent phantoms.[121] Both are used for research purposes.

The evidence suggests that automated volumetric assignment to a density grade is very consistent.[122,123] In one study of trained readers, the number of mammograms classified as dense (BI-RADS 3 or 4) ranged between 25 to 50% depending on the reader, whereas a cut-off of 22% volumetric density with Quantra correctly predicted 89% of non-dense and 90% of dense breasts.[123] There are occasions where fully automated methods may not work (for example, in very large breasted women or women with implants); Volpara can also produce erroneous readings with very high MD where it is not possible to identify a pure fat-containing pixel. Alternative approaches have been explored by the Nijmegen group to improve density estimation in this situation.[124] Other technical issues that can profoundly affect measurements include paddle tilt, resulting in variation in compressed breast thickness and therefore computation of VBD; in this situation, correction for tilt is essential.[125]

The consistency of MD measurement in serial mammograms is also clinically relevant. In a study of women from the Dutch screening programme, MD of serial mammograms was assessed visually and with Volpara.[126] Better agreement was found with the latter, with fewer instances of implausible changes from non-dense to dense categories (2.8% versus 4.2% of cases) and a significantly higher inter-examination agreement for VBD compared to group visual reading. This is important in considering which method might be appropriate to inform screening protocols. VBD has been used to quantify the potential risk of masking as well; in a retrospective study of screen-detected and interval cancers both VDG and VBD had a stronger linear relationship with mammographic sensitivity than BI-RADS classification[127] and both automated measures yielded higher odds ratios for interval cancers than BI-RADS, suggesting that they could be used to stratify women into a density-adapted protocol.

Other measures of breast density and composition

Fully automated area-based methods

A number of fully automated area-based methods of measuring PMD have been developed, some of which are commercially available and others of which are freely downloadable. These include an ImageJ-based method (developed at the Karolinska), AutoDensity (University of Melbourne), LIBRA (using fuzzy c-means segmentation and developed at the University of Pennsylvania), STRATUS (based on machine learning, also from the Karolinska) and MedDensity, developed at the University of Genova. These can work with SFM, DM, and digital breast tomosynthesis (DBT).

iReveal and Densitas[128] are commercially available (Fig 8). The main advantage of these systems is that they utilise processed ("for viewing") images without the necessity for storage of raw images, a major constraint on picture archiving and communication system (PACS) storage systems; however, there is a paucity of independent research using these methods, although one case–control study using Densitas found better risk prediction than a clinical risk model.[128] The image type (raw, analogue-like, or processed) may also affect output and association with breast cancer risk.[129] Findings from a number of other studies also support the notion that the same VBD tool should be used in serial measurements or when different populations are compared; Eng *et al.* found that VBD readings were markedly different between Volpara and Quantra (Fig 9),[115] the latter yielding much higher within-woman measurements, a finding replicated by Morrish *et al.*[130]

DBT and synthetic 2D DM

With increasing use of DBT either as an adjunctive or primary screening method, it is important to be able to assess MD as reliably as with conventional 2D DM. Although BI-RADS can be used, it is challenging to evaluate a series of reconstructions.[131] One group has developed a fully automated software using a thresholding method to analyse MD

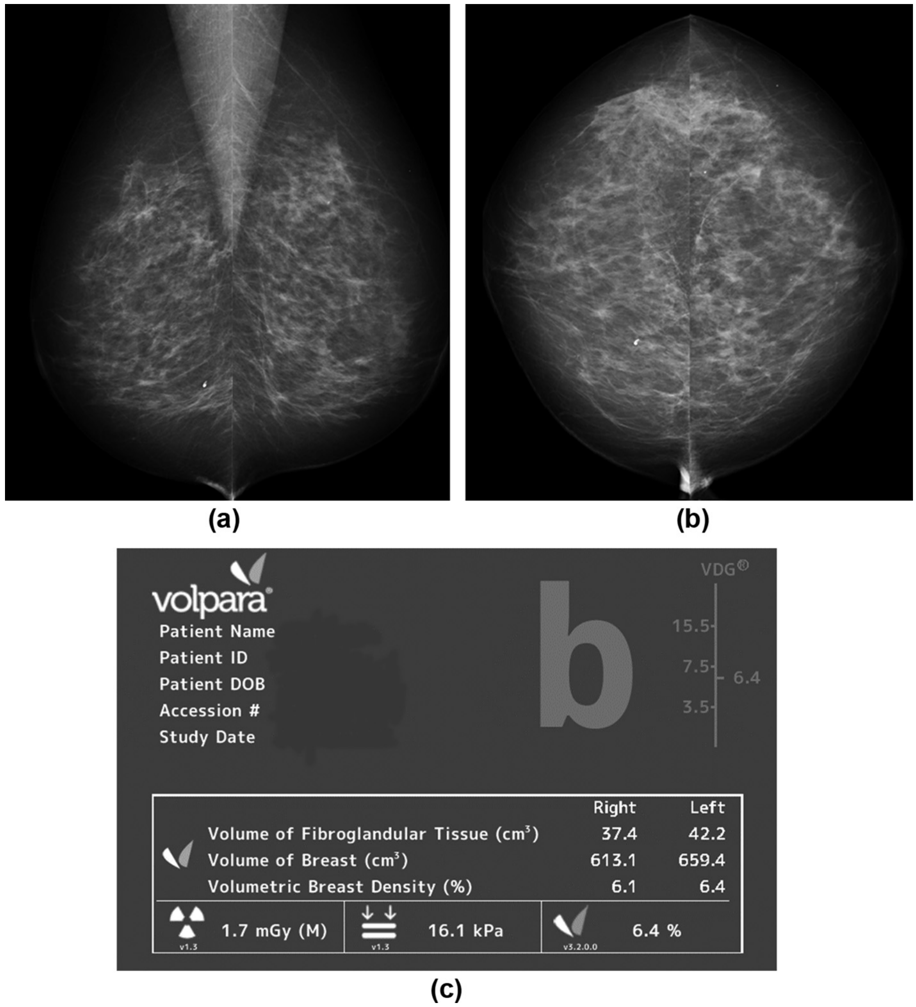


Figure 7 The output from Volpara version 1.5. (Image reproduced courtesy of VolparaSolutions.)

of each DBT reconstructed slice.[132] This demonstrated lower PMD for DBT than DM. Subsequently this software, Med-Density, was used to compare PMD readings in a cohort of women with both DM and DBT studies.[133] The difference in PMD between DM and DBT differed across BI-RADS categories in a non-linear fashion, with least difference in BI-RADS 3 breasts (3.5%) and most in BI-RADS 1 and 4 breasts (16% and 18%, respectively). The group also compared PMD in a cohort of women who underwent DM, DBT, and breast MRI.[134] Although there was a strong positive correlation between all three techniques, differences in PMD between DM and DBT and between DM and MRI were highly significant, with DM yielding 15% higher PMD, whereas no significant differences were found between DBT and MRI.

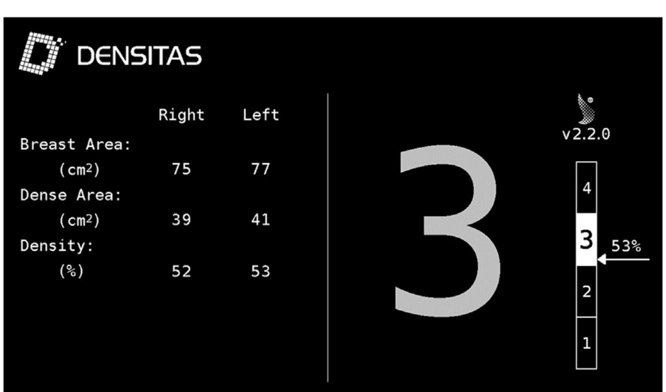


Figure 8 The outputs from Densitas. (Image reproduced courtesy of Densitas.)

Other groups have used the central projection of the DBT acquisition to estimate PMD, showing good correlation and substantial agreement with PMD measured from DM using Cumulus.[135]

Volpara version 1.5.1 is able to derive volumetric MD from the central projection and compressed breast thickness. A feasibility study using paired DM and DBT images obtained during one compression[136] demonstrated near-perfect agreement for calculated breast volume, but small although statistically significant differences for dense volume and hence VBD. Other groups have used a similar modelling approach to derive VBD using each of the DBT projections, again with closer agreement between VBD

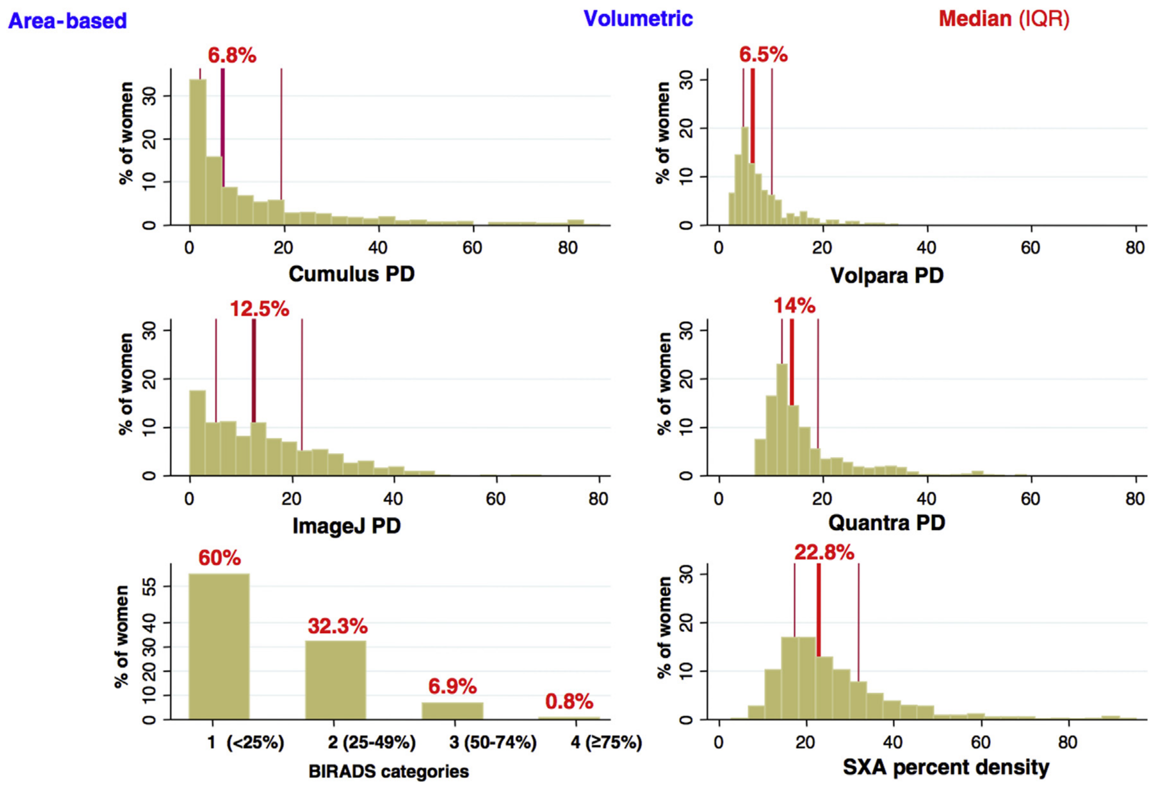


Figure 9 Taken from Eng *et al.* Distribution of MD by area-based and volumetric methods from control subjects. Notice highly significant variation in area-based and volumetric percent MD between Volpara and Quantra in particular. (Image reproduced with permission of BioMed Central.)

derived from MRI and DBT than between DM and either DBT or MRI.[137]

BI-RADS density classification of synthetic 2D mammograms derived from DBT has been compared with standard DM, with good agreement for individual readers (80%; Cohens kappa 0.73) and excellent agreement when images were dichotomised into dense and non-dense (92%).[138] Good agreement has also been demonstrated for Hologic Selenia Dimensions "C-View" synthetic mammograms and standard Selenia DM using LIBRA.[139]

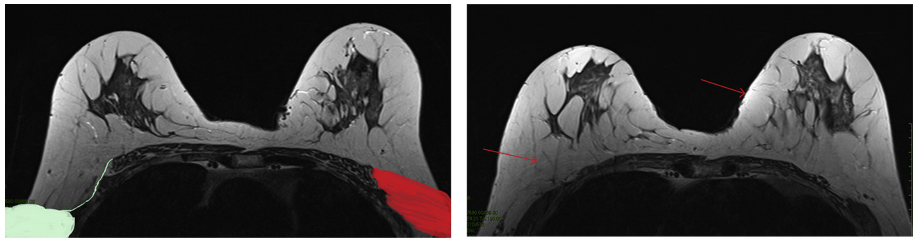
Spectral mammography

As fibroglandular and adipose tissues have different effective atomic numbers (Z), spectral decomposition can be used to quantify the thickness measurements of each tissue type, without the need for assumptions about breast thickness, height of the compression paddle, or the necessity to identify a purely fatty pixel. This can be done using dual-energy techniques, which have been shown to yield accurate estimations of breast density,[140] although at the cost of slightly higher radiation doses. It is also possible to analyse breast composition, with accurate experimental separation of water, protein, and lipid components.[141] Spectral mammography with energy-resolved photon counting detectors eliminates the need for two exposures, reducing radiation dose. A recent comparative study using BI-RADS, Cumulus, a fuzzy C-means segmentation, and spectral mammography material decomposition showed excellent right–left correlation for the latter, with much higher precision than for the other techniques,[142] an observation replicated in a recent study from Sweden.[143]

MRI

Breast MRI is an attractive means of measuring breast composition; it is a three-dimensional (3D) technique, with no tissue overlap and no necessity for compression or irradiation and has been regarded as the ground truth for measuring the accuracy of volumetric mammographic techniques.[144] With Dixon techniques it is possible to assess breast composition with measurement of fat and water volumes.[145] In a study of women >30 years and their mothers, Boyd found that PMD was strongly correlated with percent water at MRI and that percent water in the young women was strongly positively correlated with height and maternal percent water, suggesting that MD in middle age may well reflect influences on growth and development earlier in life.[146]

The MRI sequence used can have a profound effect on measured % FGV,[147,148] and bias field correction is essential as without it, non-uniformity of the B1 field and resultant variations in signal intensities across the breast makes accurate segmentation difficult (Fig 10). Furthermore measurement of % FGV necessitates accurate and consistent segmentation of the whole breast volume, which is



(a) (b)

Figure 10 (a) Note effect that different methods of segmentation of the chest wall could have on breast volume and therefore percent fibroglandular volume. (b) B_1 inhomogeneity results in shading in the posterior right breast and flare in the medial left breast in particular. Acceptable segmentation with user-defined thresholding will not be possible without bias field correction.

surprisingly difficult. Landmarks are often not specified and where they are, various boundaries have been used including a ventral line drawn coronally from the anterior border of the pectoral muscle or a line following the curve of the pectoral muscle (Fig 10). Semiautomated methods require operator intervention, which is time-consuming and subjective.[149,150] Model-based methods using templates or atlas-based algorithms are preferable[151,152] and could efficiently and reliably process large datasets for FGV estimation. Recent work from the University College London (UCL) group suggests that the optimal automatic segmentation is highly subject-specific and one size may not fit all.[153]

Small studies looking at short-term reproducibility after repositioning have shown excellent agreement.[148,154] As expected there is strong correlation with MD measures, but the level of agreement varies depending on whether area-based or volumetric measures of MD are used.[134,154,155]

Ultrasound (US) and US tomography

US reliably differentiates adipose and non-adipose tissues, is non-invasive, non-ionising, and readily available, and therefore, could be useful in assessment of breast composition. In a reader study of 40 patients with 328 reads, 2D US was used to assess the relative proportions of adipose and glandular parenchyma in each quadrant of the breast. There was good correlation with BI-RADS MD and exact agreement of 86% when scans were dichotomised into dense or non-dense.[156]

3D US has also been evaluated. Moon *et al.* found that percent density and breast volume derived from ABUS correlated very well with those derived from MRI, although the latter yielded substantially larger volumes[157]; however, the deformation of the supine breast and possibility of overlapping volumes makes this technique potentially inaccurate and poorly reproducible. The same group has developed a rapid volume density analysis[158] in which there was good correlation with whole ABUS methods. An alternative means of extracting dense volumes from ABUS uses the rib shadows to define the breast volume and shows potential.[159]

A more promising technique uses ultrasound tomography (UST) to calculate parameters such as the volume-averaged speed of sound, VASS, which is density-dependent; the higher the density, the higher the in-vivo ultrasound speed. A series of ultrasound tomograms is collected with the patient lying prone with the breast pendent in a water bath. Initial results demonstrated a strong positive association between VASS and BI-RADS MD, confirmed in larger studies comparing VASS with thresholding techniques.[160,161] VASS was positively correlated with Cumulus dense area and reduced with age and postmenopausal status, in line with the corresponding reduction in PMD. A subsequent operator study showed excellent inter- and intra-rater reproducibility[162] and a larger study of women with negative mammographic screens demonstrated that sound speed measures showed consistent associations with PMD.[163] More recently a comparative study of healthy volunteers showed an extremely strong correlation between VASS and percent water density at MRI using a Dixon technique (Fig 11).[164]

Optical imaging-based techniques

Although only being investigated in the research arena, optical imaging techniques offer the possibility of tissue characterisation. Light in the visible and near-infrared part of the spectrum is absorbed and scattered differentially by fatty and dense breast tissues, which contain chromophores in the form of water, lipids, deoxyhaemoglobin, and oxyhaemoglobin. More scattering, water-associated absorption, higher total haemoglobin, and deoxyhaemoglobin is seen in dense breast tissue. Various forms of optical spectroscopic techniques have been used, of which the best known is diffuse optical spectroscopic imaging (DOSI). Using this technique promising correlations with MD, factors associated with high MD and MRI FGV have been identified by some research groups.[165–167]

Texture

Although MD measures give a global overview of breast composition, evidence is emerging that parenchymal patterns are indicative of breast cancer risk and performance of DM at screening.[168] Preliminary analysis from the ACRIN PA 4,006 trial found that parenchymal complexity at DM was positively associated with false-positive recall rate; no such association was found with DBT. Early work suggested that parenchymal patterns were associated with breast cancer

Figure 11 (a) The 'SoftVue' unit for UST. (b) Coronal reconstructed image, pixel intensity denoting speed of sound. Note ready differentiation of fibroglandular parenchyma from adipose tissue.

risk and that this effect was independent of MD[45,169,170]; however, many of these early studies suffered from poor reproducibility compared to quantitative estimation.[171]

Texture in a medical image can be defined as a computerised mathematical method of describing spatial variations in pixel intensity, which may not be appreciable with the naked eye. Texture analysis (TA) is automated and thus subjectivity is not an issue. Within the last decade there has been renewed interest in TA of mammograms and its role in risk assessment, with many novel computerised approaches, reviewed in more detail by Gastounioti *et al.*[172]

In most early studies of TA in mammography a single region of interest (ROI) was utilised in the retroareolar area, but recently attempts have been made to capture texture features across the entire breast using multiple ROIs or a lattice structure, which may improve risk assessment. A detailed description of the texture descriptors used is outwith the scope of this article, but most studies have used grey-level histogram features (first order statistics), denoting the distribution of pixel intensities, grey-level co-occurrence matrices (which consider spatial relationships of signal intensities), run length measures (which assess uniformity by measuring the number of pixels with the same signal intensity in specified directions), structural measures (characterising tissue complexity) or spectral features, the latter using spatial frequency transforms to characterise repetitive texture structures. These techniques were initially developed for use on digitised SFM, but have now been applied to DM and a number of fully automated methods have been developed using a cross-validation approach.

Early prospective studies on SFM showed moderate relative risks with texture measures and no additional improvement in discrimination with subsequent addition of MD measures, confirmed in many retrospective studies using increasingly complex texture descriptors and combinations of TA features.[173,174] Nielsen *et al.* have developed a mammographic texture resemblance marker (MTR) which demonstrated good discrimination in two completely different cohorts, suggesting the measure is generalisable; the best discrimination was achieved with an aggregate of MTR and Cumulus PMD, with an AUC of 0.66.[175]

Studies using DM have attained AUCs of between 0.73[176] to 0.85,[177] the latter using a complex combination of texture features. Some TA features may be more predictive of certain tumour subtypes (ER positivity or negativity)[178] and whereas MD does not appear to be predictive of risk in women with BRCA mutations, TA features may be predictive for mutation status.[179,180]

Though multiparametric TA appears highly predictive of risk, comparative studies on one large dataset are lacking and more research is needed into optimised methodology, including location and size of ROIs chosen. It is also important to know whether the image format (raw or processed) and vendor unit affects the predictive abilities of TA, as this would have a significant impact upon the design of prospective multicentre and multivendor studies.[181,182] Nonetheless, the results are encouraging, particularly the fact that TA appears to confer information on risk separate from that provided by MD.[175,180] Future research is likely to focus on the relative contributions of density, texture, and parenchymal patterns, a recent case–control study finding that while BI-RADS density, Tabar classification, and texture scores were all predictive, the AUC was greatest for a combination of the three.[183] Deep learning is also likely to prove highly valuable in the application of TA to raw DM images[184] and TA lends itself to radiogenomics. Finally, with increasing use of DBT in the screening setting, a major challenge is application of TA to volumetric DBT data. Preliminary data applying various TA measures to an ROI from the retroareolar region has shown that texture features are strongly correlated with MD at DBT, but a relationship with risk has yet to be proven.[185,186]

Clinical implications of MD

Risk-adapted screening protocols

Public recognition of the impact of MD on mammographic screening performance, together with concerns over overdiagnosis, has resulted in a significant shift in the perception of the utility of mammographic screening and a demand for density-tailored screening. Possible strategies to deal with this include increased frequency of mammographic screening; alternative tests (either DBT or abbreviated MRI techniques or, to a lesser extent, molecular breast imaging) or supplemental tests such as whole-breast ultrasound (either automated or hand-held). Space precludes a detailed review here (please see reference[106]), but some key considerations are summarised below.

In the absence of definitive results from randomised controlled trials of screening protocols according to risk of masking, simulation studies can provide useful information on risk-benefit analysis. Schousboe *et al.* considered costs per quality-adjusted-life-year (QALY) of various screening strategies according to age, breast density, family history, or a previous breast biopsy. They found that annual mammography was not cost-effective for any age group regardless of age or breast density; biennial mammography cost under $50,000 per QALY for women aged 40–49 years with BI-RADS 3 or 4 density and a previous breast biopsy or family history.[187] Another study found that for women at two-to fourfold increased risk (very dense breasts and/or a family history) annual screening from the age of 40 had comparable risks and benefits to those of average risk women undergoing biennial screening from the ages of 50 and 74 years.[188] A further study estimated screening outcomes for women aged between 50–74 years for various mammographic screening intervals by breast density and risk.[189] Whereas screening benefits and overdiagnosis rates increased with breast density, false positives decreased. For women at average risk and low breast density, triennial screening was as effective as biennial screening. Conversely, for high-risk women and BI-RADS 3 or 4 density breasts, annual screening averted more deaths, but harms were twofold higher.

DBT is now being evaluated as a standalone technique for screening in women with dense breasts. The development of synthetic 2D images of comparable quality to standard DM (except for microcalcifications) goes some way to relieve concerns about radiation dosages[190,191] and DBT with either synthetic or standard 2D DM is substantially more sensitive than 2D DM alone.[192] Subgroup analysis of the UK TOMMY trial demonstrated that DBT was significantly more sensitive than 2D DM in women with >50% MD (93% and 86% respectively, p=0.03).[193] A rapid review and meta-analysis of DBT performance in women with dense breasts yielded a pooled incremental cancer detection rate (ICDR) for DBT over 2D DM of 3.9/1000 screens in four prospective studies set in population-based European screening programmes[194]; however, there is, to date, insufficient evidence on the biological importance of additional cancers detected by DBT, with most being grade 1 or 2 spiculate cancers. Thus, DBT could add to the problem of overdiagnosis and as yet the impact of DBT on T/N stage and interval cancer rates, a proxy for mortality reduction, is unknown. Encouragingly, initial results from the University of Pennsylvania suggest that the annual cancer detection rate with DBT is maintained, with significant recall reduction, a higher positive predictive value (PPV) for recall year on year and, and a suggestive decline in interval cancer rates.[195]

The available evidence to date suggests that supplemental ultrasound detects more cancers than DBT,[106] with an ICDR of approximately 4/1,000 ultrasound screens, but whereas studies of DBT included women with no other risk factor than dense breasts, most studies of supplemental ultrasound have been in women with additional risk factors as well.[196–198] A key concern is the false-positive rate and low PPV; in the ACRIN 6666 study, the PPV for biopsy (PPV3) was 16% compared to 38% for mammography alone.[197] The number of screens needed to detect one cancer was 127 for DM, 234 for supplemental ultrasound, but only 68 for MRI after negative DM and ultrasound. Although the risk of false positives decreased between prevalent and incident ultrasound screens, it was still substantial, with only 7.4% of those biopsied after incidence screening ultrasound proving to have cancer. The cancer detection rate year on year was maintained, but doubts have been raised about the cost-effectiveness of screening ultrasound for women with dense breasts.[199]

Results from the Japanese J-START study suggest that supplemental ultrasound may decrease interval cancer rates,[200] although results by breast density were not given. The Italian prospective ASTOUND trial comparing DBT and ultrasound for adjunctive screening in women with dense breasts recently reported interim results, with a cancer detection rate of 7.1/1,000 screens for ultrasound and 4/1,000 for DBT.[201] In this study, false-positive recall and biopsy rates for ultrasound and DBT were comparably low, reflecting the fact that many of the ultrasound screens were incident screens with availability of prior studies. Potential advantages of ultrasound over DBT include wide availability, good tolerance, and lack of ionising radiation; on the other hand, even with an automated system, there is still operator dependency, there is often a need for supplemental hand-held ultrasound, interpretation times are long, and there is a lack of personnel to read the scans.[202]

In her systematic review of supplemental screening in women with dense breasts, Melnikow found that breast MRI had high sensitivity and variable specificity (up to 94%) and PPV (3–33%).[106] There is little doubt that MRI will detect additional cancers, as shown by Berg *et al.*,[197] where the supplemental yield of MRI after negative DM and ultrasound was 14.7 cancers/1,000 screens, but the prohibitive cost of MRI together with resource constraints mean that it is not cost-effective to offer screening MRI for any group other than the high-risk group (lifetime risk over 25–30%). This may change with the advent of abbreviated MRI protocols.[203,204] The ongoing Dutch randomised controlled trial of supplemental MRI screening in women with dense breasts, DENSE, aims to assess reductions in interval cancer rates as well as the number of MRI screen-detected cancers.[205] An important consideration will be false-positive recall rates, as many lesions may only be visible at MRI, necessitating either short-term follow-up or MRI-guided biopsy, neither of which are desirable in a cost-limited healthcare system. Another critical factor is client acceptability; in the ACRIN 6666 study, 42% of the women offered supplemental screening MRI declined it, even though possible costs to the women were covered by the study.[206] Reasons cited included claustrophobia and time constraints, both of which might be partly alleviated by abbreviated MRI protocols. Studies addressing the impact of such protocols have shown dramatic reductions in MRI room usage.[207]

Like MRI, contrast-enhanced spectral mammography (CESM) could detect more biologically important vascular cancers.[208] It appears to be as sensitive as MRI but quicker, cheaper, and better tolerated, despite the fact that it involves irradiation and an injection of contrast material.[209,210]

Currently most international guidelines do not recommend supplemental screening for women with dense breasts and no other risk factor, although the American College of Radiology considers that supplemental ultrasound is appropriate in women with dense breasts and one other risk factor.[211] This is supported by the findings of a recent study evaluating the effect of breast density and Breast Cancer Surveillance Consortium (BCSC) 5-year risk on interval cancer rates.[212] In this prospective study, women with heterogeneously or extremely dense breasts but low to average BCSC 5-year risk had acceptably low interval cancer rates. Thus global MD alone may be insufficient reason to offer supplemental screening; increasingly the focus is on regional MD and breast tissue organisation[213] and volumetric density maps may be used to define women at increased risk of an interval cancer.[214] It has been shown that cancers are far more likely to arise in focal areas of MD identified on pre-diagnostic screening mammograms.[215]

MD as a measure of risk

Although MD is a very strong population-attributable risk factor, its value in determining whether an individual woman will develop breast cancer is limited. The ability of any risk assessment tool to predict whether an individual will develop breast cancer is judged by the ROC curve; the greater the AUC, or *c*-statistic, the more discriminatory a risk factor is. The best known clinical tools are the Gail, Claus, BRCA-Pro, Boadicea, and Tyrer–Cuzick models[216] and in the literature these have *c*-statistics between roughly 0.6 and 0.7, depending on the population evaluated and how well calibrated the tool is for that population. Until very recently, MD was not included in any of the commonly used risk prediction models. Early studies of the addition of MD used either BI-RADS or planimetric classifications of MD and the Gail model and consistently demonstrated a small increase in the *c*-statistic from around 0.6 to 0.65.[217–220] In a study of over 1 million ethnically diverse women, Tice *et al.* found that addition of BI-RADS density to the Gail model improved the *c*-statistic from 0.61 to 0.66, but, importantly, with low MD the 5-year risk was $<1.67\%$ unless there was another risk factor such as family history or age >65 years.[219] This suggests that MD could help inform screening programmes for individual women by defining a low-risk group of women for whom little or no screening is needed. The addition of percent MD (assessed by VAS or 5% bins) adjusted for age and BMI (the density residual) to the Tyrer–Cuzick and Gail models improved the AUC in two recent studies, both of which also demonstrated that MD as a univariate risk factor was slightly more discriminatory than the Tyrer–Cuzick model alone.[221,222] Other studies have used area-based thresholding techniques (ImageJ) with similar results.[223]

A measure of MD has now been added to the Breast Cancer Surveillance Consortium risk model (version 2), which uses BI-RADS, and to the Tyrer–Cuzick model, version 8, which allows use of BI-RADS, VAS, or an automated density tool such as Volpara.[224] It might be anticipated that automated volumetric measures of MD could improve risk assessment for individual women, especially as many women fall into the middle two BI-RADS categories, but available data from the PROCAS study suggests that Volpara VBD performs no better than VAS[103,224]; however, visual measures may not be reproducible with different readers. Volumetric and area-based methods, although correlated, are not the same and might not be equivalent when used in a model; indeed, other studies comparing area-based and volumetric methods have shown stronger associations with volumetric measures.[115,225,226]

One recent study found that the combination of Volpara dense volume and BI-RADS category refined the BCSC risk model more than either measure alone; among women with BIRADS 4 breasts, only those with 3rd and 4th quartile dense volume were at significantly increased risk. Adding Volpara dense volume to the BCSC v.2 risk tool (which includes BI-RADS density) improved the *c*-statistic from 0.614 to 0.639 ($p<0.001$) and women with BIRADS d category breasts and first quartile Volpara dense volume had a 5-year risk $<1.8\%$.[227] This important research suggests that automated volumetric measures could be used to better identify women at risk and refine screening strategies for such women; however, it is not clear which metric is most informative in risk prediction; some studies suggest that PMD or VBD are more discriminatory than absolute measures of MD and it is unclear whether the non-dense area is important. Furthermore, although studies have clearly shown that volumetric measures are associated with risk, the strength of the association varies considerably[115,119,225] with some studies demonstrating highest ORs with volumetric measures and others, much higher odds ratios with BIRADS assessment. The BIRADS classification yields a maximum OR of around 4 in most studies, which is not dissimilar to Cumulus, whereas the maximum OR with the volumetric methods (comparing the lowest quintile of MD with the highest) is 8.[115] Additionally, there are striking differences between volumetric methods, even though they are well correlated.[115,228] It should also be borne in mind that the widely cited relative risks of 4–6 refer to women at the extremes of MD; the highest categories of MD confer a relative risk of nearer twofold when average MD is considered.

MD as a biomarker for clinical interventions

Tamoxifen, a selective ER modulator (SERM), was shown in the IBIS-1 study to reduce breast cancer risk in women at increased risk.[229] Women on tamoxifen whose mammograms demonstrated a reduction in MD of >10% had a 63% reduction in breast cancer risk; no such reduction occurred if the fall in MD was <10%.[6] This protective effect has been sustained at follow-up.[230] Similar findings were reported by Li *et al.*[231] in a study of postmenopausal women receiving adjuvant tamoxifen for 10 years; patients on tamoxifen with a 20% reduction in MD had a 50% reduction in risk of breast cancer death compared to women with stable MD, as measured by a Cumulus-based thresholding method. Nyante *et al.*, in another case–control study, also showed that reductions in breast cancer death on tamoxifen only occurred in patients in the middle and upper tertiles of MD at baseline prior to commencement of adjuvant therapy.[232] Similarly reduction in MD in premenopausal women on tamoxifen is associated with a lower risk of locoregional or distant recurrence.[233]

It has also been shown that in patients receiving adjuvant tamoxifen, a reduction in MD of >10% as measured with Cumulus decreases the odds of metachronous contralateral breast cancer at follow-up by 55%; no such protective effect occurred in women with smaller reductions in MD.[234] This suggests that MD could perhaps be used as a biomarker for the protective effect of tamoxifen, either as adjuvant therapy or as chemoprevention for high-risk women. At least one small study has correlated the likelihood of breast cancer recurrence after adjuvant tamoxifen with reductions in MRI FGV, finding that PMD reduction on tamoxifen was the only independent factor associated with recurrence; mean reduction was around 20% in the group without recurrence and only 2–6% in the group with recurrence.[235]

The Biomarker Definition Working Group of the National Institute of Health in the US defines a biomarker as any objectively measurable characteristic that could either indicate an underlying physiological or pathological process, such as breast cancer risk (in which case it is regarded as prognostic), or evaluate the response to an intervention (e.g., tamoxifen as chemopreventive or adjuvant therapy), where it is predictive. MD appears to meet many of the criteria for a biomarker, as it is quantifiable, serially measurable, and applicable to preventive and adjuvant scenarios. Thus it is critical to be able to measure MD accurately and reliably, such that the size of any effect secondary to the intervention easily exceeds any measurement error. Results of studies using fully automated volumetric measures of MD are few, but Engmann *et al.* have shown that in women with breast cancer treated with adjuvant tamoxifen (premenopausal) or an aromatase inhibitor (postmenopausal) there were significantly greater reductions in dense volume and VBD in cases compared to controls using Volpara and Quantra; reductions were greatest when baseline VBD was >10%.[236] Concerning other SERMs, such as raloxifene, and AIs, the data for the use of MD as a biomarker is less robust and reported reductions in MD appear to be less and very heterogeneous; however as AIs are generally given in the postmenopausal setting, it is not surprising that effects on MD are less profound, and greatest reductions in MD on tamoxifen are seen in those with greatest baseline MD. Many questions remain unanswered, such as what threshold reduction in MD predicts a favourable outcome, which method should be used (is BI-RADS or VAS sufficient?), and if automated methods are used, which parameter is most discriminatory (absolute or percent dense areas/volumes)?

Unanswered questions

Although MD undoubtedly shows promise as a biomarker, many issues need to be addressed before MD can be used either to determine screening strategy or the value of risk reducing interventions. A critical question is the consistency of measures of MD and measurement error; if for example the reduction in VBD associated with response to tamoxifen was 6%, but similar variability could result from changes in positioning, compression or use of a different mammographic unit, measured reductions would be meaningless. A number of studies have investigated this question. With BI-RADS and PMD estimation, variability within and between observers after short-term reimaging is substantial especially in women with higher MD.[237] Volumetric measurements do appear more reproducible in the short term, especially with Volpara and Quantra compared to Cumulus and CumulusV, but these studies are small.[238,239]

Another key question is whether the different manufacturer algorithms affect visual or volumetric measures of MD. The automated methods rely on image pixel intensity values, so alterations in relative values could affect PMD measurements whether area-based or volumetric. Two studies have found that visual assessment of PMD may be higher on GE than Hologic mammograms taken 1-year apart in different cohorts of 100 and 40 women, respectively,[240,241] to the extent that BI-RADS categorisation was different in 10% of the women in the larger study; however, there were no significant differences in VBD or VDG in either study.

A further consideration is the effect of the normal physiological reduction in MD over time in a given woman.[21,77] Although MD changes track, women with higher MD undergo greater changes at the time of the menopause, and it is baseline MD that is most strongly predictive of risk[61,242]; however, it remains unclear whether absolute or percent measures of MD should be measured. In a meta-analysis of 13 case–control studies, percent dense area was more predictive of risk than absolute dense area in premenopausal and postmenopausal women, and though absolute non-dense area was inversely associated with risk, it was not clear whether this effect was independent of absolute dense area.[243] Conversely, Lokate *et al.* found that in postmenopausal women, non-dense area was independently associated with breast cancer risk; the highest risk was found in women with dense and non-dense areas greater than the median.[244] In this study, MLO views were used and it is possible that the measured fat included non-breast axillary fat, which would be increased with high BMI, a risk factor for postmenopausal breast cancer. In addition more work is needed to establish whether MD is solely a risk factor for ER-positive cancers; Yaghjyan *et al.* found that absolute dense area was associated more with non-basal tumours and non-dense area had stronger negative associations for ER negative and basal tumours.[245] In a case-only study from Sweden, women designated high risk by the Tyrer–Cuzick model and a SNP polygenic risk score were more likely to be diagnosed with good prognosis tumours (ER positive, low grade) especially <50 years, whereas area-based MD was not associated with any of the measured tumour-related prognostic factors.[246] Using volumetric measures, absolute measures of density were found to be more predictive than percent measures, but the best results were obtained with a combined area/volumetric model.[247] A recent publication also found that women with HER2-positive tumours had the highest volumetric PD and this association was also significant with quantitative measures[248]; more research along these lines is needed.

Conclusions

MD has profound implications for all those involved in the care and management of women with, or at risk of, breast cancer. It is key in the evolution of risk-adapted personalised screening, density-tailored imaging, and evaluation of the efficacy of therapeutic interventions. With ever more robust automated measures of MD and parenchymal texture in the pipeline, and the development of non-mammographic methods of assessing breast composition, the future for this field of breast imaging is dynamic and full of promise.

Acknowledgement

S.J.V. is in receipt of grants from: Breast Cancer Now, The Chief Scientist's Office of Scotland, Prostate Cancer UK/CSO (TCS/17/05).

References

1. D'Orsi C, Mendelson E, Ikeda D. *Breast imaging reporting and data system: ACR BI-RADS—breast imaging Atlas*. 4th edn. Reston, VA: American College of Radiology; 2003.
2. Pisano E, Gatsonis C, Hendrick E, *et al.* Diagnostic performance of digital versus film mammography for breast cancer screening. *N Engl J Med* 2005;**353**(17):1773–83.
3. Mandelson MT, Oestreicher N, Porter PL, *et al.* Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000;**92**(13):1081–7.
4. Britton P, Warwick J, Wallis MG, *et al.* Measuring the accuracy of diagnostic imaging in symptomatic breast patients: team and individual performance. *Br J Radiol* 2012;**85**(1012):415–22.
5. McCormack VA, Dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(6):1159–69.
6. Cuzick J, Warwick J, Pinney E, *et al.* Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case–control study. *J Natl Cancer Inst* 2011;**103**(9):744–52.
7. Greendale GA, Reboussin BA, Slone S, *et al.* Postmenopausal hormone therapy and change in mammographic density. *J Natl Cancer Inst* 2003 Jan;**95**(1):30–7.
8. Stuedal A, Ma H, Bjorndal H, *et al.* Postmenopausal hormone therapy with estradiol and norethisterone acetate and mammographic density: findings from a cross-sectional study among Norwegian women. *Climacteric* 2009 Jun;**12**(3):248–58.
9. Hawes D, Downey S, Pearce CL, *et al.* Dense breast stromal tissue shows greatly increased concentration of breast epithelium but no increase in its proliferative activity. *Breast Cancer Res* 2006;**8**(2):R24.
10. Li T, Sun L, Miller N, *et al.* The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**(February):343–9.
11. Ghosh K, Brandt K, Reynolds C, *et al.* Tissue composition of mammographically dense and non-dense breast tissue. *Breast Cancer Res Treat* 2012;**131**(1):267–75.
12. Lin SJ, Cawson J, Hill P, *et al.* Image-guided sampling reveals increased stroma and lower glandular complexity in mammographically dense breast tissue. *Breast Cancer Res Treat* 2011;**128**(2):505–16.
13. Alowami S, Troup S, Al Haddad S, *et al.* Mammographic density is related to stroma and stromal proteoglycan expression. *Breast Cancer Res* 2003;**5**:R129–35.
14. Guo Y, Martin LJ, Hanna W, *et al.* Growth factors and stromal matrix proteins associated with mammographic density. *Cancer Epidemiol Biomarkers Prev* 2001;**10**(March):243–8.
15. McConnell JC, O'Connell OV, Brennan K, *et al.* Increased peri-ductal collagen micro-organization may contribute to raised mammographic density. *Breast Cancer Res* 2016;**18**(1):5.
16. Huo CW, Chew G, Hill P, *et al.* High mammographic density is associated with an increase in stromal collagen and immune cells within the mammary epithelium. *Breast Cancer Res* 2015;**17**(1):79.
17. Vachon CM, Kuni CC, Anderson K, *et al.* Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control* 2000 Aug;**11**(7):653–62. Netherlands.
18. Burton A, Maskarinec G, Perez-gomez B, *et al.* Mammographic density and ageing : a collaborative pooled analysis of cross-sectional data from 22 countries worldwide. *PLoS Med* 2017;**14**(6):1–20.
19. McCormack VA, dos SSI, De Stavola BL, *et al.* Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. *Br J Cancer* 2003;**89**:852–9.
20. McCormack VA, Perry N, Vinnicombe SJ, *et al.* Ethnic variations in mammographic density: a British multiethnic longitudinal study. *Am J Epidemiol* 2008;**168**(4):412–21.
21. McCormack VA, Perry NM, Vinnicombe SJ, *et al.* Changes and tracking of mammographic density in relation to Pike's model of breast tissue aging: a UK longitudinal study. *Int J Cancer* 2010;**127**(2):452–61.
22. Stomper P, Voorhuis B, Ravnikar V, *et al.* Mammographic changes associated with postmenopausal hormone replacement therapy: a longitudinal study. *Radiology* 1990;**174**:487–90.
23. Byrne C, Ursin G, Martin CF, *et al.* Mammographic density change with estrogen and progestin therapy and breast cancer risk. *J Natl Cancer Inst* 2017;**109**(9):1–7.
24. Boyd N, Dite G, Stone J, *et al.* Heritability of mammographic density, a risk factor for breast cancer. *N Engl J Med* 2002;**347**(12):886–94.
25. Stone J, Dite GS, Gunasekara A, *et al.* The heritability of mammographically dense and nondense breast tissue. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(4):612–7.
26. Boyd N, Martin L, Rommens J, *et al.* Mammographic density: a heritable risk factor for breast cancer. *Methods Mol Biol* 2009;**472**:343–60.
27. Dite GS, Gurrin LC, Byrnes GB, *et al.* Predictors of mammographic density: insights gained from a novel regression analysis of a twin study. *Cancer Epidemiol Biomarkers Prev* 2008;**17**(12):3474–81.
28. Lindström S, Thompson DJ, Paterson AD, *et al.* Genome-wide association study identifies multiple loci associated with both mammographic density and breast cancer risk. *Nat Commun* 2014;**5**:5303.

29. Keller BM, McCarthy A, Chen J, *et al*. Associations between breast density and a panel of single nucleotide polymorphisms linked to breast cancer risk: a cohort study with digital mammography. *BMC Cancer* 2015;**15**(1):143.
30. Vachon CM, Scott CG, Fasching PA, *et al*. Common breast cancer susceptibility variants in LSP1 and RAD51L1 are associated with mammographic density measures that predict breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2012;**21**(7):1156–66.
31. Stone J, Thompson DJ, Dos Santos Silva I, *et al*. Novel associations between common breast cancer susceptibility variants and risk-predicting mammographic density measures. *Cancer Res* 2015;**75**(12):2457–67.
32. Stomper PC, Souza DJD, Dinitto PA, *et al*. Analysis of parenchymal density on mammograms in 1353 women 25–79 years old. *AJR Am Roentogenol* 1996;**167**(November):1261–5.
33. Sprague BL, Gangnon RE, Burt V, *et al*. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst* 2014;**106**(10).
34. van der Waal D, Emaus MJ, Bakker MF, *et al*. Geographic variation in volumetric breast density between screening regions in The Netherlands. *Eur Radiol* 2015;**25**(11):3328–37.
35. Egan RL, Mosteller RC. Breast cancer mammography patterns. *Cancer* 1977;**40**(5):2087–90.
36. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* 1976;**37**:2486–92.
37. Sala E, Warren R, McCann J, *et al*. Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme. *J Med Screen* 1998;**5**:207–12.
38. Carney PA. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med* 2003;**138**:168–75.
39. Barlow WE, Lehman CD, Zheng Y, *et al*. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. *J Natl Cancer Inst* 2002;**94**(15):1151–9.
40. Leconte I, Feger C, Galant C, *et al*. Mammography and subsequent whole-breast sonography of nonpalpable breast cancers: the importance of radiologic breast density. *AJR Am J Roentgenol* 2003;**180**(6):1675–9.
41. Devolli-Disha E, Manxhuka-Kerliu S, Ymeri H, *et al*. Comparative accuracy of mammography and ultrasound in women with breast symptoms according to age and breast density. *Bosn J Basic Med Sci* 2009 May;**9**(2):131–6.
42. Chiu SYH, Duffy S, Yen AMF, *et al*. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev* 2010;**19**(5):1219–28.
43. Aiello EJ, Buist DS, White E, *et al*. Association between mammographic breast density and breast cancer tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:662–8.
44. Porter GJR, Evans AJ, Cornford EJ, *et al*. Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. *AJR Am J Roentgenol* 2007;**188**(3):676–83.
45. Sala E, Solomon L, Warren R, *et al*. Size, node status and grade of breast tumours: association with mammographic parenchymal patterns. *Eur Radiol* 2000;**10**(1):157–61.
46. Pisano ED, Hendrick RE, Yaffe MJ, *et al*. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology* 2008;**246**(2):376–83.
47. Wanders JOP, Holland K, Veldhuis WB, *et al*. Volumetric breast density affects performance of digital screening mammography. *Breast Cancer Res Treat* 2017;**162**(1):95–103.
48. Wanders JOP, Holland K, Karssemeijer N, *et al*. The effect of volumetric breast density on the risk of screen-detected and interval breast cancers: a cohort study. *Breast Cancer Res* 2017;**19**(1):67.
49. Redmond CE, Healy GM, Murphy CF, *et al*. The use of ultrasonography and digital mammography in women under 40 years with symptomatic breast cancer: a 7-year Irish experience. *Ir J Med Sci* 2017 Feb;**186**(1):63–7.
50. Häberle L, Fasching PA, Brehm B, *et al*. Mammographic density is the main correlate of tumors detected on ultrasound but not on mammography. *Int J Cancer* 2016;**139**(9):1967–74.
51. Bertrand KA, Tamimi RM, Scott CG, *et al*. Mammographic density and risk of breast cancer by age and tumor characteristics. *Breast Cancer Res* 2013;**15**(6):R104.
52. Gierach GL, Ichikawa L, Kerlikowske K, *et al*. Relationship between mammographic density and breast cancer death in the breast cancer surveillance consortium. *J Natl Cancer Inst* 2012;**104**(16):1218–27.
53. Eriksson L, Czene K, Rosenberg LU, *et al*. Mammographic density and survival in interval breast cancers. *Breast Cancer Res* 2013;**15**(3):R48.
54. Holm J, Humphreys K, Li J, *et al*. Risk factors and tumor characteristics of interval cancers by mammographic density. *J Clin Oncol* 2015;**33**(9):1030–7.
55. Domingo L, Salas D, Zubizarreta R, *et al*. Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. *Breast Cancer Res* 2014;**16**(1):R3.
56. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case–control study. *AJR Am J Roentgenol* 1987;**148**(6):1087–92.
57. Whitehead J, Carlile T, Kopecky KJ, *et al*. Wolfe mammographic parenchymal patterns. A study of the masking hypothesis of Egan and Mosteller. *Cancer* 1985;**56**(6):1280–6.
58. Boyd NF, Guo H, Martin LJ, *et al*. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007;**356**(3):227–36.
59. Palomares MR, Machia JRB, Lehman CD, *et al*. Mammographic density correlation with Gail model breast cancer risk estimates and component risk factors. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(July):1324–30.
60. Vachon CM, van Gils CH, Sellers TA, *et al*. Mammographic density, breast cancer risk and risk prediction. *Breast Cancer Res* 2007;**9**(6):217.
61. Yaghjyan L, Colditz GA, Rosner B, *et al*. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to the time since the mammogram. *Cancer Epidemiol Biomarkers Prev* 2013;**22**(6):1110–7.
62. Byrne C, Schairer C, Wolfe J, *et al*. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst* 1995;**87**(21):1622–9.
63. Peto J, Collins N, Barfoot R, *et al*. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *J Natl Cancer Inst* 1999;**91**(11):943–9.
64. Engmann NJ, Golmakani MK, Miglioretti DL, , *et al*Breast Cancer Surveillance Consortium. Population-attributable risk proportion of clinical risk factors for breast cancer. *JAMA Oncol* 2017 Sep 1;**3**(9):1228–36.
65. Grove JS, Goodman MJ, Gilbert FIJ, *et al*. Factors associated with mammographic pattern. *Br J Radiol* 1985 Jan;**58**(685):21–5. England.
66. Sellers TA, Vachon CM, Pankratz VS, *et al*. Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. *Am J Epidemiol* 2007;**166**(4):456–64.
67. Lawlor D, Okasha M, Gunnell D, *et al*. Associations of adult measures of childhood growth with breast cancer: finding from the British Women's Heart and Health Study. *Br J Cancer* 2003;**89**:81–7.
68. Hunter DJ, Willett WC. Diet, body size, and breast cancer. *Epidemiol Rev* 1993;**15**(1):110–32.
69. Boyd NF, Rommens JM, Vogt K, *et al*. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol* 2005;**6**(10):798–808.
70. Rice M, Bertrand K, VanderWeele T, *et al*. Mammographic density and breast cancer risk: a mediation analysis. *Breast Cancer Res* 2016;**18**:94.
71. Pike MC, Krailo MD, Henderson BE, *et al*. "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. *Nature* 1983 Jun;**303**(5920):767–70.
72. Rosner BA, Colditz GA, Hankinson SE, *et al*. Validation of Rosner–Colditz breast cancer incidence model using an independent data set, the California Teachers Study. *Breast Cancer Res Treat* 2013;**142**(1):187–202.
73. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. For the Nurses' Health Study Research Group. *J Natl Cancer Inst* 1996 Mar;**88**(6):365–71.
74. Boyd NF, Jensen HM, Cooke G, *et al*. Mammographic densities and the prevalence and incidence of histological types of benign breast disease. Reference Pathologists of the Canadian National Breast Screening Study. *Eur J Cancer Prev* 2000 Feb;**9**(1):15–24.

75. Turashvili G, McKinney S, Martin L, *et al*. Columnar cell lesions, mammographic density and breast cancer risk. *Breast Cancer Res Treat* 2009 Jun;**115**(3):561–71.
76. Vierkant RA, Degnim AC, Radisky DC, *et al*. Mammographic breast density and risk of breast cancer in women with atypical hyperplasia: an observational cohort study from the Mayo Clinic Benign Breast Disease (BBD) cohort. *BMC Cancer* 2017;**17**:84.
77. Ghosh K, Hartmann LC, Reynolds C, *et al*. Association between mammographic density and age-related lobular involution of the breast. *J Clin Oncol BioMed Cent* 2010;**28**(13):2207–12.
78. Ghosh K, Vachon CM, Pankratz VS, *et al*. Independent association of lobular involution and mammographic breast density with breast cancer risk. *J Natl Cancer Inst* 2010;**102**(22):1716–23.
79. Maskarinec G, Ju D, Horio D, *et al*. Involution of breast tissue and mammographic density. *Breast Cancer Res* 2016;**18**(1):128.
80. Gabrielson M, Chiesa F, Paulsson J, *et al*. Amount of stroma is associated with mammographic density and stromal expression of oestrogen receptor in normal breast tissues. *Breast Cancer Res Treat* 2016;**158**(2):253–61.
81. Pang J-MB, Byrne DJ, Takano EA, *et al*. Breast tissue composition and immunophenotype and its relationship with mammographic density in women at high risk of breast cancer. *PLoS One* 2015;**10**(6):e0128861.
82. Hattar R, Maller O, McDaniel S, *et al*. Tamoxifen induces pleiotropic changes in mammary stroma resulting in extracellular matrix that suppresses transformed phenotypes. *Breast Cancer Res* 2009;**11**(1):R5.
83. Chew GL, Huo CW, Huang D, *et al*. Effects of tamoxifen and oestrogen on histology and radiographic density in high and low mammographic density human breast tissues maintained in murine tissue engineering chambers. *Breast Cancer Res Treat* 2014;**148**(2):303–14.
84. Acerbi I, Cassereau L, Dean I, *et al*. Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. *Integr Biol* 2015;**7**(10):1120–34.
85. Boyd NF, Li Q, Melnichouk O, *et al*. Evidence that breast tissue stiffness is associated with risk of breast cancer. *PLoS One* 2014;**9**(7):1–8.
86. Conklin MW, Eickhoff JC, Riching KM, *et al*. Aligned collagen is a prognostic signature for survival in human breast carcinoma. *Am J Pathol* 2011;**178**(3):1221–32.
87. Provenzano PP, Inman DR, Eliceiri KW, *et al*. Collagen density promotes mammary tumor initiation and progression. *BMC Med* 2008;**6**(1):11.
88. Yaghjyan L, Colditz GA, Collins LC, *et al*. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. *J Natl Cancer Inst* 2011;**103**(15):1179–89.
89. Conroy SM, Pagano I, Kolonel LN, *et al*. Mammographic density and hormone receptor expression in breast cancer: the Multiethnic Cohort Study. *Cancer Epidemiol* 2011;**35**(5):448–52.
90. Ding J, Warren R, Girling A, *et al*. Mammographic density, estrogen receptor status and other breast cancer tumor characteristics. *Breast J* 2010;**16**(3):279–89.
91. Olsen A, Bihrmann K, Jensen M-B, *et al*. Breast density and outcome of mammography screening: a cohort study. *Br J Cancer* 2009;**100**:1205–8.
92. Antoni S, Sasco AJ, Dos Santos Silva I, *et al*. Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. *Breast Cancer Res Treat* 2013;**137**(2):337–47.
93. Maskarinec G, Pagano I, Little M, *et al*. Mammographic density as a predictor of breast cancer survival: the multiethnic cohort. *Breast Cancer Res* 2013;**15**(R7).
94. Cil T, Fishell E, Hanna W, *et al*. Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery. *Cancer* 2009;**115**(24):5780–7.
95. Park CC, Rembert J, Chew K, *et al*. High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer. *Int J Radiat Oncol Biol Phys* 2009 Jan;**73**(1):75–9.
96. Habel LA, Dignam JJ, Land SR, *et al*. Mammographic density and breast cancer after ductal carcinoma in situ. *J Natl Cancer Inst* 2004;**96**(19):1467–72.
97. Habel LA, Capra AM, Achacoso NS, *et al*. Mammographic density and risk of second breast cancer after ductal carcinoma in situ. *Cancer Epidemiol Biomarkers Prev* 2010;**19**(10):2488–95.
98. Gram IT, Funkhouser E, Tabár L, *et al*. The Tabár classification of mammographic parenchymal patterns. *Eur J Radiol* 1997;**24**(2):131–6.
99. D'Orsi CJ, Sickles EA, Mendelson EB, *et al*. *ACR BI-RADS Atlas, breast imaging reporting and data system*. 5th edn. Reston, VA: American College of Radiology; 2013.
100. Boyd NF, Byng JW, Jong RA, *et al*. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* 1995;**87**(9):670–5.
101. Duffy SW, Nagtegaal ID, Astley SM, *et al*. Visually assessed breast density, breast cancer risk and the importance of the craniocaudal view. *Breast Cancer Res* 2008;**10**(4):R64.
102. Brisson J, Diorio C, Mâsse B. Wolfe's parenchymal pattern and percentage of the breast with mammographic densities: redundant or complementary classifications? *Cancer Epidemiol Biomarkers Prev* 2003;**12**(8):728–32.
103. Evans DG, Astley S, Stavrinos P, *et al*. *Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study*. Southampton (UK): NIHR Journals Library; 2016 Aug. Programme Grants for Applied Research.
104. Ang T, Harkness EF, Maxwell AJ, *et al*. Visual assessment of breast density using visual analogue scales: observer variability, reader attributes and reading time. In: *Medical imaging 2017: image perception, observer performance, and technology assessment. SPIE medical imaging, 2017, Orlando, Florida*; 2017. 1013608, https://doi.org/10.1117/12.2253797.
105. Spayne MC, Gard CC, Skelly J, *et al*. Reproducibility of BI-RADS breast density measures among community radiologists: a prospective cohort study. *Breast J* 2012;**18**(4):326–33.
106. Melnikow J, Fenton JJ, Whitlock EP, *et al*. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016;**164**(126):268–78.
107. Lobbes MBI, Cleutjens JPM, Lima Passos V, *et al*. Density is in the eye of the beholder: visual versus semi-automated assessment of breast density on standard mammograms. *Insights Imaging* 2012;**3**(1):91–9.
108. Ekpo EU, Ujong UP, Mello-Thoms C, *et al*. Assessment of interradiologist agreement regarding mammographic breast density classification using the fifth edition of the BI-RADS atlas. *AJR Am J Roentgenol* 2016;**206**(5):1119–23.
109. Youk JH, Kim SJ, Son EJ, *et al*. Comparison of visual assessment of breast density in BI-RADS 4th and 5th editions with automated volumetric measurement. *AJR Am J Roentgenol* 2017;**209**(3):703–8.
110. Irshad A, Leddy R, Ackerman S, *et al*. Effects of changes in BI-RADS density assessment guidelines (fourth versus fifth edition) on breast density assessment: intra-and interreader agreements and density distribution. *AJR Am J Roentgenol* 2016;**207**(6):1366–71.
111. Raza S, Mackesy MM, Winkler NS, *et al*. Effect of training on qualitative mammographic density assessment. *J Am Coll Radiol* 2016;**13**(3):310–5.
112. Byng JW, Boyd NF, Fishell E, *et al*. The quantitative analysis of mammographic densities. *Phys Med Biol* 1994;**39**(10):1629–38.
113. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology* 2004 Jan 1;**230**(1):29–41.
114. Boyd NF, Martin LJ, Bronskill M, *et al*. Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst* 2010;**102**(16):1224–37.
115. Eng A, Gallant Z, Shepherd J, *et al*. Digital mammographic density and breast cancer risk: a case–control study of six alternative density assessment methods. *Breast Cancer Res* 2014;**16**(5):439.
116. Nguyen TL, Aung YK, Evans CF, *et al*. Mammographic density defined by higher than conventional brightness thresholds better predicts breast cancer risk. *Int J Epidemiol* 2017;**46**(2):652–61.
117. Kopans DB. Basic physics and doubts about relationship between mammographically determined tissue density and breast cancer risk. *Radiology* 2008 Feb;**246**(2):348–53.
118. Lau S, Ng KH, Abdul Aziz YF. Volumetric breast density measurement: sensitivity analysis of a relative physics approach. *Br J Radiol* 2016;**89**(1066):20160258.
119. Brand JS, Czene K, Shepherd JA, *et al*. Automated measurement of volumetric mammographic density: a tool for widespread breast cancer risk assessment. *Cancer Epidemiol Biomarkers Prev* 2014;**23**(9):1764–72.

120. Shepherd J, Herve L, Landau J, *et al*. Novel use of single X-ray absorptiometry for measuring breast density. *Technol Cancer Res Treat* 2005;**4**(2):173–82.
121. Alonzo-Proulx O, Jong RA, Yaffe MJ. Volumetric breast density characteristics as determined from digital mammograms. *Phys Med Biol* 2012;**57**(22):7443–57.
122. Gweon HM, Youk JH, Kim JA, *et al*. Radiologist assessment of breast density by BI-RADS categories versus fully automated volumetric assessment. *AJR Am J Roentgenol* 2013;**201**(3):692–7.
123. Ciatto S, Bernardi D, Calabrese M, *et al*. A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification. *Breast* 2012;**21**(4):503–6.
124. Holland K, Gubern-M'erida A, Mann RM, *et al*. Optimization of volumetric breast density estimation in digital mammograms. *Phys Med Biol* 2017;**62**:3779–97.
125. Kallenberg MGJ, van Gils CH, Lokate M, *et al*. Effect of compression paddle tilt correction on volumetric breast density estimation. *Phys Med Biol* 2012 Aug 21;**57**(16):5155–68.
126. Holland K, van Zelst J, den Heeten GJ, *et al*. Consistency of breast density categories in serial screening mammograms: a comparison between automated and human assessment. *Breast* 2016;**29**:49–54.
127. Destounis S, Johnston L, Highnam R, *et al*. Using volumetric breast density to quantify the potential masking risk of mammographic density. *AJR Am J Roentgenol* 2017;**208**(1):222–7.
128. Abdolell M, Tsuruda KM, Lightfoot CB, *et al*. Utility of relative and absolute measures of mammographic density vs clinical risk factors in evaluating breast cancer risk at time of screening mammography. *Br J Radiol* 2016;**89**(1059):20150522.
129. Busana MC, Eng A, Denholm R, *et al*. Impact of type of full-field digital image on mammographic density assessment and breast cancer risk estimation: a case–control study. *Breast Cancer Res* 2016;**18**(1):96.
130. Morrish OWE, Tucker L, Black R, *et al*. Mammographic breast density: comparison of methods for quantitative evaluation. *Radiology* 2015 May;**275**(2):356–65.
131. Regini E, Mariscotti G, Durando M, *et al*. Radiological assessment of breast density by visual classification (BI-RADS) compared to automated volumetric digital software (Quantra): implications for clinical practice. *Radiol Med* 2014 Oct;**119**(10):741–9. Italy.
132. Tagliafico A, Tagliafico G, Astengo D, *et al*. Mammographic density estimation: one-to-one comparison of digital mammography and digital breast tomosynthesis using fully automated software. *Eur Radiol* 2012;**22**(6):1265–70.
133. Tagliafico AS, Tagliafico G, Cavagnetto F, *et al*. Estimation of percentage breast tissue density: comparison between digital mammography (2D full field digital mammography) and digital breast tomosynthesis according to different BI-RADS categories. *Br J Radiol* 2013;**86**(1031).
134. Tagliafico A, Tagliafico G, Astengo D, *et al*. Comparative estimation of percentage breast tissue density for digital mammography, digital breast tomosynthesis, and magnetic resonance imaging. *Breast Cancer Res Treat* 2013;**138**(1):311–7.
135. Bakic PR, Carton A-K, Kontos D, *et al*. Breast percent density: estimation on digital mammograms and central tomosynthesis projections. *Radiology* 2009;**252**(1):40–9.
136. Machida Y, Saita A, Namba H, *et al*. Automated volumetric breast density estimation out of digital breast tomosynthesis data: feasibility study of a new software version. *Springerplus* 2016;**5**(1):780.
137. Pertuz S, McDonald ES, Weinstein SP, *et al*. Fully automated quantitative estimation of volumetric breast density from digital breast tomosynthesis images: preliminary results and comparison with digital mammography and MR imaging. *Radiology* 2016;**0**(0):1–10.
138. Alshafeiy TI, Wadih A, Nicholson BT, *et al*. Comparison between digital and synthetic 2D mammograms in breast density interpretation. *AJR Am J Roentgenol* 2017;**209**(1):W36–41.
139. Conant EF, Keller BM, Pantalone L, *et al*. Percentage density estimations from standard-dose versus synthetic digital mammograms : results from a large screening cohort using automated measures. *Radiology* 2017;**283**(0):673–80.
140. Ducote JL, Molloi S. Quantification of breast density with dual energy mammography: an experimental feasibility study. *Med Phys* 2010;**37**(2):793–801.
141. Laidevant AD, Malkov S, Flowers CI, *et al*. Compositional breast imaging using a dual-energy mammography protocol. *Med Phys* 2009;**37**(1):164–74.
142. Molloi S, Ding H, Feig S. Breast density evaluation using spectral mammography, radiologist reader assessment and segmentation techniques: a retrospective study based on left and right breast comparison. *Acad Radiol* 2015;**22**(8):1052–9.
143. Johansson H, von Tiedemann M, Erhard K, *et al*. Breast-density measurement using photon-counting spectral mammography. *Med Phys* 2017 Jul;**44**(7):3579–93.
144. Wang J, Azziz A, Fan B, *et al*. Agreement of mammographic measures of volumetric breast density to MRI. *PLoS One* 2013;**8**(12):1–8.
145. Clendenen TV, Zeleniuch-Jacquotte A, Moy L, *et al*. Comparison of 3-point dixon imaging and fuzzy C-means clustering methods for breast density measurement. *J Magn Reson Imaging* 2013;**38**(2):474–81.
146. Boyd N, Martin L, Chavez S, *et al*. Breast-tissue composition and other risk factors for breast cancer in young women: a cross-sectional study. *Lancet Oncol* 2009;**10**(6):569–80.
147. Tagliafico A, Bignotti B, Tagliafico G, *et al*. Breast density assessment using a 3T MRI system: comparison among different sequences. *PLoS One* 2014;**9**(6):1–6.
148. Ledger AEW, Scurr ED, Hughes J, *et al*. Comparison of Dixon sequences for estimation of percent breast fibroglandular tissue. *PLoS One* 2016;**11**(3):e0152152.
149. Chang DH-E, Chen J-H, Lin M, *et al*. Comparison of breast density measured on MR images acquired using fat-suppressed versus nonfat-suppressed sequences. *Med Phys* 2011;**38**(11):5961–8.
150. Nie K, Chen J, Chan S, *et al*. Development of a quantitative method for analysis of breast density based on three- dimensional breast MRI Development of a quantitative method for analysis of breast density based on three-dimensional breast MRI. *Med Phys* 2008;**35**(12):5253–62.
151. Wu S, Weinstein SP, Conant EF, *et al*. Automated chest wall line detection for whole-breast segmentation in sagittal breast MR images. *Med Phys* 2013;**40**(4):042301. 1–12.
152. Wu S, Weinstein SP, Conant EF, *et al*. Automated fibroglandular tissue segmentation and volumetric density estimation in breast MRI using an atlas-aided fuzzy C-means method. *Med Phys* 2013;**40**(October):122302.
153. Doran SJ, Hipwell JH, Denholm R, *et al*. Breast MRI segmentation for density estimation: do different methods give the same results and how much do differences matter? *Med Phys* 2017 Sep;**44**(9):4573–92.
154. Wengert GJ, Helbich TH, Vogl W-D, *et al*. Introduction of an automated user-independent quantitative volumetric magnetic resonance imaging breast density measurement system using the Dixon sequence: comparison with mammographic breast density assessment. *Investig Radiol* 2014;**50**(2):73–80.
155. Gubern-Merida A, Kallenberg M, Platel B, *et al*. Volumetric breast density estimation from full-field digital mammograms: a validation study. *PLoS One* 2014;**9**(1).
156. Kim WH, Moon WK, Kim SJ, *et al*. Ultrasonographic assessment of breast density. *Breast Cancer Res Treat* 2013;**138**(3):851–9.
157. Moon WK, Shen Y-W, Huang C-S, *et al*. Comparative study of density analysis using automated whole breast ultrasound and MRI. *Med Phys* 2011 Jan;**38**(1):382–9.
158. Moon WK, Lo C-M, Chang JM, *et al*. Rapid breast density analysis of partial volumes of automated breast ultrasound images. *Ultrasound Imaging* 2013 Oct 30;**35**(4):333–43.
159. Chen J-H, Lee Y-W, Chan S-W, *et al*. Breast density analysis with automated whole-breast ultrasound: comparison with 3-D magnetic resonance imaging. *Ultrasound Med Biol* 2016;**42**(5):1211–20.
160. Glide-Hurst CK, Duric N, Littrup P. Volumetric breast density evaluation from ultrasound tomography images. *Med Phys* 2008 Aug 11;**35**(9):3988–97.
161. Duric N, Boyd N, Littrup P, *et al*. Breast density measurements with ultrasound tomography: a comparison with film and digital mammography. *Med Phys* 2013;**40**(1):13501.
162. Khodr ZG, Sak MA, Pfeiffer RM, *et al*. Determinants of the reliability of ultrasound tomography sound speed estimates as a surrogate for volumetric breast density. *Med Phys* 2015;**42**(10):5671–8.

163. Sak M, Duric N, Littrup P, *et al.* Using speed of sound imaging to characterize breast density. *Ultrasound Med Biol* 2017 Jan;**43**(1):91–103.
164. O'Flynn EAM, Fromageau J, Ledger AE, *et al.* Ultrasound tomography evaluation of breast density. *Investig Radiol* 2017;**52**(6):1.
165. Taroni P, Quarto G, Pifferi A, *et al.* Optical identification of subjects at high risk for developing breast cancer. *J Biomed Opt* 2013;**18**(6):60507.
166. Taroni P, Quarto G, Pifferi A, *et al.* Breast tissue composition and its dependence on demographic risk factors for breast cancer: non-invasive assessment by time domain diffuse optical spectroscopy. *PLoS One* 2015;**10**(6):1–16.
167. O'Sullivan TD, Leproux A, Chen J-H, *et al.* Optical imaging correlates with magnetic resonance imaging breast density and reveals composition changes during neoadjuvant chemotherapy. *Breast Cancer Res* 2013;**15**(1):R14.
168. Ray S, Chen L, Keller BM, *et al.* Association between breast parenchymal complexity and false-positive recall from digital mammography versus breast tomosynthesis. Preliminary investigation in the ACRIN PA 4006 trial. *Acad Radiol* 2016;**23**(8):977–86.
169. Saftlas AF, Wolfe JN, Hoover RN, *et al.* Mammographic parenchymal patterns as indicators of breast cancer risk. *Am J Epidemiol* 1989 Mar;**129**(3):518–26.
170. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiol Rev* 1993;**15**(1):196–208.
171. Gram IT, Bremnes Y, Ursin G, *et al.* Percentage density, Wolfe's and Tabár's mammographic patterns: agreement and association with risk factors for breast cancer. *Breast Cancer Res* 2005;**7**(5):R854.
172. Gastounioti A, Conant EF, Kontos D. Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. *Breast Cancer Res* 2016;**18**(1):91.
173. Manduca A, Carston MJ, Heine JJ, *et al.* Texture features from mammographic images and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2009;**18**(3):837–45.
174. Häberle L, Wagner F, Fasching PA, *et al.* Characterizing mammographic images by using generic texture features. *Breast Cancer Res* 2012;**14**(2):R59.
175. Nielsen M, Vachon CM, Scott CG, *et al.* Mammographic texture resemblance generalizes as an independent risk factor for breast cancer. *Breast Cancer Res* 2014;**16**(2):R37.
176. Sun W, Tseng T-LB, Qian W, *et al.* Using multiscale texture and density features for near-term breast cancer risk analysis. *Med Phys* 2015;**42**(6):2853–62.
177. Zheng Y, Keller BM, Ray S, *et al.* Parenchymal texture analysis in digital mammography: a fully automated pipeline for breast cancer risk assessment. *Med Phys* 2015;**42**(7):4149–60.
178. Malkov S, Shepherd JA, Scott CG, *et al.* Mammographic texture and risk of breast cancer by tumor type and estrogen receptor status. *Breast Cancer Res* 2016 Dec 6;**18**(1):122.
179. Li H, Giger ML, Lan L, *et al.* Computerized analysis of mammographic parenchymal patterns on a large clinical dataset of full-field digital mammograms: robustness study with two high-risk datasets. *J Digit Imaging* 2012;**25**(5):591–8.
180. Gierach GL, Li H, Loud JT, *et al.* Relationships between computer-extracted mammographic texture pattern features and BRCA1/2 mutation status: a cross-sectional study. *Breast Cancer Res* 2014;**16**(4):424.
181. Gastounioti A, Oustimov A, Keller BM, *et al.* Breast parenchymal patterns in processed versus raw digital mammograms: a large population study toward assessing differences in quantitative measures across image representations. *Med Phys* 2016;**43**(11):5862–77.
182. Moschidis E, Chen X, Taylor C, *et al.* Texture-based breast cancer prediction in full-field digital mammograms using the dual-tree complex wavelet transform and random forest classification. *Int Work Digit Mammogr* 2014:209–16.
183. Winkel RR, von Euler-Chelpin M, Nielsen M, *et al.* Mammographic density and structural features can individually and jointly contribute to breast cancer risk assessment in mammography screening: a case–control study. *BMC Cancer* 2016;**16**(1):414.
184. Kallenberg M, Petersen K, Nielsen M, *et al.* Unsupervised deep learning applied to breast density segmentation and mammographic risk scoring. *IEEE Trans Med Imaging* 2016;**35**(5):1322–31.
185. Kontos D, Bakic PR, Carton A-K, *et al.* Parenchymal texture analysis in digital breast tomosynthesis for breast cancer risk estimation. *Acad Radiol* 2009;**16**(3):283–98.
186. Kontos D, Ikejimba LC, Bakic PR, *et al.* Analysis of parenchymal texture with digital breast tomosynthesis: comparison with digital mammography and implications for cancer risk assessment. *Radiology* 2011;**261**(1):80–91.
187. Schousboe JT, Kerlikowske K, Loh A, *et al.* Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med* 2011 Jul 5;**155**(1):10–20.
188. Mandelblatt JS, Stout NK, Schechter CB, *et al.* Collaborative modeling of the benefits and harms associated with different U.S. Breast cancer screening strategies. *Ann Intern Med* 2016;**164**(4):215–25.
189. Trentham-Dietz A, Kerlikowske K, Stout N, *et al.* Tailoring breast cancer screening intervals by breast density and risk for women 50 and older: Collaborative modeling of screening outcomes. *Ann Int Med* 2016;**165**(10):700–12.
190. Choi JS, Han B-K, Ko EY, *et al.* Comparison between two-dimensional synthetic mammography reconstructed from digital breast tomosynthesis and full-field digital mammography for the detection of T1 breast cancer. *Eur Radiol* 2016;**26**(8):2538–46.
191. Peters S, Hellmich M, Stork A, *et al.* Comparison of the detection rate of simulated microcalcifications in full-field digital mammography, digital breast tomosynthesis, and synthetically reconstructed 2-dimensional images performed with 2 different digital X-ray mammography systems. *Investig Radiol* 2017;**52**(4):206–15.
192. Bernardi D, Macaskill P, Pellegrini M, *et al.* Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. *Lancet Oncol* 2016;**17**(8):1105–13.
193. Gilbert FJ, Tucker L, Gillan MGC, *et al.* Accuracy of digital breast tomosynthesis for depicting breast cancer subgroups in a UK retrospective reading study (TOMMY trial). *Radiology* 2015;**277**(3):697–706.
194. Houssami N. Expert review of medical devices digital breast tomosynthesis (3D-mammography) for screening women with dense breasts. *Expert Rev Med Devices* 2016;**4440**(May):515–7.
195. McDonald ES, Oustimov A, Weinstein SP, *et al.* Effectiveness of digital breast tomosynthesis compared with digital mammography. *JAMA Oncol* 2016 Feb 18;**19014**:1–7.
196. Berg WA, Blume JD, Cormack JB, *et al.* Combined screening with ultrasound and mammography compared to mammography alone in women at elevated risk of breast cancer : results of the first-year screen in ACRIN 6666. *JAMA* 2008;**299**(18):2151–63.
197. Berg WA, Zhang Z, Lehrer D, *et al.* Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA* 2012 Apr 4;**307**(13):1394–404.
198. Berg WA, Bandos AI, Mendelson EB, *et al.* Ultrasound as the primary screening test for breast cancer: analysis from ACRIN 6666. *J Natl Cancer Inst* 2016;**108**(4).
199. Sprague BL, Stout NK, Schechter C, *et al.* Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med* 2015 Feb 3;**162**(3):157–66.
200. Ohuchi N, Suzuki A, Sobue T, *et al.* Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan strategic anti-cancer randomized trial (J-START): a randomised controlled trial. *Lancet* 2016;**387**(10016):341–8.
201. Tagliafico AS, Calabrese M, Mariscotti G, *et al.* Adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts: interim report of a prospective comparative trial. *J Clin Oncol* 2016;**34**(16):1882–8.
202. Chang JM, Moon WK, Cho N, *et al.* Breast cancers initially detected by hand-held ultrasound: detection performance of radiologists using automated breast ultrasound data. *Acta Radiol* 2011;**52**(1):8–14.
203. Kuhl CK, Schrading S, Strobel K, *et al.* Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection — a novel approach to breast cancer screening with MRI. *J Clin Oncol* 2014;**32**(22):2304–10.

204. Chen S, Huang M, Shen Y, *et al*. Application of abbreviated protocol of magnetic resonance imaging for breast cancer screening in dense breast tissue. *Acad Radiol* 2017;**24**(3):316–20.
205. Emaus MJ, Bakker MF, Peeters PHM, *et al*. MR Imaging as an additional screening modality for the detection of breast cancer in women aged 50-75 years with extremely dense breasts: the DENSE trial study design. *Radiology* 2015;**277**(2):141827.
206. Berg WA, Blume JD, Adams AM, *et al*. Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666. *Radiology* 2010;**254**(1):79–87.
207. Harvey SC, Di Carlo PA, Lee B, *et al*. An abbreviated protocol for high-risk screening breast MRI saves time and resources. *J Am Coll Radiol* 2016;**13**(4):374–80.
208. Tagliafico AS, Bignotti B, Rossi F, *et al*. Diagnostic performance of contrast-enhanced spectral mammography: systematic review and meta-analysis. *Breast* 2016;**28**:13–9.
209. Phillips J, Miller MM, Mehta TS, *et al*. Contrast-enhanced spectral mammography (CESM) versus MRI in the high-risk screening setting: patient preferences and attitudes. *Clin Imaging* 2017 Mar;**42**:193–7.
210. Hobbs MM, Taylor DB, Buzynski S, *et al*. Contrast-enhanced spectral mammography (CESM) and contrast enhanced MRI (CEMRI): Patient preferences and tolerance. *J Med Imaging Radiat Oncol* 2015;**59**(3):300–5.
211. Mainiero MB, Lourenco A, Mahoney MC, *et al*. ACR appropriateness criteria breast cancer screening. *J Am Coll Radiol* 2016 Nov;**13**(11):R45–9.
212. Kerlikowske K, Zhu W, Tosteson ANA, *et al*. Identifying women with dense breasts at high risk of interval cancer: a cohort study. *Ann Int Med* 2015;**162**(10):673–81.
213. Ali MA, Czene K, Eriksson L, *et al*. Breast tissue organisation and its association with breast cancer risk. *Breast Cancer Res* 2017;**19**(1):103.
214. Holland K, can Gils C, Mann R, *et al*. Quantification of masking risk in screening mammography with volumetric breast density maps. *Breast Cancer Res Treat* 2017;**162**:541–8.
215. Pinto Pereira SM, McCormack VA, Hipwell JH, *et al*. Localized fibroglandular tissue as a predictor of future tumor location within the breast. *Cancer Epidemiol Biomarkers Prev* 2011;**20**(8):1718–25.
216. Amir E, Freedman OC, Seruga B, *et al*. Assessing women at high risk of breast cancer: a review of risk assessment models. *J Natl Cancer Inst* 2010;**102**(10):680–91.
217. Chen J, Pee D, Ayyagari R, *et al*. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *J Natl Cancer Inst* 2006;**98**(17):1215–26.
218. Tice JA, Cummings SR, Ziv E, *et al*. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. *Breast Cancer Res Treat* 2005;**94**(2):115–22.
219. Tice JA, Cummings SR, Smith-Bindman R, *et al*. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med* 2008;**148**(5):337–47.
220. Barlow WE, White E, Ballard-Barbash R, *et al*. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst* 2006;**98**(17):1204–14.
221. Warwick J, Birke H, Stone J, *et al*. Mammographic breast density refines Tyrer–Cuzick estimates of breast cancer risk in high-risk women: findings from the placebo arm of the International Breast Cancer Intervention Study I. *Breast Cancer Res* 2014 Jan;**16**(5):451.
222. Brentnall AR, Harkness EF, Astley SM, *et al*. Mammographic density adds accuracy to both the Tyrer–Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. *Breast Cancer Res* 2015;**17**(1):147.
223. Lee CP, Choi H, *et al*. Mammographic breast density and common genetic variants in breast cancer risk prediction. *PLoS One* 2015;**10**(9).
224. Astley S, Harkness E, Sergeant J, *et al*. A comparison of four methods of mammographic density measurement in the UK predicting risk of breast cancer at screening (PROCAS) study. *Eur J Cancer* 2016;**61**(s6):S6.
225. Brandt KR, Scott CG, Ma L, *et al*. Comparison of clinical and automated breast density measurements: implications for risk prediction and supplemental screening. *Radiology* 2016;**279**(3):710–9.
226. Shepherd JA, Kerlikowske K, Ma L, *et al*. Volume of mammographic density and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2011 Jul;**20**(7):1473–82.
227. Kerlikowske K, Ma L, Scott CG, *et al*. Combining quantitative and qualitative breast density measures to assess breast cancer risk. *Breast Cancer Res* 2017;**19**(1):97.
228. Youk JH, Gweon HM, Son EJ, *et al*. Automated volumetric breast density measurements in the era of the BI-RADS fifth edition: a comparison with visual assessment. *AJR Am J Roentgenol* 2016;**206**(5):1056–62.
229. Cuzick J, Forbes JF, Sestak I, *et al*. Long-term results of tamoxifen prophylaxis for breast cancer-96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007;**99**(4):272–82.
230. Cuzick J, Sestak I, Cawthorn S, *et al*. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol* 2015;**16**(1):67–75.
231. Li J, Humphreys K, Eriksson L, *et al*. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. *J Clin Oncol* 2013;**31**(18):2249–56.
232. Nyante SJ, Sherman ME, Pfeiffer RM, *et al*. Prognostic significance of mammographic density change after initiation of tamoxifen for ER-positive breast cancer. *J Natl Cancer Inst* 2015;**107**(3). 425–425.
233. Ko KL, Shin IS, You JY, *et al*. Adjuvant tamoxifen-induced mammographic breast density reduction as a predictor for recurrence in estrogen receptor-positive premenopausal breast cancer patients. *Breast Cancer Res Treat* 2013;**142**(3):559–67.
234. Sandberg MEC, Li J, Hall P, *et al*. Change of mammographic density predicts the risk of contralateral breast cancer—a case–control study. *Breast Cancer Res* 2013;**15**(4):R57.
235. Kim JY, Cho N, Jeyanth JX, *et al*. Smaller reduction in 3D breast density associated with subsequent cancer recurrence in patients with breast cancer receiving adjuvant tamoxifen therapy. *AJR Am J Roentgenol* 2014;**202**(4):912–21.
236. Engmann NJ, Scott CG, Jensen MR, *et al*. Longitudinal changes in volumetric breast density with tamoxifen and aromatase inhibitors. *Cancer Epidemiol Biomarkers Prev* 2017 Jun;**26**(6):930–7.
237. Kim WH, Moon WK, Kim SM, *et al*. Variability of breast density assessment in short-term reimaging with digital mammography. *Eur J Radiol* 2013;**82**(10):1724–30.
238. Ko ES, Kim RB, Han BK. Reproducibility of automated volumetric breast density assessment in short-term digital mammography reimaging. *Clin Imaging* 2015;**39**(4):582–6.
239. Alonzo-Proulx O, Mawdsley GE, Patrie JT, *et al*. Reliability of automated breast density measurements. *Radiology* 2015;**275**(2):366–76.
240. Vinnicombe S, Evans A, Hart K, *et al*. Visual and automated volumetric assessment of mammographic density: do measurements depend on the digital mammography unit? In: *Proceedings of the European congress of radiology*; 2014.
241. Damases CN, Brennan PC, McEntee MF. Mammographic density measurements are not affected by mammography system. *J Med Imaging* 2015;**2**(1):15501.
242. Vachon CM, Pankratz VS, Scott CG, *et al*. Longitudinal trends in mammographic percent density and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(5):921–8.
243. Pettersson A, Graff RE, Ursin G, *et al*. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. *J Natl Cancer Inst* 2014 May;**106**(5).
244. Lokate M, Peeters PHM, Peelen LM, *et al*. Mammographic density and breast cancer risk: the role of the fat surrounding the fibroglandular tissue. *Breast Cancer Res* 2011;**13**(5):R103.
245. Yaghjyan L, Pettersson A, Colditz GA, *et al*. Postmenopausal mammographic breast density and subsequent breast cancer risk according to selected tissue markers. *Br J Cancer* 2015;**113**(7):1104–13.
246. Holm J, Li J, Darabi H, *et al*. Associations of breast cancer risk prediction tools with tumor characteristics and metastasis. *J Clin Oncol* 2016;**34**(3):251–8.
247. Keller BM, Conant EF, Oh H, *et al*. Breast cancer risk prediction via area and volumetric estimates of breast density. In: Maidment AD, Bakic PR, Gavenonis S, editors. *Breast Imaging. 11th International Workshop, IWDM 2012. Lect Notes Comput Sci*, **7361**; 2012. p. 236–43. LNCS.
248. Edwards BL, Atkins KA, Stukenborg GJ, *et al*. The association of mammographic density and molecular breast cancer subtype. *Cancer Epidemiol Biomarkers Prev* 2017 Oct;**26**(10):1487–92.