



Original Research Article

Mammographic Breast Density Assessed with Fully Automated Method and its Risk for Breast Cancer

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ABSTRACT

Objectives: We evaluated the association between breast cancer and breast density (BD) measured using fully automated software. We also evaluated the performance of cancer risk models such as only clinical risk factors, density related measures, and both clinical risk factors and density-related measures for determining cancer risk.

Materials and Methods: This is a retrospective case-control study. The data were collected from August 2015 to December 2018. Two hundred fifty women with breast cancer and 400 control subjects were included in this study. We evaluated the BD qualitatively using breast imaging-reporting and data system density and quantitatively using 3D slicer. We also collected clinical factors such as age, familial history of breast cancer, menopausal status, number of births, body mass index, and hormonal replacement therapy use. We calculated the odds ratio (OR) for BD to determine the risk of breast cancer. We performed receiver operating characteristic (ROC) curve to assess the performance of cancer risk models.

Results: The OR for the percentage BD for second, third, and fourth quartiles was 1.632 (95% confidence intervals [CI]: 1.102–2.416), 2.756 (95% CI: 1.704–4.458), and 3.163 (95% CI: 1.356–5.61). The area under ROC curve for clinical risk factors only, mammographic density measures, combined mammographic, and clinical risk factors was 0.578 (95% CI: 0.45, 0.64), 0.684 (95% CI: 0.58, 0.75), and 0.724 (95% CI: 0.64, 0.80), respectively.

Conclusion: Mammographic BD was found to be positively associated with breast cancer. The density related measures combined clinical risk factors, and density model had good discriminatory power in identifying the cancer risk.

Keywords: Breast density, Breast imaging-reporting and data system, 3D slicer, Body mass index, Breast cancer

INTRODUCTION

Breast screening is widely recommended as women are at risk of breast cancer. There is number of risk factors associated with increased risk of breast cancer such as age, family history, menopausal status, and hormone replacement therapy (HRT). There are many cancer risk models used in practice such as the Gail, Claus, BRCAPRO, BOADICEA, and Rosner-Colditz models. They have not assessed the mammographic breast density (BD). The fibroglandular tissue in the breast on mammogram represents the mammographic BD and found to be independent risk factor of breast cancer. The estimated odds ratio (OR) ranges from 2.9 to 6.0. Females having extremely dense breasts are at higher risk of cancer than those with fatty breasts.^[1-9]

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There are qualitative and quantitative methods for assessing the mammographic BD. The qualitative method includes American College of Radiology's breast imaging-reporting and data system (BI-RADS), which has four qualitative BD categories: Almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense. BI-RADS is commonly used in clinical practice for reporting mammographic BD. However, there was too much variability in assigning grades by the radiologists; hence, there arise need for quantitative methods. Several quantitative methods have been proposed by different studies. The quantitative methods for measuring BD include interactive thresholding, semiautomatic, fully automatic, area based, and volumetric based methods. To the best of our knowledge, studies have evaluated the use of volumetric versus area density measures in breast cancer risk assessment who have primarily focused on determining which individual measure is a better predictor of risk and reported mixed.^[10-13] Hence, aim of the study is to determine the association between breast cancer and BD in a case-control setting after adjusting for clinical risk factors and measured using fully automated 3D slicer software. We also evaluated the performance of cancer risk models such as only clinical risk factors, density related measures, and both clinical risk factors and density related measures.

MATERIALS AND METHODS

This is a retrospective age-matched case-control study. The study was approved by the Institutional Ethical Committee (IEC: 267/2018). A total of 250 women who underwent screening mammography at our hospital between August 2015 and December 2018 who were diagnosed with breast cancer were included as cases. A total of 400 women without history of breast cancer who underwent screening at our hospital between August 2015 and December 2018 were included as controls. The women who underwent two or more screening mammograms negative for cancer were included as controls. For all the women X-ray, mammography and ultrasonography (USG) breast was performed. All the mammograms were obtained using GE Senographe DMR plus Mammography (GE Healthcare Systems, Milwaukee, Wisconsin, United States). The USG breast was performed using Philips HD 11XE ultrasound (Philips Healthcare systems, Amsterdam, Netherlands).

BD assessment

The quantitative assessment of BD was performed using 3D slicer version 3.6.3 (Harvard University, Boston, UK). To avoid the effect of presence of cancer on the density measurement, density was calculated on the contralateral breast which is noncancerous. We calculated BD on craniocaudal view of the noncancerous breast for the patients

and left craniocaudal view for the matched control subjects. The software automatically identifies the pixel with higher intensities [Figure 1a and b]. The density was measured in percentage. The percentage area density was calculated as the dense area divided by the total breast area.

The qualitative assessment of BD was performed using BI-RADS (5th edition, American College of Radiology) Visual method. Two radiologists who have experience of more than 10 years have performed the qualitative assessment.

Clinical risk factors

Data regarding clinical risk factors were obtained from the medical records. Risk factors which are included in the study were: Age (years), number of births, family history of breast cancer (yes/no), HRT use at the time of screen (yes/no), body mass index (BMI), and menopausal status (premenopausal/postmenopausal).

Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 18.0. Descriptive analysis was performed for clinical risk factors and percentage mammographic density and expressed as mean and standard deviations or frequencies and proportions as appropriate. Logistic regression was performed to examine the effects of BI-RADS density on invasive breast cancer risk. Associations were expressed in OR and 95% confidence intervals (CI). The receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of three risk models, such as risk factor model, mammographic density breast model, and combined risk factor, and mammographic density model. Pearson's correlation was done to determine

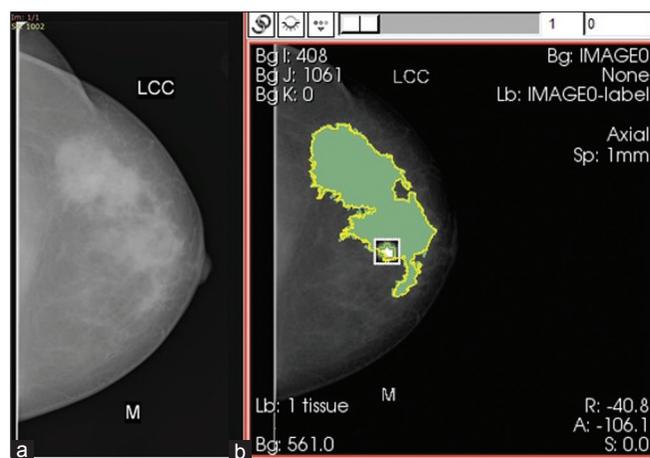


Figure 1: (a) Left craniocaudal mammogram of a 41-year-old woman with a negative screening exam (b) example of density segmentation using 3D slicer software tool showing automatic identification of mammographic density.

the correlation between qualitative and quantitative analysis. The interobserver variability about BD according to BI-RADS category was assessed using kappa value.

RESULTS

A total of 250 women with invasive cancer and 400 control subjects were included in the study. The results of the

Table 1: The characteristics of cases and control subjects.

Patient characteristics	Cases n=250	Controls n=400
Age (years) mean (SD)	50.15 (10.5)	50.15 (10.5)
Number of births n (%)		
0	4 (1.6)	12 (3)
1	72 (28.8)	136 (34)
2	116 (46.4)	162 (40.5)
3	46 (18.4)	66 (16.5)
4	12 (4.8)	24 (6)
Familial history of breast cancer n (%)		
Yes	83 (33.2)	94 (23.5)
HRT use n (%)		
Yes	29 (11.6)	27 (6.75)
BMI n (%)		
<25	65 (26)	148 (37)
25–29	89 (35.6)	118 (29.5)
30+	96 (38.4)	134 (33.5)
Menopausal status		
Pre	50 (20)	287 (21.7)
Post	200 (80)	113 (78)
Percentage area density	23.04 (11.29)	17.86 (12.09)
BI-RADS density (%)		
BI-RADS A–Predominantly fatty	32 (12.8)	109 (27.25)
BI-RADS B–Scattered fibroglandular	100 (40)	160 (40)
BI-RADS C–Heterogeneously dense	92 (36.8)	107 (26.75)
BI-RADS D–Extremely dense	26 (10.4)	24 (6)
3D slicer area density n (%)		
<15.54	28 (11.2)	93 (23.25)
15.54–30.19	85 (34)	152 (38)
30.19–45.28	88 (35.2)	101 (25.25)
>45.28	49 (19.6)	54 (13.5)

HRT: Hormone replacement therapy, BMI: Body mass index, BI-RADS: Breast imaging-reporting and data system

descriptive analysis of clinical risk factors and mammographic densities are mentioned in Table 1. The cases were found to have a larger proportion of patients who have familial history of breast cancer, who use HRT, postmenopausal, had BMI >30 kg/m². The cases were found to have higher number of heterogeneously or extremely dense breasts. There was good correlation between the quantitative and qualitative measurement; Pearson's correlation coefficient (*r*) was 0.79. The kappa value was 0.68, which shows good agreement in estimating BI-RADS category between two readers.

Association of BD and risk of cancer measured with 3D slicer and BI-RADS

The association of BD with cancer measured with quantitative measurement is given in Table 2. The association of BD with cancer was more in heterogeneous (OR 2.75, 95% CI 1.704–4.458) and extreme dense breasts (OR 3.16, 95% CI 1.356–5.610) compared to fatty and scattered heterogeneous (OR 1.63, 95% CI 1.102–2.416). The association of BD with cancer measured with BI-RADS category is given in Table 3. Clinical assessment with BI-RADS allowed slightly better discrimination of patients from controls.

Discriminatory ability of the models

Figure 2 shows the ROC curves for the risk factor model, density model, combined risk factor, and density model. The ROC curve for the first model of association between breast cancer risk and clinical risk factors had area under curve of 0.578 (95% CI: 0.45, 0.64). The ROC curve for the second model of association between breast cancer risk and BD had area under curve of 0.684 (95% CI: 0.58, 0.75). The ROC curve for third model of association between breast cancer risk and combined clinical factors and BD had area under curve of 0.724 (95% CI: 0.64, 0.80). All three models have good significance in differentiating cases and controls and suggesting the risk of cancer more in patients compared to controls. However, the density related model performed significantly better than the first model (*P* < 0.001). The third model performed better than the first and second models (*P* < 0.001).

DISCUSSION

In our age-matched case–control study, we assessed area BD using open source software 3D slicer; we found that scattered

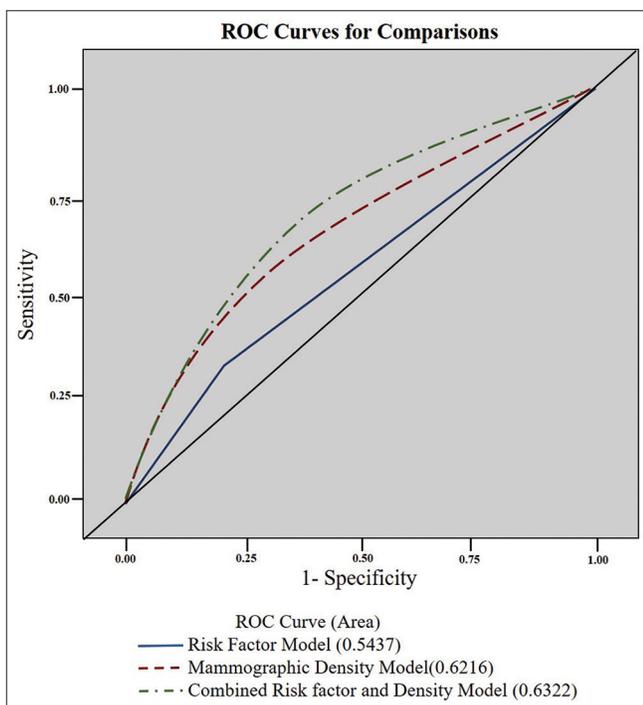
Table 2: The breast cancer risk associated with quantitative assessment of mammographic density.

Percentage density quartiles	Cases (n)	Controls (n)	Fully adjusted odds ratio	P-value	Confidence interval
<15.54% (reference)	28	93	-	-	-
15.54–30.19	85	152	1.63	<0.015	1.102–2.416
30.19–45.28	88	101	2.75	<0.001	1.704–4.458
>45.28	49	54	3.16	<0.013	1.356–5.610

Table 3: Breast cancer risk associated with BI-RADS and 3D slicer categories.

Density category	BI-RADS (OR, CI)	3D slicer (OR, CI)
Entirely fatty	Reference	Reference
Scattered fibroglandular	1.76 (1.309–2.735)	1.63 (1.102–2.416)
Heterogeneously dense	3.00 (1.916–4.352)	2.75 (1.704–4.458)
Extremely dense	3.67 (1.586–5.924)	3.16 (1.356–5.610)
P-value	<0.001	<0.05

BI-RADS: Breast imaging-reporting and data system, OR: Odds ratio, CI: Confidence interval

**Figure 2:** Comparison of receiver operating characteristic curves for the three models.

fibro glandular, heterogeneously dense, extremely dense breasts were found to be at risk of cancer. The finding of our study is concordant with the literature that increased levels of BD are associated with increased risk of breast cancer.^[1-9] It is established that mammographic density reduces the diagnosis due to masking of the underlying pathology.^[14,15] In our study, we noticed in 53 cases the breast lesions were found to be missing on X-ray mammography but detected in USG. Out of 53 cases, 45 cases belong to BI-RADS B, C, and D categories, which is evident of masking effect of BD in detection of breast lesions.

We found that mammographic density model, combined density, and clinical risk factor model improve discriminatory accuracy especially in women with dense

breasts. The quantitative method of BD assessment such as area and volume based may improve the discrimination of women with dense breasts who are at risk of breast cancer, as qualitative assessment showed poor agreement among the readers.^[16,17]

Our study noticed a good correlation ($r = 0.79$) between qualitative and quantitative assessment which is supported by literature. There are several studies which assessed the correlation between qualitative and quantitative and found good agreement between the two methods.^[18-20]

In our study, the OR (1.63 CI 1.102–2.416, 2.75 CI 1.704–4.458, 3.16 CI 1.356–5.601) was slightly higher compared to the studies who assessed BD using fully automated methods such as Libra (OR 1.66 CI 1.23–2.24, 2.17 CI 1.37–3.44, 2.71 CI 1.5–4.91) and Image J (OR 0.64 CI 0.26–1.59, 0.84 CI 0.53–1.36, 2.14 CI 1.44–3.16).^[21,22]

Our study found an inverse relationship between patients age and mammographic density consistent with results of other studies.^[23-26] We found higher density breasts in the menopausal age of 40–50 years. Checka *et al.*^[27] found dense breasts in extreme age of 70–79 and >80. However, our study did not find dense breasts in an extreme age.

First, the strength of our study was the combined use of clinical risk factors and BD in assessing the risk of breast cancer in patients. The second strength of our study was the use of screening mammograms and images of noncancerous breast to avoid the influence of the presence of cancer on the density assessments.

There are few limitations of our study. First, our study did not include all the clinical risk factors of breast cancer. Second, sample size was less, a larger sample of may have revealed further relationships, and further studies should focus on recruiting larger sample sizes.

CONCLUSION

We found that mammographic density measured by a fully automated method using 3D slicer was a significant factor contributing to risk of cancer. Besides, its significance in breast cancer quantitative mammographic density assessment is not currently considered in screening programs. Our study findings recommend inclusion of quantitative BD measurements done using fully automated software in diagnostic radiology to improve the discriminatory accuracy of risk of cancer.

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Declaration of patient consent

Patient's consent not obtained as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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