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Breast Composition: Measurement and Clinical Use

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Breast density is a measure of the extent of radiodense fibroglandular tissue in the breast. The risk of developing breast cancer and the risk of missing cancer at screening rise with higher breast density. In this paper, the historical background to breast density measurement is outlined and current evidence based practice is explained. The relevance of breast density knowledge to mammographic practice and image interpretation is considered in the light of clinical assessment and notification of mammographic breast density (MBD). The current work also discusses risk stratification for decision-making regarding screening frequency and better modalities for earlier detection of breast cancer in the dense breast. Automated volumetric approaches are explained while ultrasound, digital breast tomosynthesis, molecular breast imaging, and magnetic resonance imaging are introduced as valuable adjuncts to digital mammography for imaging the dense breast. The work concludes on the important note that screened women should be notified of their breast density, and such notification should be accompanied with clear and adequate information about breast density and cancer risk, strategies associated with lower MBD, as well as best screening intervals and pathways for women with dense breasts. Adoption of these strategies may be crucial to early detection and treatment of cancer and improving survival from the disease.

Introduction

Breast density is a measure of the extent of radiodense fibroglandular tissue in the breast.[1] A meta-analysis of breast cancer risk factors indicates that the risk of breast cancer from high breast density is twice higher than other risk factors except family history of the disease in women 40 – 49 years.[1] However, it is still contentious whether density is an independent risk factor or merely stimulates other risk factors to cause cancer. Regardless of these contentions, studies have shown that high breast density is associated with a 4-6 fold increased risk of breast cancer,[2-5] and that a 1% increase in breast density is associated with 2% increase in breast cancer risk.[4]

Dense breast tissue has been shown to offer more opportunities for breast cancer to develop, especially in younger women.[3, 6-8] Additionally, there is a genetic predisposition to breast density,[9, 10] and other established risk factors for breast cancer such as hormonal agents,[11, 12] lifestyle, and reproductive characteristics are associated with high breast density.[13-16] Importantly, breast density is a potentially modifiable risk factor for breast cancer,[17, 18] and lower density has been shown to be a prognostic factor for the effect of interventions on breast cancer risk.[19] Some lifestyle parameters responsible for high breast density and breast cancer are controllable,[20] and consumption of food

species such as vegetables, vitamin D, and calcium may have an ameliorative impact on the breast density and breast cancer risk.[21, 22]

Breast density is also a significant factor in interval breast cancer (cancer detected within 12 months after a normal screening mammogram), accounting for about 50%.[3, 5] Women with dense breasts are 4.7 to 17.8 times at risk of interval breast cancer relative to those with non-dense breasts.[3, 23-25] Mammographic breast density also reduces mammographic sensitivity and limits earlier detection of breast cancer with 2-dimensional mammography through masking effects.[23, 26] Therefore, it is increasingly important to assess breast density of women undergoing screening mammography and inform women of their density. Such breast density data can improve women's awareness of their risks of breast cancer and interval cancer, and the potential of cancer being missed in their mammograms. This will allow for shared decision-making between screened women and their physicians concerning strategies to reduce the associated risks and facilitate better decisions regarding screening.[17, 19, 27]

National level breast density information will enable breast cancer risk stratification,[27, 28] leading to selection of appropriate imaging pathways such as ultrasound,[29, 30] digital breast tomosynthesis (DBT),[31] and magnetic resonance imaging (MRI)[30] to improve cancer detection in the dense breast. Breast density data can also be used to select personalised and appropriate screening intervals for screened women, such as screening less often and with digital mammography only for lower risk, fatty breasts and more frequently with DBT and whole breast Ultrasound for the denser breast. Data on breast density will enable use of breast density as a marker for monitoring the effect of breast cancer prevention and control interventions.[17, 19]

The relevance of breast density information in clinical decision-making for screened women underscores the need for methods of breast density assessment to be standardized, reliable, and reproducible, as this will support clinical decisions made from breast density assessment. In this paper we revisit breast morphological and radiographic anatomy. We also examine the link between breast density and breast cancer, and approaches that have been employed to categorize mammographic breast density before tackling clinical uses.

Breast Composition and Radiographic appearances

Breast consists of fibroglandular tissue and fat, and their relative concentration determines the radiographic appearance of the breast.[3] X-ray attenuation is higher in fibroglandular tissue than fat; as a result, fibroglandular tissue appears radiopaque (white) and constitutes a dense area of the breast and fat appears radiolucent (black).[3] The dense portion of the breast contains high concentration of epithelial and stromal cells and collagen.[3, 32, 33]

Dense breasts are highly radiosensitive due to the high proliferation of epithelial and stromal cells in such breasts.[34] To reduce the potential effect of radiation on the breast, there is a need to optimise the imaging procedure. Optimisation is aimed at producing good quality images at acceptable radiation dose.[35] The key radiographic determinant of image quality and dose is the detective quantum efficiency of the detector and composition of the X-ray spectrum, which in turn depends on the target material, tube voltage (kVp), and filtration.[35] These technical parameters impact not only on the diagnostic value of the image, but also the appearance of breast density to the human visual system. [36, 37] This is worrisome in film-screen mammography where radiographers have to manually select these factors.[37] With automatic exposure control (AEC), exposure parameters are selected according to the physical characteristics of the breast or compressed breast thickness.[38] Therefore, the same target/filter/kVp is chosen for a given breast density. Spectral and breast thickness information also influence the accuracy of volumetric breast density assessment.[39, 40] Studies have shown that higher atomic number target/filter combinations such as Tungsten/Rhodium (W/Rh) and Tungsten/Silver (W/Ag) produce the optimum spectrum for imaging the dense breast, and improve visualization of the dense breasts and features of cancer at lower doses.[41, 42] Therefore, for systems that do not have functional AEC, manual selection of the filter that produces the optimum spectrum for a given breast density is encouraged. Alternatively, dense breasts could be imaged with digital breast tomosynthesis (DBT). The high detector quantum efficiency (DQE), fast read-out ability, and low noise levels of digital detectors used in DBT have enabled acquisition of good quality images at low doses in dense breasts.[43] DBT produces pseudo-cross-sectional images that reduce tissue superimposition and synthetic (reconstructed) 2-dimensional (2D) images which can be used as substitute for standard 2D images of digital mammography. The combined use of 3D images of DBT and standard 2D images of digital mammography (DM) has been shown to improve diagnostic accuracy,[44, 45] but is associated with increased radiation dose.[43] However, use of reconstructed 2D images as substitute for standard 2D images has been found to be associated with a 45% reduction in mean glandular dose.[43, 46]

Mechanisms linking breast density to breast cancer

Two theories have been postulated to explain the mechanisms linking breast density and breast cancer. The first mechanism involves mitogen (a chemical substance that encourages a cell to commence cell division, triggering mitosis),[47] and mutagen effects (a physical or chemical agent that changes the genetic material of an organism and thus increases the frequency of mutations above the natural background level).[48] The second mechanism involves biological interaction among epithelial and stromal cells, collagen and the breast microenvironment.[32, 33]

It has been shown that mitogenic followed by mutagenic activity are at least in part, responsible for high breast density and breast cancer, where individuals with both high breast density and breast cancer demonstrate similar mitogen[47] and mutagen characteristics.[48] It is well known that mitogens

induce cell proliferation, primarily affecting epithelial and stromal cells leading to increased fibroglandular tissue and higher levels of breast density mostly in premenopausal women.[47, 49] Concomitantly, this increased presence of proliferating cells is very sensitive to mutagens resulting in changes and potential errors in DNA replication and strand recombination.[50] Examples of specific mitogens that are responsible for both high breast density and breast cancer are insulin-like growth factor 1 and prolactin.[47, 49] A mutagen of oxidative stress that has been shown to be associated with breast density and cancer is cytochrome P450 1A2 (CYP1A2).[48]

It has also been shown that breasts with high density and those with cancer exhibit similar biological characteristics such as increased concentration of epithelial and stromal cells and collagen.[32, 33, 51] Epithelial cell proliferation is necessary for breast density increases, however since breast cancer primarily evolve from epithelial cells, increased numbers of epithelial cells in the dense breast increase the possibility of cancer.[33] Stromal cells induce cancer by modulating epithelial cells through epidermal growth factor receptor, IGF-1, and TGF-β.[52] Stromal cells are also progenitors, of collagen and stromal matrix which promote mammary gland development and tumour invasion [52-54] and since collagen is linked to IGF-1 quantities and tumour reorganization,[53] there are increased opportunities for cell proliferation and transformation to cancer. Also, the extracellular matrix expresses increased concentration of proteoglycans (lumican and decorin) in stroma associated with high breast density and cancer. These proteoglycans bind growth factors and increase breast tissue stiffness implicated in breast cancer.[51] Together these intercellular interactions in the breast microenvironment result in each cell type becoming more tensile and more rigid, generating mechanical forces that can increase breast density and cancer risk.[51, 55]

Breast density is associated with established risk factors for breast cancer except age and body mass index.[11, 12] Genome-wide studies have shown that breast cancer susceptibility genetic variants such as 8q (rs13281615), RAD51L1 (rs10483813), LSP1 (rs3817198), TOX3 (rs3803662) and MAP3K1 (rs889312) and many more are associated with breast density measures.[56-59] There is also evidence that hormone replacement therapy, [11] alcohol intake, [16] and reproductive factors such as early menarche, nulliparity, late first term birth, [60] and reduced breastfeeding (<12 months) are associated with higher breast density.[61, 62] Anthropometric factors such as high birth weight and lower prepubertal weight are associated with higher breast density.[63] The data produced shows that breast density information can be used in combination with other risk factors for stratification of breast cancer risk. Barlow et al.[27] have shown an improvement in breast cancer risk prediction model with addition of breast density data.

An important characteristic of breast density is that it is reducible,[64-69] and preliminary studies have shown that breast density may serve as a biomarker for the effect of preventive interventions on breast cancer risk.[17] The first International Breast Cancer Intervention Study (IBIS) trial of Tamoxifen™ versus placebo showed that women in the Tamoxifen group who had a 10% or greater reduction in breast density demonstrated a 63% reduction in breast cancer risk but those who experienced less than 10% breast density reduction showed no risk reduction.[17] Li et al.[19] showed that women treated with tamoxifen who experienced a relative density reduction of more than 20% had a 50% reduced risk of death from breast cancer. Randomized control trials demonstrated changes in breast density with intake of low-fat high carbohydrate diet.[70, 71] Cross-sectional studies have shown calcium and vitamin D, [72-76] and vegetables[75, 77] to be associated with lower breast density.

Breast density assessment will enable monitoring of the effect of interventions that mitigate breast density and breast cancer risk. Therefore, it could become the responsibility of radiographers and radiologists to inform screened women of their breast density status, and to advise patients of the implications of high breast density including, informing them of their elevated risk of developing breast cancer, and the increased potential of cancer being concealed in their mammograms if they are dense. It may also be important that patients are provided with adequate information on how regularly they may need to be screened and other imaging modalities that may improve visualization of the dense areas for features of cancer. It is also increasingly important that screened women with dense breasts are advised to avoid lifestyles such as alcohol intake and exogenous hormone use that have been shown to increase cancer risk in women with dense breast. Also, consumption of food species associated with lower breast density[22, 72, 75, 77] and physical activity[78] is encouraged as these may mitigate their risk of developing breast cancer.

The history of qualitative breast density classification

Interest in breast density classification dates back to 1969 when Wolfe and colleagues observed that breast with prominent ducts was associated with breast cancer risk. They considered prominent ducts a desmoplastic reaction which precedes breast cancer development in most breasts.[79] In 1976, they developed the Wolfe method of breast density classification based on the appearance of breast parenchyma and prominence of ducts[80]: N1, P1, P2, DY, and Qdy (Table 1). This system classifies N1, P1 as low-risk densities and P2, DY as high risk breast densities.[81] More than 40 studies have assessed associations with Wolfe grade or percentage breast density and the majority reported 2- to 6-fold increased risks for the highest compared with the lowest risk categories.[82]

Table 1: Summary of Wolfe, Boyd, and Tabăr breast density classifications

Wolfe patterns	**Boyd SCC**	**Tabăr patterns**

N1: Completely fatty with a few fibrous connective tissue	0% : No dense tissue	I: Symmetry of all components with slightly greater fibrous tissue
P1: Fatty with prominent ducts ≤4mm in diameter	<10% dense tissue	II: Bulk of fat tissue
P2: Higher concentration of prominent triangular ducts in the central portion	10-25% dense tissue	III: More fat tissue with fibrous tissue in the retroareolar region
DY: Homogenous density with few ductal prominence	26-50% dense tissue	VI: Mainly nodular densities
Qdy: Breast with spongy texture	51-75% dense tissue	V: Predominantly fibroglandular
	>75%: Extremely dense	

SCC: Six category classification

In 1980, Boyd and colleagues proposed a six category classification system and subjectively classifies mammographic breast density as percentages based on the relative proportions of dense tissue and fat.[83] Boyd's categories range from absence of dense tissue to excess density (Table 1), and considers breast with density >75% at risk of cancer. The method has shown strong positive association between breast density and cancer risk.[84, 85] The driver for Boyd's work, although still subjective, was to try and introduce a more quantitative approach than offered by Wolfe.

In 1997, Tabår and colleagues argued that the breast density classification by Wolfe has limited application in clinical practice and proposed a five scale mammographic breast density classification system based on histologic-mammographic correlations and on the relative proportions of four breast components.[86] The method categorizes mammographic density into five parenchymal patterns (Table 1), with I, II and III considered as low-risk and IV and V as high-risk patterns.[81, 86] The method has shown strong positive association with breast cancer risk.[81]

In 2000, the American College of Radiology (ACR) modified and simplified the Wolfe and Boyd methods and proposed the breast imaging reporting and data systems (BIRADS) scheme. In 2003, the ACR updated BIRADS to the 4th edition using Boyd method to propose a quantitative breast density classification based on the percentage of fibroglandular tissue in the breast. This scheme was last updated to the 5th edition in 2013,[87] and subjectively classifies mammographic breast density based on the relative appearance of dense tissue and fat into four categories (A – D) (Figures 1 and 2). In the 5th edition emphasis is on classification based on the potential for masking the risk of breast cancer. For example, breasts having >50% fatty tissue, but with very dense tissue posterior to the nipple may be classified as category C or D.[88] BIRADS is almost universally accepted and widely used qualitative methodology, and encourages users to describe the implications of the assigned breast density category, and areas on the mammogram where cancer is likely to be missed.[87] For example, it encourages users to inform patients that small lesions may be missed in BIRADS C and that

mammography sensitivity is lower in category D.[89] Previous editions of BIRADS have demonstrated consistent association between breast density and cancer risk particularly in postmenopausal women.[28, 82] However, BIRADS suffers from reduced reproducibility and has shown wide inter-reader agreement (κ) ranging from 0.37 – 0.91.[90-92] Therefore, an assessment of the extent of inter-reader agreement with the 5th edition is increasingly relevant.

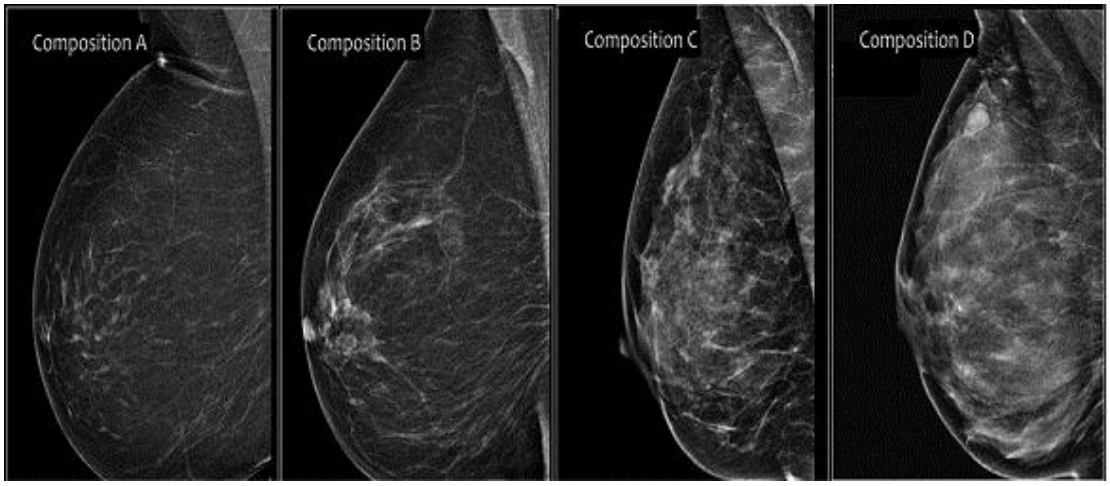

Figure 1: Breast imaging reporting and data systems (5th edition) categories A – D. Note higher amount of dense tissue (white areas) in C and D (Labelled for reuse)

Table 2: Breast imaging reporting and data systems classification scheme in the 4th and 5th editions

	4th Edition		5th Edition
1	The breast is almost entirely fat (<25% glandular)	**a**	The breasts are almost entirely fatty
2	There are scattered areas of fibroglandular densities (approximately 25-50% glandular)	**b**	There are scattered areas of fibroglandular density
3	The breast is heterogeneously dense, which could obscure detection of small masses (approximately 51-75% glandular)	**c**	The breasts are heterogeneously dense, which may obscure small masses
4	The breast is extremely dense. This may lower the sensitivity of mammography (>75% glandular)	**d**	The breasts are extremely dense, which lowers the sensitivity of mammography

Table 2: Description of BIRADS classification in the 4th and 5th edition scheme (Labelled for reuse)

Visual approaches have shown strong positive association between mammographic breast density and breast cancer risk.[81, 84, 86] However, variation in image acquisition parameters (kVp and mAs) may cause variations in image appearance, perception of radiographic features and therefore mammographic breast density.[93-96] Consequently, the subjectivity of visual approaches and variation in image quality may cause inter-reader variability in mammographic breast density assessment. Subjective variability will consistently lead to variability in cancer risk stratification and unnecessary difference in clinical decision-making from mammographic breast density assessment. These deficiencies may limit the use of mammographic breast density information as biomarker for monitoring the effect of breast cancer preventive interventions.[97, 98] Consequently, quantitative methodologies have been designed for mammographic breast density assessment in the clinical setting.

Categorisation of Breast Composition Using "Quantitative Area-Based" Techniques

Quantitative area-based techniques for mammographic breast density include semi-automated interactive thresholding techniques such as Cumulus (University of Toronto, Canada) and Madena (University of Southern California, US) and automated techniques such as AutoDensity (University of Melbourne, Australia), Image J (National Institute of Health), and MedDensity (University of Genova, Italy).[92]

Interactive thresholding methods use segmentation and thresholding techniques to select two grey levels for percentage mammographic density calculation.[99] The first of these separates the image of the breast from the background, and aggregation of the pixels over the intensity range gives the maximum intensity and provides a measure of breast area (A_B). The second threshold outlines the dense tissue (excluding the pectorialis muscle), and sums the pixels in this area to calculate area of dense tissue (A_D) (Figure 2). The software packages calculate percentage mammographic density (PMD) as the ratio of the dense tissue and the total breast area multiplied by 100.[100]

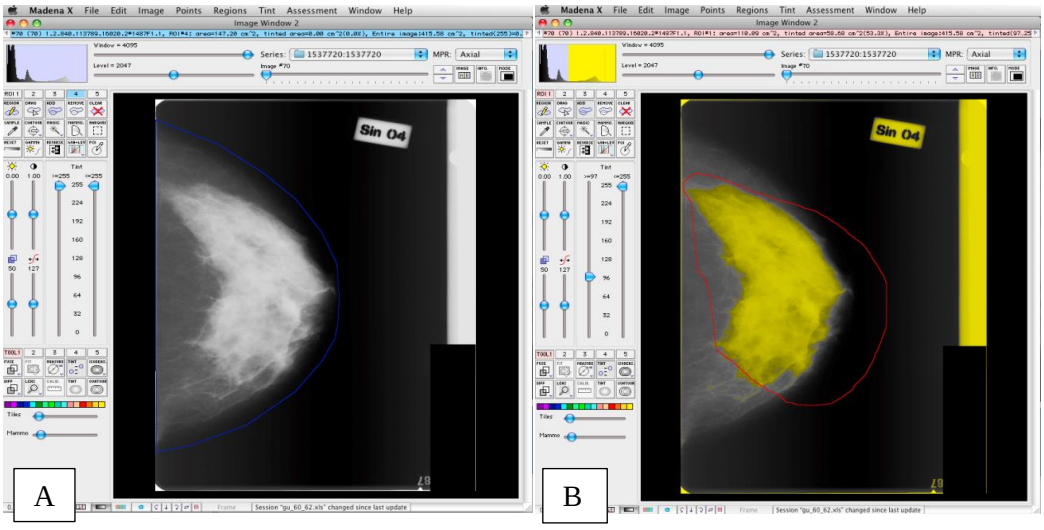

Figure 2: Example of Cumulus breast density assessment. (A) Cumulus interface, (B) thresholding taking place (Labelled for reuse).

Cumulus has demonstrated good association between breast density and cancer risk in multiple global studies.[3, 101, 102] AutoDensity has been shown to be comparable to Cumulus for risk assessment[24]. MedDensity has been shown to demonstrate moderate correlation with BIRADS for breast density assessment.[103-106] Image J has demonstrated strong correlation with Cumulus and BIRADS [107] and positive association between breast density and cancer risk.[28, 108] However, quantum and anatomical noise reduce the reliability of AutoDensity and MedDensity.[24, 109] Image quality may limit accurate outlining of the dense area with semi-automated methods.[110] Although semi-automated thresholding methods have better reproducibility than visual approaches, they are labour-intensive, time-consuming, and still demonstrate intra- and inter-user variability.[3, 111-114] Furthermore, area-based techniques measure percentage dense area and treat the breast as a two-dimensional structure, ignoring the three-dimensional features of the breast.[115]

There are doubts that area measurement of breast density as percentage mammographic density (PMD) may not accurately reflect the quantity of dense tissue in the breast.[115] This is because the quantity of dense tissue may vary in different breasts with the same dense area, and measured PMD of the same dense area may vary with variation in breast size (Figure 3). Therefore, area-based techniques may not be able to show change in breast density following intervention.[97, 98] These limitations have necessitated the introduction of volumetric methodologies for mammographic breast density assessment.

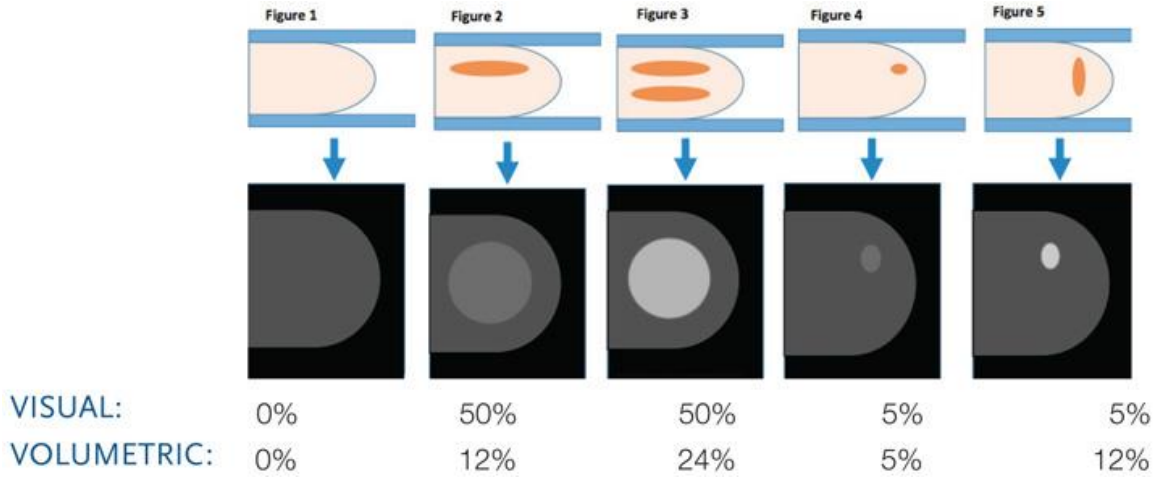

Figure 3: Illustration of how breast density can be under- or over-estimated by visual/area-based approaches. The second and third images show how dense area of different thicknesses given the

same score by visual/area-based approaches and different scores by volumetric techniques (Reproduced with permission)

Categorisation of Breast Composition Using Automated, Volumetric Techniques

Volumetric techniques employ physics principles to volumetric breast density. Commercially available volumetric techniques include Quantra™, Volpara™, and academic versions include CumulusV and Dual-energy X-ray absorptiometry.[92, 110] The commercial products come as networked/server-based software packages and are installed between the acquisition and display systems. They perform volumetric breast density assessment without any human intervention and send their output to the radiologist or technologist workstation where the results can be viewed immediately after image acquisition (Figure 4 A&B).

Quantra™ (Hologic Inc.) uses a physical physics principle to calculate volumetric breast density. Volumetric breast density assessment is based on data related to the physical composition of the breast, compressed breast thickness, and the X-ray spectra (tube potential (kVp), tube current (mAs), and filter type and thickness).[39, 40] Quantra estimates the thickness of the dense tissue above each pixel in the mammographic image and combines these pixel values to compute the total volume of the dense tissue in the breast (Vfg(cm^3)).[116] It aggregates the pixel values over the whole breast to calculate the volume of the breast, and then calculates percentage volumetric breast density (Vbd%) as a percentage of the dense tissue volume and the total breast volume. The software calculates the breast density make-up of the patient by segmenting the Vbd% into a total Quantized breast density (Q_abd) value. These Q_abd values range from 1 – 4 and used to map the ACR BIRADS breast density categories (Figure 4B). Quantra has been shown to be an reliable[117, 118] and reproducible[119, 120] for mammographic breast density assessment, and a strong predictor of breast cancer risk from breast density.[28] Quantra has also been shown to accurately reproduce radiologists' BIRADS assessment on a two-category scale. [121, 122]

Volpara™ (Matakina Technology Limited) is also based on relative physics principles, and measures mammographic breast density by finding a reference point of entirely fat (P_{FAT}) in each image and then estimating X-ray attenuation relative to that point for all other points in the image.[123] Volpara calculates volume of dense tissue by integrating the thickness of dense tissue at each pixel level values over the image; it then computes the volume of the breast by multiplying the area of the breast by the recorded breast thickness.[124] It calculates percentage volumetric breast density as a percentage ratio of the volume of fibroglandular and the total volume of the breast. The software generates four volumetric density grades (VDGA – D) corresponding to the four ACR BIRADS breast density categories (Figure 4A).[123-125] Volpara has demonstrated a strong positive correlation with BIRADS,[124,

[126] and has been shown to be more reliable and reproducible,[39, 117, 118] and a better risk predictor from breast density assessment [28] than other mammographic breast density assessment tools.

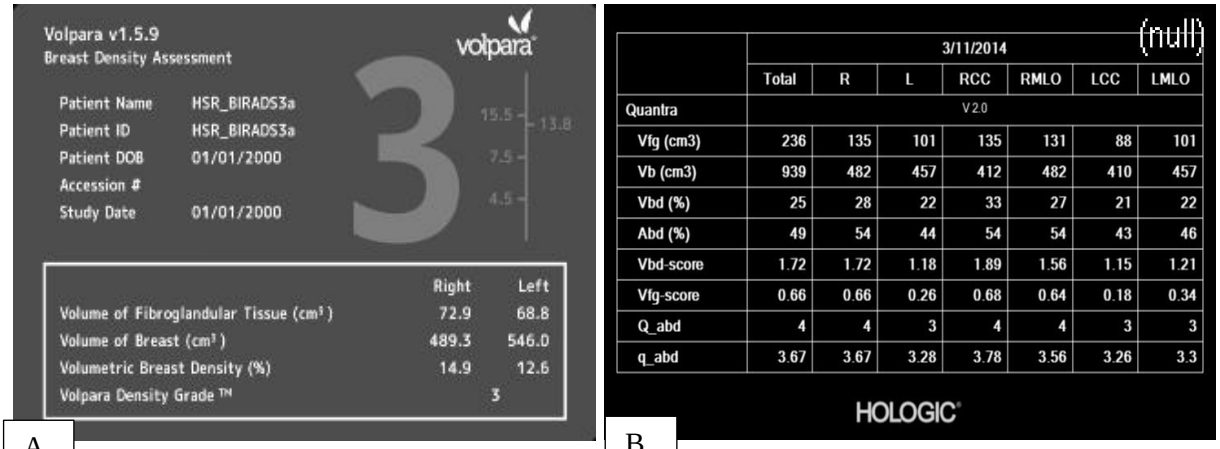

Figure 4: Display of assessed volumetric breast density results: In A,the Volpara Density grade is 3, and in B, Quantra the breast density grade (total Q_abd) is 4.

Currently, there is increased advocacy for breast density notification in the United States,[127] and 22 states have already passed laws mandating disclosure of breast density information to screened women.[128] Given the increased advocacy and legislation for breast density notification, it is worthwhile to employ tools that are robust enough for clinical use and devoid of subjectivity for mammographic breast density assessment. Interestingly, Volpara™ and Quantra™ are robust and provide breast density score to the practitioner within 2 minutes after the mammographic procedure. Their reliability and reproducibility as well as the ready availability of their results will allow for consistency and timely utilization of breast density information in clinical decision-making. Where these software packages are available, radiologists and technologists only have to review the breast density information generated by the software and provide a statement on the patient report about her breast density. It should however be noted that Volpara™ and Quantra™ are used as adjuncts to radiologist assessment, and although shown now to correlate to sensitivity,[129] they may not account for all the potential masking effects of breast density. Therefore, it is the responsibility of the image interpreter to accept or override the breast density report generated by the software based on their perceived masking effect.

Radiographic Factors that can impact on Breast density measurement

Volumetric methods rely on image acquisition parameters and compressed breast thickness to estimate volumetric breast density. It has been shown that when compression is applied with a flexible compression paddle, the upper plate may be tilted. Paddle tilt causes a variation in breast thickness from the thoracic wall to the breast edges,[130, 131] and results in a smooth intensity inhomogeneity field

that distorts the image, limiting computerized image analysis.[132, 133] This is most often seen in fatty breasts where it creates a region of intensity inhomogeneity which is usually misinterpreted as a dense tissue component, leading to overestimation of a woman's breast density.[134] The effect of the paddle tilt in dense breasts may be indeterminate.[134] Positioning has been shown to cause density variation in digital mammography and digital breast tomosynthesis,[109] and implants can be treated as a component of the breast by these volumetric techniques and cause errors in mammographic breast density estimation if the images are not tagged appropriately in the DICOM headers.[135] Quantum noise influences the appearance of breast parenchyma in mammograms and determines that amount of fibroglandular tissues which can be quantified as volumetric breast density. This has been shown to reduce volumetric breast density estimated from mammograms. [136] The foregoing demonstrate that factors under the radiographer's control may influence the accurate assessment of breast density with both visual and quantitative approaches, and emphasizes the need for correct technical parameters and procedures to be used for breast imaging. Additionally, quality assurance is very important to produce mammograms with normalized breast density value scale in order to overcome errors which may arise from variation in the technical parameters used for different breast compositions.[137] Failure of calibration may cause poor dose control and strange density reports for breast thicknesses which are 2cm greater than actual thickness. Mammograms with uncalibrated information may lead to errors in mammographic breast density assessment.[138]

Imaging the dense breast

The literature demonstrates that mammography suffers reduced sensitivity in dense breasts due to masking effect on high breast density,[139] although it does appear to be very good for women with fatty breasts. Therefore, women with dense breasts who are elevated risk of breast cancer may benefit from adjunctive screening. Given that 31% – 43% of screened women have high breast density,[82] it is increasingly important to image dense breasts with appropriate imaging modalities to enhance visualization of the breast for cancer features. Also, since 50% of interval breast cancer is attributed to high mammographic breast density,[3] it is essential to assess breast density of screened women in order to identify women who may need to be screened more regularly. Existing evidence shows that ultrasound,[29, 30] digital breast tomosynthesis,[31] or MRI [30] improves cancer detection in dense breasts although it remains unclear which one suits which breasts best.

Clinical trials have shown that supplemental screening breast ultrasound significantly improves detection of node-negative breast cancer in dense breasts. The reported diagnostic yield of supplemental breast ultrasound ranged from 3.5 – 14.6 per 1000 women.[29, 30, 140-145] Ultrasound has been shown to be particularly useful for detection of non-palpable lesions,[145] invasive cancer ranging from 5 – 40mm in size,[29, 30] as well as mammographically occult cystic malignant lesions in dense

parenchyma.[140, 146] Therefore, ultrasound should be recommended as the first choice supplemental modality for dense patients.

The ability of digital breast tomosynthesis (DBT) to produce cross-sectional images removes superimposed tissues that may conceal breast cancer.[147] Increasingly, the synthesis of 3-dimensional (3D) images from DBT and the use of combined 2D and 3D improve detection of breast cancer in mammographically dense breasts.[148, 149] Studies have reported 7.2% – 53% increase in cancer detection and 20% – 59% reduction in recall rates with supplemental DBT.[31, 44, 45, 150, 151] Importantly, radiation dose to the dense tissue is lower for DBT than digital mammography (DM) for dense breasts;[43] therefore DBT is preferable to DM in terms of performance and dose, albeit it appears women with fatty breasts get higher dose on DBT.[152]

Another approach suitable for imaging the dense breast is molecular breast imaging (MBI) or Breast-Specific Gamma Imaging (BSGI). This modality allows for use of probes as biomarkers to image particular targets or pathways. Studies have shown an improvement in breast cancer detection in dense breast, with cancer detection rate per 1000 women increasing from 3.2 for mammography alone to 12.0% with supplemental MBI.[153] A review of the literature shows sensitivity ranging from 91% – 96%, with specificity of 60% – 77% for MBI alone,[154] and meta-analysis of published literature reported 95% sensitivity and 80% specificity.[155] A major limitation of MBI is its high radiation dose which has the potential to cause mutation to the rapidly dividing cells in dense breasts.[156] Work is underway to lower the dose.

Magnetic resonance imaging (MRI) is used as an adjunct to mammography, and has demonstrated high sensitivity and specificity.[157] In addition to slice-by-slice evaluation of the breast parenchyma, MRI offers high resolution required for lesion identification and characterization. Studies have shown that the sensitivity of MRI for breast cancer detection range from 91% – 100%.[158-161] Supplemental MRI has been shown to improve diagnostic yield by 18.2% per 1000 women.[159] Importantly, MRI is very accurate in excluding the risk of tumour recurrence, with enhancement indicating risk of tumour recurrence and vice-versa.[162-164] MRI has been shown to be the most accurate imaging modality for examination of the dense breast.[161] Therefore breast density assessment is important for radiographers and radiologists advise women with dense breasts of the most suitable imaging modality and screening interval so that cancer is detected early.[165]

Conclusion

High breast density is a significant determinant of breast cancer risk, mammographic sensitivity, and interval breast cancer. Breast density is associated with established risk factors for breast cancer

related to genetics and lifestyle parameters. Importantly, breast density can be reduced by interventions such as Tamoxifene and low-fat high carbohydrate diet. Therefore, clinical assessment and notification of mammographic breast density (MBD) is relevant for the purpose of risk stratification, decision-making regarding screening frequency, and for tailoring women's imaging pathways to facilitate earlier detection of breast cancer. Mammographic breast density assessment will also enable monitoring of the effect of interventions on breast density and therefore breast cancer risk. Automated volumetric approaches are more preferable for MBD assessment, and ultrasound, digital breast tomosynthesis, molecular breast imaging, and magnetic resonance imaging are valuable adjuncts to digital mammography for imaging the dense breast. It is therefore increasingly relevant that screened women are notified of their breast density, and such notification accompanied with clear and adequate information about breast density and cancer risk, strategies associated with lower MBD, as well as best screening intervals and pathways for women with dense breasts. Adoption of these strategies may be crucial to breast cancer risk reduction, early detection and treatment of cancer, and improving survival from the disease.

Table 2: Breast imaging reporting and data systems classification scheme in the 4th and 5th editions

	4th Edition		**5th Edition**
1	The breast is almost entirely fat (<25% glandular)	**a**	The breasts are almost entirely fatty
2	There are scattered areas of fibroglandular densities (approximately 25-50% glandular)	**b**	There are scattered areas of fibroglandular density
3	The breast is heterogeneously dense, which could obscure detection of small masses (approximately 51-75% glandular)	**c**	The breasts are heterogeneously dense, which may obscure small masses
4	The breast is extremely dense. This may lower the sensitivity of mammography (>75% glandular)	**d**	The breasts are extremely dense, which lowers the sensitivity of mammography

Table 1: Summary of Wolfe, Boyd, and Tabăr breast density classifications

Wolfe patterns	**Boyd SCC**	**Tabăr patterns**
N1: Completely fatty with a few fibrous connective tissue	0% : No dense tissue	I: Symmetry of all components with slightly greater fibrous tissue
P1: Fatty with prominent ducts ≤4mm in diameter	<10% dense tissue	II: Bulk of fat tissue
P2: Higher concentration of prominent triangular ducts in the central portion	10-25% dense tissue	III: More fat tissue with fibrous tissue in the retroareolar region
DY: Homogenous density with few ductal prominence	26-50% dense tissue	VI: Mainly nodular densities
Qdy: Breast with spongy texture	51-75% dense tissue	V: Predominantly fibroglandular
	>75%: Extremely dense	

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