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Pathological macroscopic evaluation of breast density versus mammographic breast density in breast cancer conserving surgery

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ABSTRACT

Correlation between imaging and anatomopathological breast density has been superficially explored and is heterogeneous in current medical literature. It is possible that mammographic and pathological findings are divergent. The aim of this study is to evaluate the association between breast density classified by mammography and breast density of pathological macroscopic examination in specimens of breast cancer conservative surgeries. Post-hoc, exploratory analysis of a prospective randomized clinical trial of patients with breast cancer candidates for breast conservative surgery. Breast mammographic density (MD) was analyzed according to ACR BI-RADS® criteria, and pathologic macroscopic evaluation of breast density (PMBD) was estimated by visually calculating the ratio between stromal and fatty tissue. From 412 patients, MD was A in 291 (70,6%), B in 80 (19,4%) B, C in 35 (8,5%), and D in 6 (1,5%). Ninety-nine percent (201/203) of patients classified as A+B in MD were correspondently classified in PMBD. Conversely, only 18.7% (39/209) of patients with MD C+D were classified correspondently in PMBD ($p < 0.001$). Binary logistic regression showed age (OR 1.06, 1.01–1.12 95% CI, p 0.013) and nulliparity (OR 0.39, 0.17–0.96 95% CI, p 0.039) as predictors of A+B PMBD.
Conclusion: Mammographic and pathologic macroscopic breast density showed no association in our study for breast C or D in breast image. The fatty breast was associated with older patients and the nulliparity decreases the chance of fatty breasts nearby 60%.

1. Introduction

Mammographic breast density (MD), which is currently used as synonymous to breast density by the medical community, corresponds to fibroglandular tissue in breast parenchyma, which is radiopaque in the mammographic image. Among the most important categorizations for MD, ACR-BIRADS® is currently the most widely adopted [1].

In the past few decades, breast density has been in the spotlight due to its implication in reducing sensitivity on breast cancer screening and its intrinsic risk for breast cancer [2,3]. In asymptomatic women, sensitivity decreases significantly when comparing dense and non-dense breasts (62.9% versus 87%, $p < 0.001$) [2]. In a large meta-analysis by McCormack et al. [3] comparing breast density and cancer incidence, the results were striking: from the 42 articles included, presenting aggregated data from 14,134 cases and 226,871 controls stratified according to the percentage of breast density, the relative risk for incidence of breast cancer was 4.64 (95% CI, 3.64–5.91) for the > 75% category, while in the 5–24% category the risk was 1.79 (95% CI,

Abbreviations: MD, mammographic density; PMBD, pathologic macroscopic evaluation of breast density; BCS, breast-conserving surgery; ER, Estrogen Receptor; PR, Progesterone Receptor.

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1.48–2.16), both compared to the < 5% group, suggesting an impressive association between risk for breast cancer and increased MD. Boyd et al., in an extensive review, concluded that MD is strongly associated with breast cancer risk and proliferative lesions. The authors speculated that one-third of all breast cancer cases could be linked solely to high breast density [4].

On the other hand, the study of breast density in pathology has been superficially explored and is heterogeneous in the current medical literature. The studies have no standardized macro or microscopic assessment. Moreover, their correlation with imaging exams in the evaluation of high density breasts is not consistent, which directly impacts the external validity of such results, consequently limiting clinical applicability [5].

The aim of this study is to evaluate the association between pathological macroscopic breast density (PMBD) and MD, as well as its association among multiple clinical and tumoral characteristics.

2. Methods

2.1. Patient population

This is an exploratory post-hoc analysis of data from a randomized, controlled trial (Clinical Trials Identifier: NCT02798796) involving patients with breast cancer candidates for breast conservative surgery, as described in detail elsewhere [6]. The original trial was approved by the Local Ethics Committee, and for this exploratory analysis, an amendment including the assessment of macroscopic breast density was submitted and approved by the committee (Approval number 974.504, 602/14). The trial was conducted in accordance the CONSORT Statement (Consolidated Standards of Reporting Trials) [7].

Inclusion and exclusion criteria for the BREAST trial were published elsewhere [6]. For our study, all patients who were included in the original trial were eligible for inclusion. Patients were eligible for inclusion if they met the following inclusion criteria: i) female patients; ii) 18 years of age or older; and iii) who were candidates for breast-conserving surgery (BCS) to breast cancer stage 0 to III treatment according to AJCC 7th Edition guideline. Patients were excluded from our analysis if they i) underwent mastectomy instead of the originally planned BCS; or ii) data from PMBD were missing or unavailable.

2.2. Pathology analysis

The classification of PMBD is routinely performed for every surgery in our service during macroscopic specimen examination in frozen section examination or after formalin fixation by our Pathology division. To perform this classification, the whole macroscopic sample specimen was evaluated prior to slicing as follows: 1) visually assessing the entire specimen; 2) calculating the percentage of fatty tissue in the surgical specimen (total specimen area – total stromal area / total specimen area). All analyses were performed by an experienced pathologist with at least 5 years of experience and were described as the percentage of fatty tissue in the surgical specimen in the final anatomopathological report. Patients were then classified into four categories of PMBD, according to the fatty percentage of breast tissue in the surgical sample (A: 76–100%; B 51–75%; C25–50%; D: 0–24%). These four categories were standardized in a similar way to the ACR BI-RADS® 4th edition classification to facilitate comparisons (Fig. 1).

2.3. Statistical analysis

Continuous variables are presented as median and interquartile range and were analyzed using the Mann-Whitney U test. Categorical variables are presented as count and percentages and were analyzed using Chi-Square or Kruskal-Wallis tests when appropriated. Correlations between categorical variables were analyzed using the Phi coefficient. A two-sided p-value of 0.05 was considered to be statistically significant. All analyses were performed using SPSS for Windows version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

From 445 eligible patients, a total of 412 patients were included in our analysis. All of them underwent breast-conserving surgery (Fig. 2). The median age was 57.1 years [50.1; 64.7], most of patients were diagnosed in stages I and II (40.8% and 41.3%, respectively), while 11.7% were stage 0 and only 6.3% stage III. Median pathologic tumor size was 1.9 cm [1.2–2.5] and median surgical sample weight was 44.9 g [26.6–78.8].

According to PMBD, patients were distributed as follows: 291 (70,6%) were classified as A, 80 (19,4%) as B, 35 (8,5%) as C, and 6 (1,5%) as D. Baseline and tumoral characteristics of the population according PMBD are presented in Table 1. Patients with a higher percentage of fatty breast tissue were significantly older and more frequently post-menopausal and non-nulliparous (Table 1).

Due to a small number of extremely dense (D) breasts, we combined PMBD into two groups: A+B and C+D. In this dichotomized sample, patients in the A+B group were older (58.7 versus 48.2 years, $p < 0.001$), with higher BMI (28.9 versus 26.7 kg/m^2, p 0.028), more frequently post-menopausal (77.3% versus 41.5%, $p < 0.001$), and, nonnulliparous (9.2% versus 22%, p 0.026) (Table 2). Tumoral characteristics, such as pathological tumor size, clinical stage and immunohistochemistry did not differ between groups. To further explore the relationship between PMBD and clinical characteristics, we performed a binary logistic regression. The predictors of PMBD A+B were age (OR 1.06, 1.01 – 1.12 95% CI, p 0.013) and nulliparity (OR 0.39, 0.17–0.96 95% CI, p 0.039) (Table 3).

In Table 4, we present the matching of MD and PMBD classifications. Breasts that were classified as A+B in MD were concordantly classified

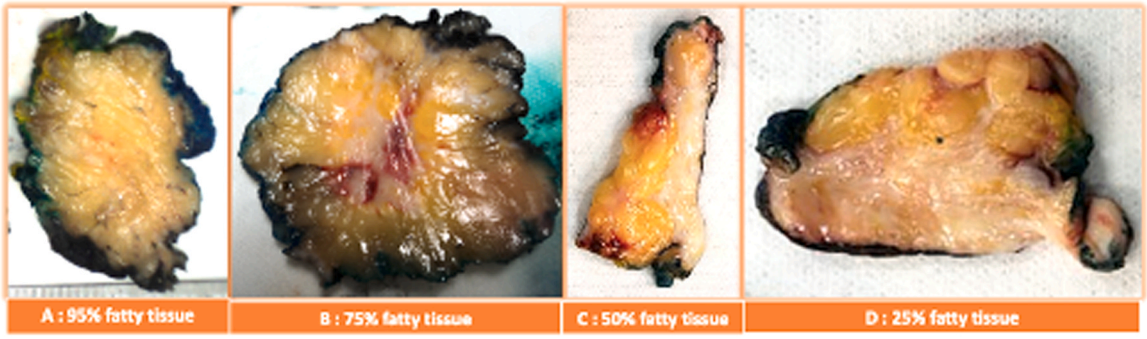

Fig. 1. Exemplification of pathological macroscopic breast density (PMBD) categorization. Four categories were standardized according to the fatty percentage of breast tissue in the surgical sample (A: 76–100%; B 51–75%; C25–50%; D: 0–24%).

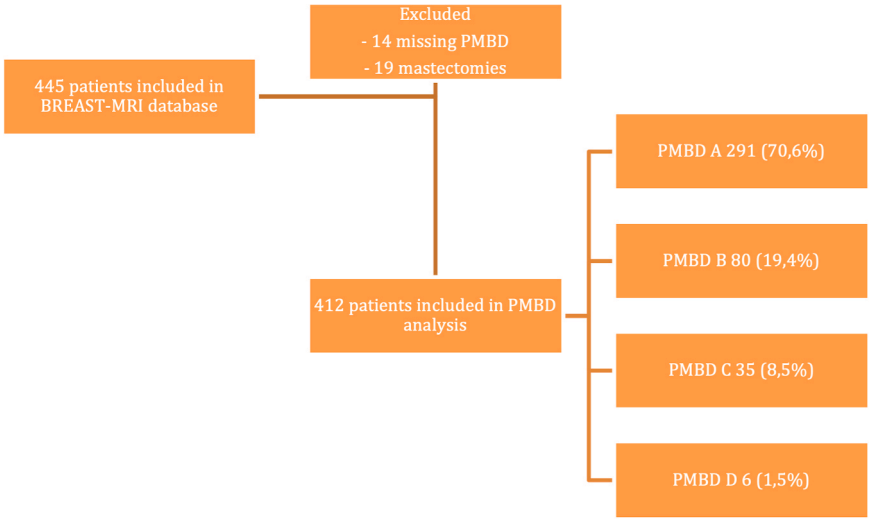

Fig. 2. Flowchart of patients included in the macroscopic examination breast density analysis.

Table 1
Clinical and tumoral characteristics, according to macroscopic examination breast density in four groups.

		Pathological macroscopic breast density				
		A (291)	B (80)	C (35)	D (6)	p
Age (years)		60.1 (51–66.7)	55.5 (49–61.4)	48.2 (45.8–55.6)	47.6 (42.9–50.4)	< 0.001
BMI (kg/m2)		29.1 (25.6–33.1)	28.5 (24.6–32.2	28 (25–30.1)	25.3 (24.2–26.7)	0.06
Nulliparity		25 (8.6%)	9 (11.4%)	6 (17.1%)	3 (50%)	0.005
Menopause		255 (77.3%)	61 (77.2%)	15 (42.9%)	2 (33.3%)	< 0.001
HR		90% (261)	89.7% (70)	100% (35)	83.1% (5)	0.238
Tumor Pathologic size (cm)		1.9 (1.2–2.5)	1.7 (1.2–2.5)	2.3 (1.5–3)	2.1 (1.2–2.5)	0.293
Stage						0.120*
	0	27 (9.3%)	14 (17.5%)	6 (17.1%)	1 (16.7%)	
	I	125 (43%)	34 (42.5%)	7 (20%)	2 (33.3%)	
	II	119 (40.9%)	30 (37.5%)	18 (51.4%)	3 (50%)	
	III	20 (6.9%)	2 (2.5%)	4 (11.4%)	0	
IHC						0.461*
	ER/PR	233	72	27	6	
	ER/PR + HER 2	23	2	4	0	
	HER 2	6	1	0	0	
	Triple negative	25	3	2	0	

BMI: body mass index; HR: hormonal replacement; IHC: immunohistochemistry; ER: estrogen receptor; PR: progesterone receptor.

Table 2
Clinical and tumoral characteristics, according to pathological macroscopic breast density, combined in two groups.

		Pathological macroscopic breast density		
		A + B (371)	C + D (41)	p
Age (years)		58.7 (50.9–65.6)	48.2 (45.5–54.6)	< 0.001
BMI, (kg/m2)		28.9 (25.5–33.1)	26.7 (24.9–29.9)	0.028
Nulliparity		9.2% (34)	22% (9)	0.026
Menopause		77.3% (286)	41.5% (17)	< 0.001
HR		10.1% (37)	2.4% (1)	0.155
Pathologic size (cm)		1.8 (1.2–2.5)	2.3 (1.5–3.0)	0.070
Stage				0.070*
	0	11.1% (41)	17.1% (7)	
	I	42.9% (159)	22% (9)	
	II	40.2% (149)	51.2% (21)	
	III	5.9% (22)	9.8% (4)	
IHQ				0.732*
	ER/PR	305 (83.6%)	33 (84.6%)	
	ER/PR + HER 2	25 (6.8%)	4 (10.3%)	
	HER 2	7 (1.9%)	0	
	Triple negative	28 (7.7%)	2 (5.1%)	

BMI: body mass index; HR: hormonal replacement; IHC: immunohistochemistry; ER: estrogen receptor; PR: progesterone receptor.

Table 3
Logistic binary regression according to pathological macroscopic breast density (A+B).

	OR	95% CI	p
BMI	1.06	0.99–1.15	0.054
Age	1.06	1.01–1.12	0.013
Nulliparity	0.39	0.17–0.96	0.039
Menopause	1.73	0.68–4.45	0.247
Hormonal Therapy	0.55	0.07–4.48	0.578

Table 4
Classification according to breast density groups.

		Pathological macroscopic breast density			p
		A+B	C+D		< 0.001 *
Mammographic Breast Density	A+B	99% (201)	1% (2)	203	
	C+D	81.3% (170)	18.7% (39)	209	
		371	41	412	

in the A+B PMBD group in 99% (201/203) of the cases. On the other hand, breasts that were classified as C+D in MD were classified in the C+D PMBD group in only 18.7% (39/209) of the cases ($p < 0.001$) (Table 4).

4. Discussion

We found no association between MD and PMBD in our study when the breast was classified as C or D by the image. To the best of our knowledge, ours is the first article to explore the correlation between mammographic and macroscopic findings. This retrospective analysis is meant to be hypothesis-generating regarding a subject of paramount importance in current clinical practice. We must ask ourselves: are we properly evaluating breast density?

The concept of breast density has been advocated as being analogous to mammographic density. With this premise being true, we expected that macroscopic evaluation from surgical specimens, which was done similarly to the assessment of mammographic density by the radiologist (visual scale), would be comparable (i.e., lower mammographic density should be matched with higher histological fatty content). Despite that, in our sample, there was no correspondence comparing both classifications.

Currently, a formal definition of breast density in pathological anatomy does not exist, thus hindering comparison with radiological classification systems. We found few publications exploring the relationship between breast tissue in pathological anatomy and mammographic imaging. Among them, an American cohort stands out with 3400 patients with benign breast diseases [8], where dense breasts were associated with two histological findings: fibrosis and lack of lobular involution. Regarding fibrosis, this finding follows several other studies that also demonstrated this association [9–12]. Lack of lobular involution was also related to dense breasts in other studies [13–15]. Additionally, type 1 lobules were associated with increased mammographic density (p 0.021) [12].

Most studies were based on breast tissue with breast cancer or benign disease, which is a potential bias and might not be representative of reality. Li et al. [16] avoided this potential bias studying breast tissue from a forensic autopsy. In 236 women, subcutaneous mastectomy was performed at the autopsy and random block tissues were selected from the breast. Mammography from specimens were also performed in all cases. As a result, a high percentage mammographic density was associated with significantly greater total nuclear area, nuclear area from epithelial cells, nuclear area from no epithelial cells, proportion of collagen and glandular structures ($p < 0.001$). Patients were stratified by age, and those with 50 years or younger remained with similar associations. Otherwise, for those older than 50 years, only a proportion of nuclear area from non-epithelial cells and collagen were significantly associated with dense breasts in mammography (p 0.01 e $p < 0.001$, respectively).

More recently, in 2012, in a daring study proposal, Ghosh et al. [14] recruited asymptomatic healthy volunteers through advertisements to perform breast biopsies in two separate areas: dense and non-dense. Mammography and ultrasound were both used to localize regions of dense and non-dense tissue. Included patients were older than 40 years old, with routine mammography screening exams in the past six months, and no previous history of breast cancer or hormonal replacement. A final number of 59 volunteers were biopsied, and dense areas of the breast had in proportion 4.8% greater epithelium, 46.1% greater stroma but 50.9% less fat in dense tissue than non-dense tissue (all $p < 0.0001$). Preliminary analyses of ki-67, Estrogen Receptor (ER) and Progesterone Receptor (PR) were performed in 24 patients, without difference (p 0.82, p 0.09 and p 0.96, respectively). However, it is worth noting that the relative difference in the expression of ER in dense areas was 2.7 times greater than in the non-dense areas.

Our findings, although purely exploratory, incite further investigation on the relationship between radiological and in-vivo breast density. Our method is simple and analogous to the most accepted classification (ACR-BIRADS®) and executed following the same rationale: a macroscopic analysis of the sample followed by classification into four categories. A more profound knowledge on this topic, mainly in the era of artificial intelligence, can help mitigate the gaps in current medical literature.

Breast density has several legal implications. In 2004, "Are You Dense" movement was created to support a group of patients with dense breasts and provide legal counseling. This action propelled specific legislation in several American states requiring patients to be informed of the potential decrease in mammographic sensitivity and increased risk for breast cancer. These legislations are designed to empower the patient, to encourage discussion between the provider and patient, and possibly prompt supplemental screening [17].

Regarding breast cancer screening, mammographic density D breasts are associated approximately two-fold increased risk of breast cancer comparing to BI-RADS density B [18]. In light of the available evidence, the European Society of Breast Imaging (EUSOBI) recommends offering screening breast MRI every 2–4 years in women aged 50–70 years with extremely dense breasts [19]. MRI supplemental screening is also recommended to those patients with a high established risk, according to clinical criteria (lifetime risk >20%) [20]. For patients recently diagnosed with breast cancer, MRI could identify additional lesions or enhancing areas surrounding index tumor, and possibly modify surgical treatment [21].

Our study presents several limitations. First, PMBD was classified according to the surgical specimen, an excerpt of one breast, when MD considers both entire breasts for classification. This convenience sample obtained for the present study aims to formulate a hypothesis of a new concept of breast density, so called PMBD. As the gap in the literature is important [22], despite this limitation, we believe there's a contribution to the study of pathologic breast density.

Second, however quantification of fatty tissue was performed by the on-call pathologists instead of a breast-specialized pathologist. The surgical specimens cannot be re-examined later after being processed for histological examination. Even though all pathologists had at least 5 years of experience, this could have produced less consistent results. Also, our sample was based on breast tissue with breast cancer, which, as we explored above, could be a potential bias of the PMBD documentation.

All mammographic breast densities were classified according to the 5th edition of the ACR-BIRADS®. On the other hand, PMBD was classified using an analogy with the 4th edition of the ACR-BIRADS®. The 5th edition of the ACR-BIRADS® allows for more subjectivity on behalf of the radiologist, with the possibility of classifying breasts as dense when supplementary investigation is deemed beneficial. Nonetheless, the mismatch between MD and PMBD was so profound, as demonstrated in these results, that we regard possible divergences in classification of MD to be irrelevant to the final result.

In the future, exploring the relationship between mammographic density of the specific quadrant of the tumor and PMBD can help us advance in our understanding of breast density. Furthermore, microscopic evaluation of surgical specimens with objective percentages of fatty, stromal and glandular tissue might yield innovative results regarding local breast density and its relation to breast imaging.

Breast density has several and vital implications for women, its thorough study and definition, are crucial for proposing personalized protocols for screenings, local staging, follow up and, hopefully in the future, to guide specific therapeutic protocols in patients with breast cancer. Understanding the best radiological classification, whether mammographic or not, e its correspondence in the mammary tissue in pathology, is the new frontier to be pioneered to guide the allocation of resources for breast cancer screening and additional imaging in oncological patient.

5. Conclusion

Our study shows that dense breast in pathological macroscopic breast density does not hold a close association with dense breast in mammography, according to ACR-BIRADS® classification. The fatty breast was associated with older patients and the nulliparity decreases the chance of fatty breasts nearby 60%. This study is exploratory, and its authors hope their findings will encourage additional studies into the correlation between mammographic and in vivo breast density.

Ethical approval

The Local Ethics Committee approved this study.

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CRediT authorship contribution statement

Reis, YN; Mota, BS; Ricci, MD; Shimizu, C; Aguiar, FN created the concept and designed the study. Reis, YN; Mota, BS collected and analyzed the data. Reis, YN; Mota BS; Filassi, JR wrote the manuscript. Mota, RMS performed statistical analyses. Soares-Jr, JM; Baracat, EC; Filassi, JR, Filassi, Reis, YN; Mota, BS contributed to the final version of the manuscript. All the authors reviewed the contents of the manuscript and approved its final version.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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