2 Mammographic Breast Density and Its Effects on Imaging

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2.1 Introduction

Mammographic breast density (MBD) is a term used to define the proportion of radiologically dense tissue in the breast, such as glandular tissue and stromal tissue, and the variable amount of water contained within the breast. This proportional representation varies greatly from one person to another due to natural structural characteristics and other factors such as age, sex hormones, menopause and specific therapies such as hormonal replacement therapy and genetic predisposition. MBD is a "dynamic" representation of radiopaque glandular and fibrous tissue unlike fat tissue, which is radiolucent.

2.2 MBD Assessment Methods

Breast cancer derives from glandular tissue; thus, the probability of breast cancer is higher when there is a larger glandular component than fat tissue. Since the mid-1970s, this knowledge has encouraged many scientists to study different methods to measure breast composition and to study its correlation with breast cancer [1].

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Interest on this topic has grown since then and has recently become controversial; therefore, a decision was made to divide breast density values into categories to provide homogenous guidelines for interpretation in clinical practice.

As mammographic images are 2D representations (*area-based*) of a 3D entity (*volume-based*), new methods to measure MBD have been developed in recent years [2, 3].

These methods can be classified based on (a) the evaluation process (visual, semi-automated, fully-automated), (b) measurement of specific parameters that are area-based or volume-based and (c) qualitative or quantitative analysis (Table 2.2).

2.2.1 Visual Methods

In 1976, John Wolfe, a pioneer of MBD studies, published the first two works based on a qualitative and descriptive evaluation of breast density (*pattern-based*). He proposed a four-category classification for the different parenchymal patterns (N1, P1, P2, DY). In the N1 pattern, the breast consists almost entirely of fat, the P1 and P2 patterns represent increasing ductal prominence, and in the DY pattern, the breast parenchyma consists of diffuse or extensive nodular densities. There was a lower risk of cancer in less-dense breasts (N1, P1), and a higher risk of cancer in denser breasts (P2, DY). It was observed

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that the risk of cancer was 37-fold higher in women with a density of DY than in those women with fatty breasts (N1 group) [4, 5].

Later, in 1977, Laszlo Tabar developed an alternative system of qualitative measurement, defining five categories (Patterns I, II, II, IV, V) with different associated cancer risks [6]. Patterns IV and V, which are denser, were those associated with higher risk of developing breast cancer.

Wolfe's qualitative method was not reproducible [7, 8], so Boyd et al. proposed a quantitative method based on the percentage of mammographic density (*area-based*). It is based on a radiologist's assessment of the proportion of dense breast tissue relative to the breast areas. The classification is known as six class categories (SCC) where the density proportions are Class 1, 0%; Class 2, 0–10%; Class 3, 10–25%; Class 4, 25–50%; Class 5, 50–75%; and Class 6, 75–100% [9]. The visual estimate of mammographic density (MD) permitted the identification of cases at higher risk based on a higher percentage value.

The American College of Radiology (ACR), with its Breast Imaging Reporting and Data System (BI-RADS), developed a new visual method that divided breasts into four categories to standardize the evaluation and interpretation of MD by the radiologist. The ACR classification criteria have changed in different editions [10–12]. In edition IV, percentage values were added to the descriptive categories and edition V, released by BIRADS in 2013, defined four new categories, a, b, c and d (Fig. 2.1), and the quantitative evaluation (% gland) was replaced by an

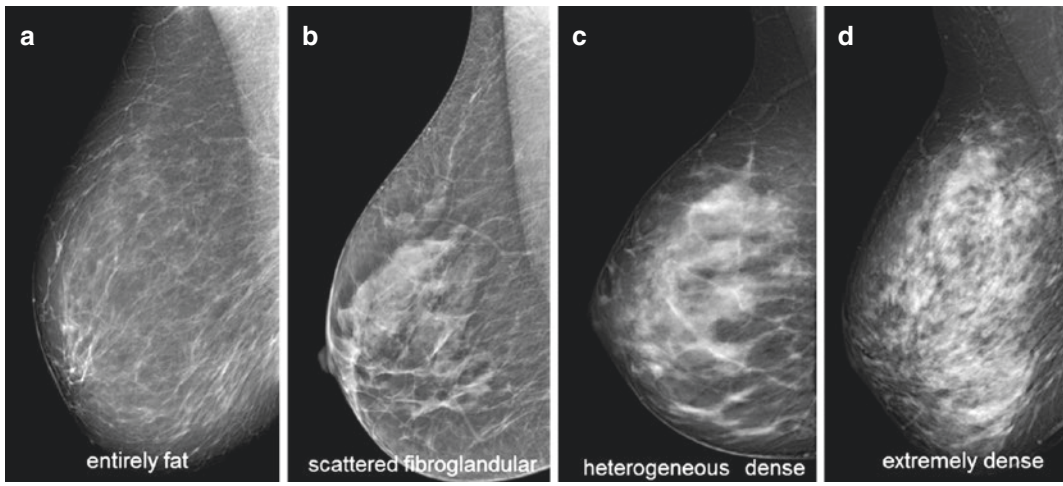

Fig. 2.1 Breast composition according to BI-RADS 5th edition. (**a**) Almost entirely fatty. (**b**) Scattered areas of fibroglandular density. (**c**) Heterogeneously dense. (**d**) Extremely dense

Table 2.1 BI-RADS categories for mammographic breast density

Classification of breast composition BI-RADS® (ACR)		
BI-RADS® 3rd edition	BI-RADS® 4th edition	BI-RADS® 5th edition
(1) Almost entirely fatty	(1) Almost entirely fatty (MBD < 25%)	(a) Breasts are almost entirely fatty
(2) Scattered fibroglandular	(2) Scattered fibroglandular (MBD 25–50%)	(b) There are scattered areas of fibroglandular density
(3) Heterogeneously dense	(3) Heterogeneously dense (MBD 51–75%)	(c) The breasts are heterogeneously dense, which may obscure small masses
(4) Extremely dense	(4) Extremely dense (MBD > 75%)	(d) The breasts are extremely dense, which lowers the sensitivity of mammography

evaluation of "masking risk"; masking risk refers to the probability that breast density may result in the misdetection of an underlying carcinoma (Table 2.1).

2.2.2 Computer-Assisted Methods

The problem with this subjective classification is the significant variability (intra- and interobserver), regardless of the system used. As a result of these limitations, new software have been developed for the semi-automated or fully-automated evaluation of breast density [13] to obtain objective measures that are easily used in clinical practice (Table 2.2).

Among these, CUMULUS is a computerized model developed by Yaffe and other researchers [14] that allows the radiologist to estimate the density area on a full-field digital mammography (FFDM), analysing every single pixel.

Such methods, developed in the last 20 years, have been regarded as the gold standard for the quantitative measurement of breast density. Many studies have demonstrated the high repeatability of CUMULUS [15, 16], and based on the results obtained, the probability of developing cancer is four- to sixfold higher in women with dense breasts than in women with fatty breasts. In the most important study to date [17], three quantitative methods (BI-RADS, CUMULUS and IMAGEJ) and three fully automated volumetric measurement methods (VOLPARA, QUANTRA and SXA) have been investigated. It was concluded that the latter methods represent a valuable alternative to quantify density and obtain a more precise assessment of the risk of developing cancer.

One of the fundamental criticisms of these methods, which is also applied to objective measurement methods, is that they evaluate 3D characteristics using 2D images [18]; evaluation parameters are influenced by breast positioning (CC, MLO), depth and the superimposition of dense tissue as well as the level of compression.

Growing interest from both industry and researchers highlights the necessity of defining a standardized evaluation method to measure breast density and, hence, the risk of breast cancer, although this goal appears difficult and demanding.

Table 2.2 Mammographic breast density measurement systems

MBD assessment			Method
Visual	Area	Parenchymal patterns	WOLFE TABAR
		Qualitative	BI-RADS
		Semi-quantitative	BOYD Visual analogue scale
Semi-automated	Area	Quantitative	CUMULUS MADENA
Fully-automated	Area	Quantitative	AutoDensity DenSeeMammo Densitas IMAGEJ iReveal STRATUS Libra MedDensity
	Volumetric	Quantitative	BDSXA CUMULUSV QUANTRA Spectral density VOLPARA

2.3 Breast Density: Clinical Relevance

In clinical practice, the relevance of this topic is related to:

1. The complexity of mammography interpretation for the radiologist when the breast is dense, which causes a reduction in the sensitivity of the test due to the masking effect, especially for lesions that are not visible or palpable, often leading to a delay in diagnosis.
2. The fact that breast density is an important and independent risk factor for breast cancer (BC).

Therefore, we affirm that a high percentage of glandular tissue reduces the diagnostic accuracy of mammography and increases the risk of developing BC.

2.3.1 Masking Effect

Breast cancer demonstrates the same radiologic attenuation as fibroglandular tissue. The detection of small lesions can be difficult in breasts with high density; therefore, under such conditions, the sensitivity of mammography is reduced. Recent studies have shown that sensitivity values differ between analogic systems (film-screen) and digital systems (FFDM) [19, 20].

Moreover, we note that there are clinical outcomes (tumour size and disease interval) that confirm the effect of breast density on the diagnosis of BC [21].

The number of BCs screen-detected at >15 mm grows with increasing breast density [22]. It seems clear that there is an association between elevated breast density and decreased sensitivity and specificity of 2D FFDM (masking effect), which is related to diagnostic delay and the detection of tumours at advanced stages, as well as biological predisposition to BC in breasts with a high percentage of glandular tissue.

The masking effect of MBD determines growth in a certain percentage of interval cancers (cancers discovered in the period between regular mammographic controls) in women with dense breasts, who may benefit from a more personalized screening programme [23]. Interval carcinomas can even be caused by different factors that are not related to MBD, such as innate biological characteristics, anatomical location or misinterpretation of the radiologist [42–44].

In 2006, McCormack's meta-analysis [24] confirmed the importance of the masking effect due to MBD and reaffirmed that the risk of malignancy is four- to sixfold higher in women with denser breasts (>75%) than in women with less glandular components (<5%).

2.3.2 Independent Risk Factors

Many studies have already established that MBD constitutes an independent risk factor for BC, persisting for 8–10 years after the first evaluation [17, 25, 26]. Breast density is associated with an increased risk of local and loco-regional relapse of BC, but it was not shown to have any influence on metastasis or survival [27, 28]; the results from larger studies confirmed that higher density is not related to increased mortality for BC [29, 30].

Although breast density is considered an independent risk factor for BC, risk can be determined by different factors; the foremost factor seems to be genetic predisposition (65%) [1], and some genetic polymorphisms contribute to the multifactorial genesis of many types of BC [31–33]. Other factors include age, lifestyle (age/number of pregnancies, nutrition), hormonal layout and replacement hormonal therapy [34].

MBD is also a potential marker for the treatment responses of drugs used to cure and prevent BC, such as tamoxifen (TAM) and aromatase inhibitors (AI), as these therapies result in a reduction in breast density. Recently, to analyse the role of these drugs, a new study was conducted to automatically measure MBD. In this study, a group of women with BC treated with TAM and AI was compared with a control group of healthy women who did not receive any

treatment [35] and volume-based measurement was shown to elucidate changes in MBD during therapy; therefore, MBD can be used as a prognostic marker [36]. Further studies are being performed to evaluate if changes in density are a biomarker of BC risk [37].

2.4 Diagnostic Tools

MBD assessment has clinical utility for identifying women at increased risk of developing breast cancer and/or having reduced mammographic sensitivity. Certain difficulties associated with the limitations of conventional mammography (film-screen and FFDM) may arise in the diagnosis of BC in dense breasts. Thus, more research involved in investigating standardized criteria to identify women at risk who may benefit from supplemental screening, prevention or genetic analysis is necessary. To date, there is still a lack of sufficient *evidence-based* proof regarding the correct interpretation of dense breast, how MBD should be measured and the best imaging modality for individual women.

There has been a notable effort within the scientific community to optimize breast screening according to individual risk, using the most advanced technologies available (Figs. 2.2 and 2.3). Interest in this topic has increased after

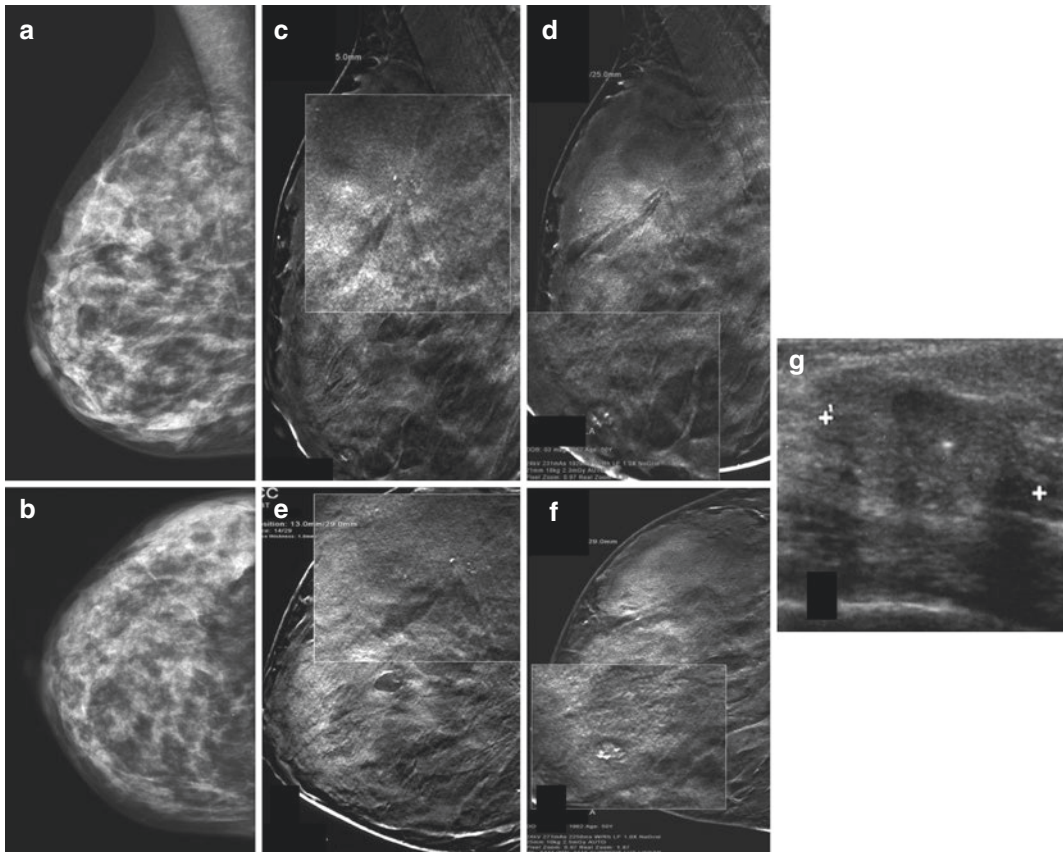

Fig. 2.2 DBT study in a 51-year-old asymptomatic woman. (**a**, **b**) FFDM: MLO and CC views demonstrating extremely dense breast parenchyma with no radiologic abnormality. (**c**–**f**) DBT, MLO and CC views show two different lesions: a stellate architectural distortion in upper outer aspect (invasive ductal carcinoma, G1 with tubular and in situ aspects) and a circumscribed lesion with intralesional calcifications in the lower inner aspect (intraductal papilloma with calcinosis). (**g**) Ultrasound shows a hypoechoic ill-defined 0.8 cm lesion in upper outer quadrant

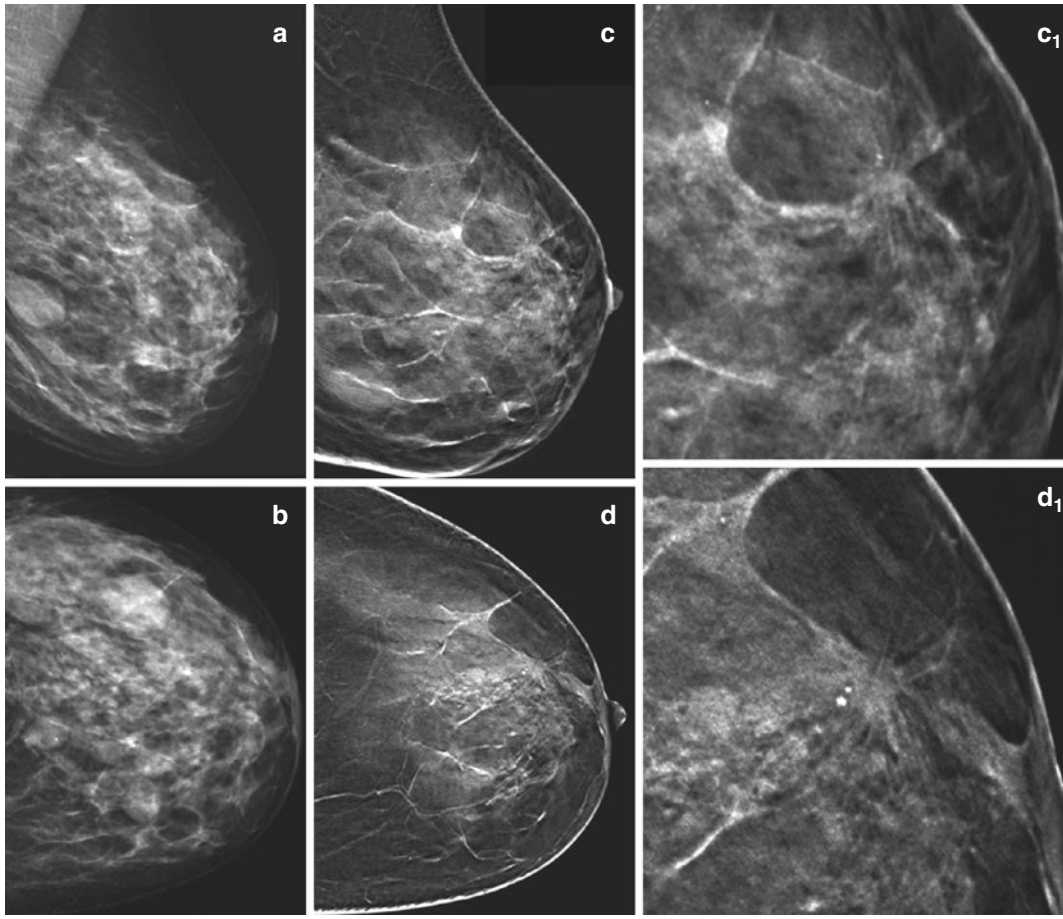

Fig. 2.3 DBT screening study in a 47-year-old asymptomatic woman. (**a**, **b**) FFDM: MLO and CC views of an extremely dense breast parenchyma demonstrating well-circumscribed opacities in the left breast. DBT MLO (**c**, $\mathbf{c_1}$) and CC (**d**, $\mathbf{d_1}$) views show a stellate lesion in the upper outer quadrant, behind the nipple. The pathology of this lesion was an invasive tubular carcinoma, G2

the launch of the campaign called "Are you dense?" [38], promoted in the United States to spread information about the risk associated with high MBD and the utility of supplemental screening. As of 2017, 31 U.S. states have adopted legislations requiring radiologists to specify breast density in the medical report.

To overcome the limitations of MBD, new imaging modalities in addition to screening mammography have been studied, such as handheld ultrasound (HHUS). Automated breast ultrasound system (ABUS) and digital breast tomosynthesis (DBT), which are based on morphological criteria, and magnetic resonance imaging (MRI) and molecular imaging (MBI) which are based on functional criteria. In a study published in 2016, Melnikow et al. [39] analysed the results of 18 studies that reported rates of additional cancers detected in association with supplemental screening and concluded that supplemental tests added to screening mammography in women with dense breasts, identified additional BC but also increased the number of false-positives. DBT, which is a relatively novel technique, may reduce recall rates (range, 0.8–3.6/100 screens) and has the potential to increase BC detection (range, 0.5–2.7/1000 screens) [40, 41].

Conclusion

At this moment, we can state that MBD is a hot topic of medical research that remains controversial. It is therefore necessary to define standardized methods of measurement to guarantee the objective evaluation of BC risk and to identify diagnostic strategies and therapies personalized for individual women.

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