Original Article

Mammographic breast density and breast cancer risk: Evaluation using volumetric breast density software

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ABSTRACT

Purpose: The study aimed to assess breast density as a risk factor for breast malignancy using automated volumetric breast density software and to study the relationship of breast density with tumor histopathological characteristics.

Materials and Methods: One hundred and thirty-four women with unilateral core biopsy-proven breast cancer were taken in the "case group." Two hundred and one women with normal bilateral screening mammograms were enrolled in the "control group." The cases and controls were further divided into pre- and post-menopausal subgroups. The mammograms of the contralateral breast of the cases and bilateral breasts of the controls were evaluated by automated volumetric breast density software and classified into four density grades. The tumor histopathological characteristics in the various density grades were also evaluated.

Results: In premenopausal women, the odds of having breast cancer was significantly higher for Grade 3 breasts (odds ratio [OR] 3.03; 95% confidence interval [CI]: [1.19–7.71]) versus Grade 1 and 2 breasts. Grade 4 premenopausal breasts also had greater odds (OR 3.09; 95% CI [0.89–10.78]) of developing breast cancer. No such relationship was established for postmenopausal women. No significant difference was seen in the histopathology of breast cancer among various breast density groups.

Conclusion: Increased breast density can be considered as an inherent, independent risk factor for breast cancer in premenopausal women.

KEY WORDS: Breast, cancer, density, volumetric

INTRODUCTION

Breast cancer is the second-most common form of cancer behind lung cancer. More than 1.3 million females worldwide are diagnosed with carcinoma breast each year.[1] In urban India, its incidence has already surpassed that of cervical cancer with a high age-adjusted rate of 25.8/100,000 women.[2] The current emphasis is on the assessment of risk factors for this malignancy which may have a preventive and prognostic predicament, and breast density is one of them. Mammographic breast density is defined as the proportion of fibroglandular tissue compared to fat in mammograms. Studies have shown that higher density grades on mammograms have higher breast cancer risk, placing density only after age and BRCA carrier status in the order of relative risks for developing breast cancer.[3-5] Very limited literature is available on the Indian population on the impact of breast density on cancer risk, with none of the studies having used an automated mammographic volumetric breast density assessment in the North-Indian population in a case–control layout. It has been already established that the density of Indian breasts is different from western counterparts.[6]

Qualitative visual breast density evaluation methods have the disadvantage of interobserver variability and are subjective. The use of two-dimensional (2D) mammograms to estimate the breast density does not consider the thickness of the breast and hence only takes into account the projected area of the breast rather than the volume. These sources of error are eliminated by the use of automated volumetric breast density measurement softwares.

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VolparaDensity (Volpara Solutions, Wellington, New Zealand) is a commercial product developed to provide automated volumetric measurements of breast density. VolapraDensity uses an algorithm approved by the US. Food and Drug Administration to produce density classifications similar to those in the Breast Imaging Reporting and Data System manual. This software calculates the ratio of the volume of fibroglandular tissue and total volume of the breast to give the value of percentage volumetric density. The software processes every mammogram and produces a Volpara scorecard that appears on the radiologist/technologist's workstation [Figure 1].

The aim of this study was to evaluate the density of breast as a risk factor for breast malignancy using volumetric breast density measurements and to study the association of breast density and carcinoma breast with other risk factors for breast cancer, namely menstrual history, parity, and body mass index (BMI). Relationships of various tumor characteristics, i.e., tumor grade, histological type, and hormone receptor status were also evaluated with respect to breast density.

MATERIALS AND METHODS

Study design and enrolment criteria

This retrospective study was approved by Institution Review Board and 134 consecutive female patients with unilateral core biopsy-proven breast cancer constituted the "case group." Patients with bilateral cancers were excluded from the case group as mammograms with masses can give false density computation. Women with a history of breast conservation surgery, radiotherapy/chemotherapy were also excluded. Standard craniocaudal and mediolateral oblique views of the contralateral breast were evaluated by the volumetric breast density software and then divided into four density groups as mentioned in the subsequent section. The control group consisted of 201 women who had undergone bilateral screening mammograms during the same period with no suspicious lesion on mammogram. Concomitant ultrasound was done in mammographic dense breasts, and women without any abnormal findings on both ultrasound and mammograms were enrolled in the "control group." These control mammograms were also evaluated with automated volumetric breast density software and assigned density grades. The cases and controls were divided into premenopausal and postmenopausal subgroups as at menopause major breast density and hormonal changes may occur. Age, age at menarche, age at first childbirth, number of children, breastfeeding, and BMI were noted for women in both subgroups.

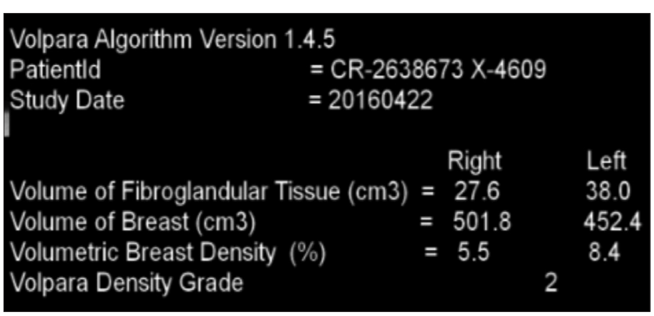

Figure 1: Image showing an example of breast density estimation by VolparaDensity Algorithm Version 1.4.5 (Volpara Solutions, Wellington, New Zealand)

Mammography

Full-field digital mammography (FFDM) was carried out on Siemens Mammomat Novation DR or Philips MicroDose Mammography systems. Both Seimens Mammomat Novation DR and Philips MicroDose use automatic exposure controls (AECs) called Opdose and Smart AEC, respectively, which adjust peak kilovoltage, target signal noise ratio and anode/filter combinations based on the compressed breast thickness.

Volumetric breast density analysis

The raw images, also called "for processing" images, produced by FFDM were evaluated using the software VolparaDensity (Volpara Research GUI v 2.0.2, Volpara Algorithm Version 1.4.5, Volpara Solutions, Wellington, New Zealand). The algorithm uses relative physics rather than absolute physics. This is done by selecting a reference point of known breast composition, such as fatty breast tissue just anterior to the chest wall, and then calculating the attenuation at each pixel with reference to the reference pixel. These calculations are then used to determine the amount of fat and fibroglandular tissue responsible for the calculated attenuation at pixels across the image. Density maps are generated which are used to calculate and then divide the volume of fibroglandular tissue by the total volume of breast and thereby provide the percentage of the fibroglandular tissue, i.e., volumetric density.[7] The volumetric breast density is classified into Volpara density grade (VDG) categories, namely VDG 1 ($<$4.5%), VDG 2 ($\geq$4.5 and $<$7.5%), VDG 3 ($\geq$7.5 and $<$ 15.5%), and VDG 4 ($\geq$15.5%) [Figure 2].

Histopathology correlation

The histological type, tumor grade, hormone receptor status, and Ki67 index were derived from core biopsies or postoperative specimens and recorded for each patient.

Statistical analysis

Continuous quantitative data such as age, age at menarche, and age at first childbirth were checked for normality by Kolmogorov–Smirnov test. As the data were skewed, it was expressed as a median and interquartile range. Nonparametric Mann–Whitney U-test was used for statistical analysis of the two groups. For discrete categorical data such as BMI categories, parity, menopausal status, family history, breast density grades, tumor grade, histopathological type, and receptor status comparisons between the two groups were made by Pearson Chi-square test. To check the association of different grades of density with BMI, Spearman correlation coefficient was derived. To evaluate predictors of breast carcinoma, logistic regression analysis was used for different risk factors and density before and after adjustment for confounders.

RESULTS

A total of 335 individuals were enrolled in the study, of which 134 were cases and 201 were controls. The median age of cases was 54 years (range 40–75 years), and controls were 50 years (range 40–75 years). The age, subject variables, menstrual profile, BMI, parity, and other parameters are tabulated in Table 1. All the forementioned factors were comparable in cases and controls except BMI.

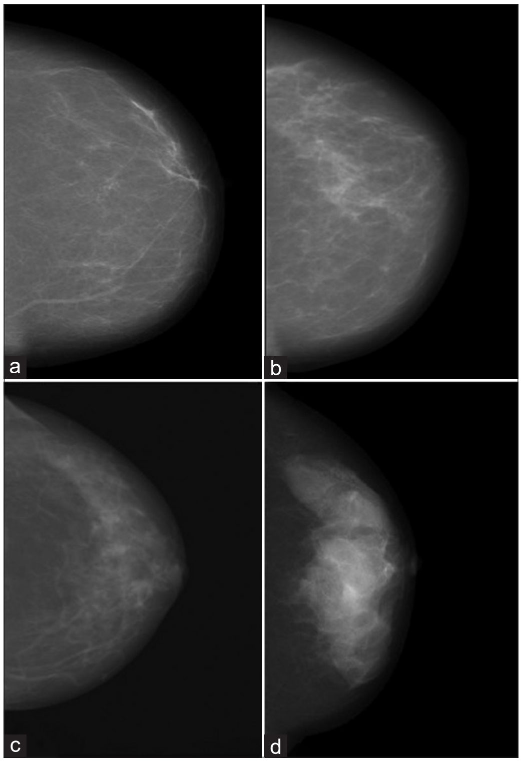

Figure 2: Craniocaudal views of mammograms of different patients showing various Volpara density grades, with quantitative volumetric density values in parentheses: (a) Grade 1 (4.2%), (b) Grade 2 (5.5%), (c) Grade 3 (11.1%), (d) Grade 4 (20%)

The mean BMI in the case group was 27 kg/m^2 (standard deviation [SD] ±5.03 kg/m^2), and in the control group was 28.8 kg/m^2 (SD ± 4.9 kg/m^2). The women were divided into two categories: normal and underweight (<25 kg/m^2) and overweight (≥25 kg/m^2). About 63.4% and 78.1% of the cases and controls respectively were overweight. The difference was significant, i.e., more controls were overweight as compared to the cases [Table 1]. The relation between BMI and the breast density grades was also found to be significant ($P = 0.045$). The two variables showed a strong negative correlation irrespective of whether the patient belonged to the case/control group or premenopausal/postmenopausal subgroup [Table 2].

Out of the 134 patients and 201 controls, 14 and 18 women respectively had undergone hysterectomies for various reasons. Of the remaining women, 63.3% of cases and 49.2% of the controls had attained menopause.

In the case group, the frequency of density Grade 2 (49.3%) was the highest, followed by Grade 3 (38.8%). Grades 1 and 4 were equally distributed (6% each). Among the controls, 50.2% had density Grade 2, 33.8% Grade 3, and 8% each had Grades 1 and 4 [Table 1]. For computation of correlation, density Grades 1 and 2 were clubbed together as low-density breasts, and density Grades 3 and 4 were taken as high-density breasts.

Risk of cancer in various density grades

Premenopausal subgroup

Women who were premenopausal with breast density Grade

Table 1: Demographic data of cases and controls

	Cases	Controls	*P*
n	134	201	
Age (years), median (range)	54 (40-75)	50 (40-75)	0.055
Age at menarche (years)[a], median (range)	14 (12-18)	14 (12-19)	0.717
Age at first childbirth (years)[b], median (range)	23 (16-38)	24 (16-35)	0.814
BMI (kg/m^2), mean (range)	26.99 (16.16-44.27)	28.83 (18.3-48.28)	0.001
Parity, *n* (%)			
0	3 (2.2)	5 (2.5)	0.925
1	8 (6)	14 (7)	
≥2	123 (91.8)	182 (90.5)	
Exclusive breastfeeding for at least 6 months, *n* (%)			
No	11 (8.2)	9 (4.5)	0.158
Yes	123 (91.8)	192 (95.5)	
BMI groups, *n* (%)			
<25	49 (36.6)	44 (21.9)	0.003
≥25	85 (63.4)	157 (78.1)	
Attained menopause, *n* (%)			
No	44 (36.7)	93 (50.8)	0.015
Yes	76 (63.3)	90 (49.2)	
Mammographic density, *n* (%)			
Grade 1	8 (6)	16 (8)	0.691
Grade 2	66 (49.3)	101 (50.2)	
Grade 3	52 (38.8)	68 (33.8)	
Grade 4	8 (6)	16 (8)	

[a]Age at menarche was available for 108 cases and 184 controls, [b]Age at first childbirth was available for 127 cases and 193 controls. BMI=Body mass index

3 had a significantly higher odds ratio (odds ratio [OR] 3.03; 95% confidence interval [CI] [1.19–7.71]) of having breast cancer than those having low breast densities (Grade 1 or 2) ($P = 0.02$). The odds of having breast cancer in the Grade 4 density group in premenopausal women was also around 3.09 times (95% CI 0.89–10.78). In the premenopausal women, logistic regression analysis was done with adjustment for the confounders which included age, BMI and parity, and the relationships were maintained, i.e., the Grade 3 breasts still had significantly higher risk as compared to Grade 1 or 2 breasts ($P = 0.04$) with an OR of 2.78 (95% CI 1.05–7.33). In the Grade 4 breasts, the odds of getting breast cancer was 2.15 times (95% CI 0.52–8.94) than of those breasts with lower density grades after adjustment of confounders. The P value was however >0.05. This could be attributed to the small sample size of the Grade 4 breast subjects in our study.

Postmenopausal subgroup

The difference was not significant between the high-density and the low-density groups in the postmenopausal women. The Grade 3 and 4 density groups had an OR of 1.6 (95% CI 0.73–3.49) and 0.25 (95% CI 0.03–1.29), respectively [Table 3]. Even after adjustment for confounders, no statistical difference was seen between the case and control groups.

Hence, the study showed a higher incidence of malignancy in Grade 3 and 4 breasts only in premenopausal women but in not postmenopausal women.

Table 2: Correlation of body mass indices and density grades

Groups	Spearman's rho (body mass indices and density grades)	P
Overall		
Patients	−0.242	0.005
Controls	−0.335	0.000
Postmenopausal		
Patients	−0.282	0.014
Controls	−0.215	0.050
Premenopausal		
Patients	−0.428	0.004
Controls	−0.550	0.000

Table 3: Odds ratios for cancer risk in premenopausal and postmenopausal groups of various density grades

Groups	P	OR* (95% CI)
Premenopausal		
Grade 3	0.02	3.03 (1.19-7.71)
Grade 4	0.77	3.09 (0.89-10.78)
Premenopausal (adjusted)[a]		
Grade 3	0.04	2.78 (1.05-7.33)
Grade 4	0.29	2.15 (0.52-8.94)
Postmenopausal		
Grade 3	0.24	1.6 (0.73-3.49)
Grade 4	0.21	0.25 (0.03-2.19)
Postmenopausal (adjusted)[a]		
Grade 3	0.35	1.49 (0.65-3.41)
Grade 4	0.17	0.21 (0.02-1.92)

*OR calculated with reference to Grade 1/2. Reference category-controls, [a]Adjusted for age, BMI and parity. OR=Odds ratio, BMI=Body mass index, CI=Confidence interval

Histopathological characteristics and density grades

The most common histopathological type was infiltrating duct carcinoma (90.3%). Histological grading of the tumors was also done, and most of the tumors were either Grade 2 (46.2%) or Grade 3 (46.2%) [Table 4].

The estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (ER, PR, and Her2) status was available for 108 patients out of 134. Ki67 index was available for 105 patients. On the basis of hormone receptor status, the tumors were classified into hormone receptor-positive tumors (Luminal A: ER+ and/PR+, Her2-), Her2 positive (ER-, PR-, Her2 positive), Triple positive, i.e., Luminal B (ER+, PR+, Her2+) and Triple negative (ER-, PR-, Her2-) categories as these types of tumors have therapeutic and prognostic implications.[8] No statistically significant difference was seen in the distribution of density of breasts among various histopathological types, grades, and hormone receptor groups [Table 4].

DISCUSSION

Mammographic density is the measure of fibroglandular tissue content, which appears radiodense against the background of radiolucent fat. The effect of breast density on risk of developing breast cancer is being greatly researched. The standardization of mammographic breast density measurements remains a problem. The 2D-visual assessment on mammograms shows large inter- and intra-observer variations. In addition, the data from various studies regarding the relationship of breast cancer risk and breast density have presented highly varied results with none of the studies having used volumetric density assessment in the Indian population.[9,10] Our study adds a preliminary insight into the limited available data in the Indian population in this regard.

As menopause plays an important role in altering breast density due to changing hormonal milieu, the cases and controls were further subdivided into pre- and post-menopausal. In the premenopausal subgroup of cancer patients, the odds of developing cancer for women having high-density breasts was 3.03 and 3.09 for Grades 3 and 4, respectively, as compared to women with low-density breasts (Grades 1 and 2). The P value for Grade 3 was 0.02 and Grade 4 was 0.077. In the postmenopausal women, no such relationship could be established between higher breast densities and cancer. These findings are in concordance with the study by Attam *et al.*[10] where the relationship between higher density grades could only be established for premenopausal women. On adjusting density values for age, BMI, and parity using logistic regression, the relationship between breast density and carcinoma breast was maintained in the premenopausal women while the postmenopausal women still showed no relationship. Attam *et al.*[10] had evaluated 100 breast cancer patients in Delhi (India) based on the six-category system of breast density classification proposed by Boyd *et al.*[11] Their study showed that females with a breast density of 50% or

Table 4: Correlation of histopathological characteristics and breast density grades

Groups	Density grade				*P*
	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	
Histopathological type					
Infiltrating duct carcinoma	8 (6.6)	59 (48.8)	47 (38.8)	7 (5.8)	0.26
Intraductal papillary carcinoma	0	1 (33.3)	2 (66.7)	0	
Invasive lobular carcinoma	0	1 (33.3)	2 (66.7)	0	
Micropapillary carcinoma	0	3 (100)	0	0	
Carcinoma of no special type	0	0	1 (100)	0	
Tubulo-lobular carcinoma	0	0	0	1 (100)	
Atypical medullary carcinoma	0	1 (100)	0	0	
Tubular carcinoma	0	1 (100)	0	0	
Histopathological grade					
I	0	5 (55.6)	3 (33.3)	1 (11.1)	0.19
II	1 (1.8)	26 (47.3)	25 (45.5)	3 (5.5)	
III	7 (12.7)	30 (54.5)	16 (29.1)	2 (3.6)	
Ki 67 index (%)					
≤15	0	16 (50)	14 (43.8)	2 (6.3)	0.27
>15	7 (9.6)	35 (47.9)	29 (39.7)	2 (6.3)	
ER status					
Positive	6 (10.2)	29 (49.2)	22 (37.3)	2 (3.4)	0.74
Negative	1 (2)	24 (49)	21 (42.9	3 (6.1)	
PR status					
Positive	3 (7.5)	21 (52.5)	15 (37.5)	1 (2.5)	0.81
Negative	4 (5.9)	32 (47.1)	28 (41.2)	4 (5.9)	
Her2 status					
Positive	1 (3.7)	13 (48.1)	11 (40.7)	2 (7.4)	0.79
Negative	6 (7.4)	40 (49.4)	32 (39.5)	3 (3.7)	
Hormone receptor groups					
Triple negative	1 (3)	16 (48.5)	15 (45.5)	1 (3)	0.63
Her2 positive	0	7 (46.7)	6 (30)	2 (13.3)	
Luminal A	5 (10.6)	23 (48.9)	17 (36.2)	2 (4.3)	
Luminal B	0	3 (6.1)	1 (2.6)	0	

PR=Progesterone receptors, ER=Estrogen receptors

more, had twice the risk of breast malignancy in comparison to women with a density of <10%. In their premenopausal group, the difference in mammographic breast density in the cases and controls was found to be significant; however, no significant difference was found between the cases and controls in the postmenopausal group, as seen in our study also. Their study, however, had several limitations, the major ones being visual breast density assessment, nonavailability of BMI, parity, weight, as well as a small sample size.

In the current study, we used automated volumetric density software (VolparaDensity) to eliminate the subjectivity of visual breast density measurement. This software has been validated by several studies which have found a high correlation between VolparaDensity estimations and magnetic resonance imaging density measurements.[12-14] Unlike the visual assessment of mammograms for 2D-breast density, the volumetric breast density measurements using softwares such as VolparaDensity are objective and lack interobserver variations, with the results being reproducible and reliable. Volumetric softwares such as VolparaDensity use "relative physics" to deduce the volumetric density, and hence are robust enough, and changes produced by any variations in mAs, kVp, and breast thickness are minimal. In a study by Lau *et al*. also, it was found that changes in mAs, filter thickness, detector gain, detector off-set, and image noise had a limited effect on volumetric breast density computation.[15] They found that it was only kVp and compressed breast thickness which created significant variations in final breast density. These variations are however negligible when mammography acquisition is done in machines with well-calibrated AEC systems, as in our case.

In our study, the number of overweight women in the control group was greater, contrary to the previous studies which predicted that raised BMI was an independent risk factor for breast cancer.[11,16] This discrepancy could be due to the cachexia associated with cancer in the case group, leading to weight loss. Our institute is a tertiary care center, with many cases of advanced breast malignancy getting referrals for treatment and these patients have already lost considerable weight. The only way to truly establish the relationship between BMI and malignancy of the breast is to prospectively follow women in various BMI groups and observe whether these women eventually develop breast carcinoma. The breasts of women having higher BMI values had significantly lower density. The correlation was very strong irrespective of whether the woman belonged to the case/control group or the premenopausal/postmenopausal group. This is expected, as in patients with high BMI values, the fat proportion of the breast increased, thereby reducing the overall density.

The relationship of the histopathological characteristics of a tumor was also studied in relation to the breast density grades in the second part of the study. The histopathological type and grade of a tumor determine its aggressiveness and prognostication.[17-20] Grades are determined by the degree of tubular/glandular differentiation of the tumor and mitotic activity. Hormonal receptor status refers to the expression of estrogen and/or progesterone receptors in the tumor making them responsive to these hormones. Hormone receptor positivity is a strong predictor of good response to endocrine therapy such as tamoxifen. Her2 proteins regulate division of the breast cells and overexpression of these proteins is denoted as Her2 receptor positivity and is associated with increased recurrence rates. Hormonal therapy is not of any benefit in such patients.[8] ER+ and/PR+ and Her2 negative tumors are classified as Luminal A lesions. Triple negative cancers are those which are ER negative, PR negative, Her2 negative and have been found to have higher response rates to chemotherapy.[21] Triple positive/Luminal B tumors are ER positive, PR positive, and Her2 positive.[22] Ki67 is a nuclear protein seen in proliferating cells and not in resting cells. A value ≤15% is considered low, 16%–30% intermediate, and >30% high.[23]

Inconsistent data exist on the linkage of mammographic breast density and tumor characteristics. Phipps *et al*. and Eriksson *et al*. found no significant association across all histological subtypes.[24,25] Ghosh *et al*. also concluded that breast density was not related to tumor size, histologic type, ER, or PR status and nuclear pleomorphism.[26]

Yaghjyan *et al*. studied breast density and risk of carcinoma according to tumor characteristics in postmenopausal women and concluded that the risk of breast cancer was 3.39 times more in women with dense breasts (>50%) than in women with fatty breast (<10%). However, no association was found between breast density and PR status, histological type, and HER2 status, as in our study.[27]

A recent study by Park *et al*. also showed that density of breast was associated with breast cancer risk regardless of histological grade, tumor size, lymph nodal status, hormone receptor status, and Ki67 index in postmenopausal women.[9]

The histological type, grade, hormone receptor status, and Ki67 indices of the tumors did not reveal relation to the grades of breast density in our study both before and after dividing the cases on the basis of menopausal status. The reason for this could be attributed to the hypothesis that breast cancer is a heterogeneous disease and both endogenous estrogen levels and mammographic breast density affect breast carcinoma risk through different pathways.[28]

Our study has several strengths; the case–control layout, division into pre- and postmenopausal subgroups for analysis, and use of quantitative, automatic volumetric density measurements. The limitation of our study is the small sample size of Grade 4 breast subjects. In North Indian population, the frequency of Grade 4 breasts is less as compared to the western population.[6] In our study, only 18 cases out of 137 (0.13%) had VDG 4 breasts in the premenopausal subgroup. In control group (screening population), 16 out of 201 (8%) had VDG 4 breasts. In the previous study by Singh *et al*.,[29] the percentage of VDG 4 breasts in screening population in North Indian population was 6.9% which is similar to our study. The second limitation of the study is lack of follow-up in the control group; hence, we cannot ensure that controls did not develop breast cancer subsequently.

CONCLUSION

Thus, this study reports for the first time, positive association between volumetrically assessed higher breast density and risk of cancer in premenopausal group of Indian women. This study reinforces that when planning the frequency of screening, information about breast density should be given weightage.

Further, advances such as the use of drugs and lifestyle modifications to decrease breast density, thereby reducing the risk of cancer in these women, could prove fruitful in reducing the high mortality due to breast cancer worldwide.

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Conflicts of interest

There are no conflicts of interest.

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