A quantitative approach to assess the correlation of mammographic breast density with selected affecting factors

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(Index words: mammographic breast density, age, body mass index, parity, quantitative breast density)

Abstract

Introduction: Breast density plays a significant role in increasing an individual's risk of breast cancer and its mortality rate.

Objectives: We aimed to assess the correlations of mammographic breast density with age, body mass index, weight, height and parity for the first time in Sri Lankan women.

Methods: 52 participants who underwent diagnostic mammographic examinations at a tertiary care hospital in Sri Lanka were selected for the study. Demographic data and digital mammograms in DICOM format were collected. Mammographic breast density was quantitatively estimated using a validated, semi-automated computer programme devised by the authors using Java programming language.

Results: 65.4% of the participants were postmenopausal, and 34.6% were premenopausal. Mammographic breast density showed a significant negative correlation with age ($r=-0.40$, $p<0.05$) and significant positive correlations with body mass index ($r = 0.49$, $p< 0.05$) and weight ($r=0.52$, $p<0.05$). The study did not find any correlation between mammographic breast density and height. Additionally, it did not find a significant difference between right and left breasts or between parous and nulliparous patients. Mammographic breast density was significantly higher among premenopausal patients compared to postmenopausal patients.

Conclusion: Quantitative mammographic breast density demonstrated significant correlations with age, body mass index and weight. The findings of the study will be constructive in predicting breast density in the future and individualizing the breast cancer screening requirements based on the breast density without radiation exposure for females in Sri Lanka.

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Introduction

Breast cancer is the first ranked cancer type causing significantly higher mortality among women [1]. From 2001 to 2010, the age-standardized crude incidence rate of breast cancer among Sri Lankan women increased from 17.3 to 24.7 [2]. In 2018, the breast cancer incident rate in Sri Lanka was 13.1% while its mortality rate was 8.4% [3]. The incident rate has increased to 13.4% by the year 2020 [4]. Sri Lanka, a lower-middle-income country [5], is still in the process of developing a national screening programme for breast cancer and adopting strategies such as clinical breast examinations and breast cancer awareness programmes [6]. Hence, Sri Lanka needs to find effective means of early detection of breast cancer to reduce its mortality rate.

The women with higher breast densities are at a four to six-fold increased risk of developing breast cancer compared to the women with lower breast densities [7]. BD increases with determinants such as pregnancy, lactation, weight loss and use of hormone replacement therapy. In contrast, BD decreases with ageing, weight gain, menopause and certain drugs used to treat breast cancers [1]. When a higher amount of fibroglandular tissues is present within the breast, there is a higher probability to have tissue components with biological properties like mutations that may contribute to carcinogenesis. Further, within the breast where the ratio of fibroblasts to adipocytes is higher, the activity of the aromatase enzyme is predominant. Its activity is greater in the pre-adipocytes rather than in the matured and differentiated adipocytes. Aromatase is a source of estrogen hormone which contributes to the epithelial cell proliferation and the growth of malignant tumours. Hence, when the breast density increases, the risk of having breast cancer also increases [8]. The dense breast tissues in mammograms may mask breast cancers and reduce the sensitivity especially for women with increased breast densities [9,10]. Further, cancer may not be visible due to the distraction by other dense tissues surrounding cancer, causing the false-negative diagnosis [9].

Mammographic breast density (MBD) is defined as the ratio of the area of dense breast tissues to the entire area of the breast tissues in a mammogram [11]. The results of the qualitative methods used for MBD assessment may vary depending on the training and experience of the observer [12,13]. Therefore, these methods are excessively subjective and associated with suboptimal reproducibility [14]. Quantitative methods are developed to assess MBD using computer programmes. They are more accurate and less subjective compared to qualitative assessment methods. This study aimed to assess the associations of the quantitative MBD with a selected set of patient-related factors (age, weight, height, BMI, parity and menopausal status). This may open up new avenues to predict the MBD without radiation exposure to the patient and will be an unprecedented advancement in the field.

Methods

This prospective and descriptive study was conducted with the female patients referred to diagnostic mammographic examinations at Teaching Hospital Peradeniya, Sri Lanka. Female patients who underwent bilateral mammographic examinations in the age range 35-80 years were considered for this study. Only the Sinhala ethnic group was selected excluding all other ethnicities to avoid possible BD variations across different ethnicities [15,16]. Further, patients who diagnosed with breast pathologies and who failed to complete mammographic examinations were excluded.

All the patients who satisfied the inclusion criteria were interviewed as per the convenience sampling method. The study included 52 participants from the 232 interviewed. Patients' data including age, weight, height, number of previous pregnancies and menopausal status were collected. BMI was calculated using the measured weight and height.

The digital mammography unit (HOLOGIC - SeleniaTM System, Model - SEL - 00047) installed at Teaching Hospital Peradeniya was used to acquire digital mammograms. Mammograms in digital imaging and communications in medicine (DICOM) format were collected for each patient including all four projections; craniocaudal (CC) and mediolateral oblique (MLO), for both breasts.

MBD was quantitatively assessed using a pre-validated semi-automated computer programme [17] developed by the authors of this article. It was designed to calculate MBD when the total breast area is manually defined as the region of interest (ROI) by experienced practitioners in the field of mammography. Once the ROI is defined, MBD is calculated as the ratio of the total number of pixels representing dense tissues to the total number of pixels within the ROI (Figure.1).

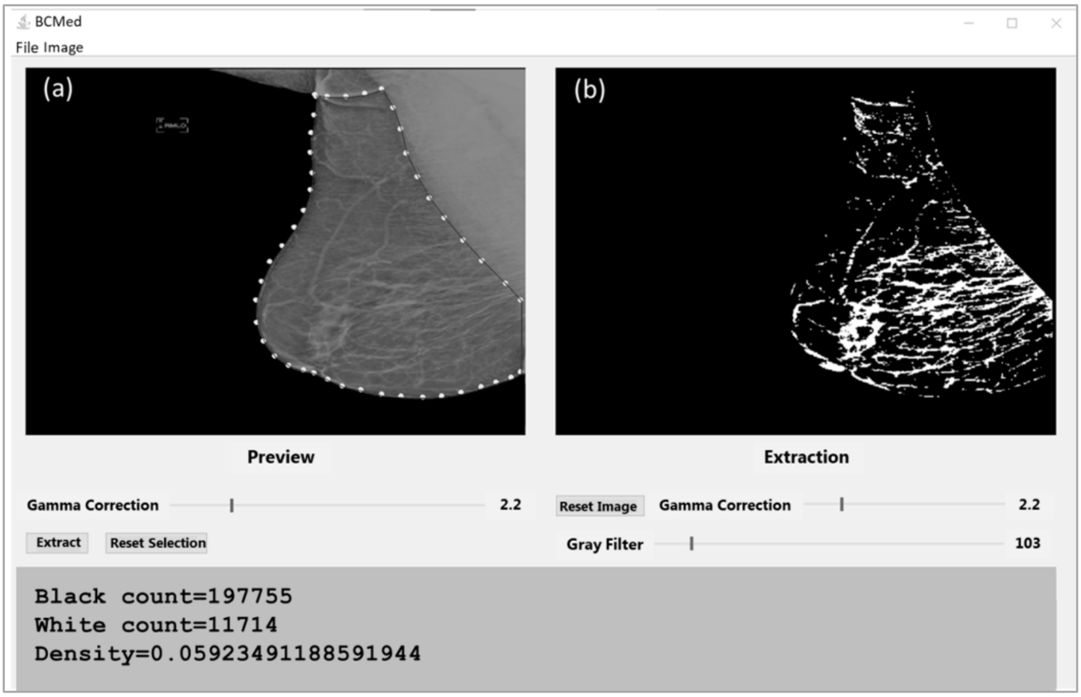

Figure 1. **Calculation of mammographic breast density (a) Selection of ROI for the breast tissues (b) Application of the threshold to differentiate dense breast tissues with “Gray Filter”.**

The calculated MBD was statistically analyzed to find out the associations with the selected variables. The analysis was performed for the whole sample as well as for the premenopausal and postmenopausal categories separately. Spearman's correlation coefficients were calculated to estimate the correlation of MBD with age, BMI, weight and height. Multivariate two-sample Hotelling's T2 test was performed for the difference in MBD between premenopausal and postmenopausal categories. The statistical analysis was performed using R (version 4.0.3) statistical software [18].

Ethics approval for the research

This research was approved by the Ethics Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka (under the protocol number 2017/EC/24).

All the participants were informed about the research and the confidentiality of the data during the interview and written informed consent was obtained from each patient to participate in this research. Self-reported ethnicity, age, reproductive history and the menstrual history of the participants were used to categorize them in the analysis of the data.

Results

Of the 52 patients included in the study, 34 (65.4%) were in the postmenopausal stage while the remaining 18 (34.6%) were in the premenopausal stage. The distributions of age, weight, height and BMI are shown in Table 1. Table 2 illustrates Spearman's correlation coefficients for the associations between MBD and the independent variables for the whole sample, premenopausal category and postmenopausal category separately. In addition, the difference in MBD was assessed for parous and nulliparous patients in each category mentioned in Table 2. The results showed no significant difference in MBD for these three categories (p>0.05). Furthermore, Spearman's correlations coefficients for the associations of MBD with the independent variables were separately assessed concerning each mammographic projection. The results are tabulated in Table 3 for each category illustrated in Table 2.

Table 1. Distribution of the independent variables

	Age (Years)	*Weight (kg)*	*Height (m)*	*BMI (kg/m^2)*
Mean	54	58.76	1.50	25.96
Standard deviation	9	12.48	0.08	5.38
Minimum	35	28.45	1.32	14.31
1st Quartile	46	49.76	1.46	22.1
Median	55	59.55	1.51	25.42
3rd Quartile	60	66.89	1.56	29.82
Maximum	70	93.73	1.66	38.03

Table 2. Association of estimated MBD with the independent variables

Category	*Variable*	*Spearman's Correlations Coefficients (r)*
Whole Sample	Age	-0.401**
	BMI	0.494***
	Weight	0.522***
	Height	0.139
Premenopausal	Age	0.317
	BMI	0.335
	Weight	0.358
	Height	-0.045
Postmenopausal	Age	-0.065
	BMI	0.463**
	Weight	0.534**
	Height	0.277

p-value: **<0.01, ***<0.001

Table 3. Association of estimated MBD with the independent variables for different mammographic projections

Category	Variable	Spearman's Correlations Coefficients (r)		
		Whole Sample	*Premenopausal*	*Postmenopausal*
RCC projection	Age	-0.417**	0.164	-0.189
	BMI	0.520***	0.313	0.496**
	Weight	0.521***	0.300	0.551***
	Height	0.078	-0.052	0.187
RMLO projection	Age	-0.385**	0.115	-0.029
	BMI	0.480***	0.285	0.428*
	Weight	0.514***	0.369	0.497**
	Height	0.162	0.036	0.295
LCC projection	Age	-0.290*	0.344	-0.004
	BMI	0.444***	0.319	0.406*
	Weight	0.457***	0.356	0.429*
	Height	0.090	-0.082	0.163
LMLO projection	Age	-0.392**	0.319	-0.097
	BMI	0.392**	0.255	0.402*
	Weight	0.446***	0.321	0.516**
	Height	0.144	-0.102	0.327

p-value: *<0.05, **<0.01, ***<0.001

Further, the mean of RMLO and RCC projections was compared with the mean of LMLO and LCC projections. However, no significant difference in the mean MBDs was found between right and left breasts (p=0.40). When the mean MBD of each projection was compared with respect to the menopausal status of the patient, a significantly higher MBD was observed for the premenopausal category than for the postmenopausal category. In addition, Bonferroni confidence intervals were calculated to identify the differences in MBD between premenopausal and postmenopausal categories. Table 4 lists the respective intervals for each projection. Results indicated that the MBDs for all projections are higher for the premenopausal category compared to the postmenopausal category.

Table 4. Bonferroni confidence intervals calculated for the mean MBD difference between Premenopausal and Postmenopausal patients for each mammographic projection

Mammographic projection	*95% Simultaneous Bonferroni confidence interval for the mean difference (μ_{pre} - μ_{post})*
RCC	(1.246, 6.367)
LCC	(0.851, 5.583)
RMLO	(1.835, 6.529)
LMLO	(1.317, 5.894)

Discussion

In our study, the age of the patient showed a significant negative correlation with MBD. The results of similar studies conducted by Pollãn *et al* [13] and Ellison-loschmann *et al* [19] also revealed that the MBD has a significant negative correlation with the age. The results of certain studies carried out by Ahmadinejad *et al* [20], Checka *et al* [21] and Gram *et al* [22] are in align with the findings of our study. The alteration in the glandular breast tissues with menopause might be a possible factor that causes breast density to decrease. [21].

Our study demonstrated a significant positive correlation between BMI and MBD. However, the results of the similar studies carried out by Vacek and Geller [23], Pollãn *et al* [13] and Gram *et al* [22] showed an inverse correlation between these variables. Ahmadinejad *et al* [20] demonstrated that the mean BMI was significantly less for the high BD group than that of the low BD group. Furthermore, the study performed by McConnell *et al* [24] found no association between BMI and MBD for the population they studied.

The weight of the patient demonstrated a significant positive correlation with MBD in our study. However, Boyd *et al* [25] and Wanders *et al* [26] found a significant negative correlation with the weight of the non-cancer patients. Further, Li *et al* [27] showed positive associations for weight and BMI with dense breast area while a negative association with MBD. Even though the discrepancies between these results are unexplained, there may be a confounding effect of multiple factors or these associations may be unique to the respective study populations [27].

Our study and a similar study [25] demonstrated no correlation between MBD and the height of the patient. In a study done by Vacek and Geller [23], it was identified that nulliparous women were more likely to have denser breasts when compared with parous women. Further, Letizia *et al* [28] and Ursin *et al* [14] claimed that the patients with primary infertility have higher breast densities than that of the parous women. However, this study did not find a significant difference in MBD between parous and nulliparous patients.

Our results indicated that MBD values for both breasts were highly correlated and no significant difference between right and left breasts was found. The results of a study done by Kontos *et al* [29] also indicated that the MBD values for both breasts were significantly positively correlated with each other. With the ageing of a woman, most of the changes of the breast occur closer to her menopausal age. With menopause, changes in the reproductive hormone levels in the body would cause changes in BD [21]. Our results revealed that the MBD of premenopausal patients was significantly higher than that of postmenopausal patients. Ahmadinejad *et al* [20] also claimed that the MBD was significantly higher in premenopausal women than the postmenopausal women.

The discrepancies found between the results of this study and similar studies could be due to the differences in the study populations, study designs and other limitations of different studies in different areas in the world. One of the major concerns of this study is the small sample size which might have led to certain discrepancies observed. Hence, this might limit the generalizability of the results. Therefore, further investigations are required to be carried out with larger study samples for Sri Lankan population.

However, this study is the first of this nature which assessed the correlation between MBD and the affecting factors for a Sri Lankan population. Hence, these results are constructive in predicting the BD without radiation exposure and individualizing the screening requirements according to the BD among females in Sri Lanka.

Conclusions

Our study revealed that MBD is negatively correlated with age. BMI and weight demonstrated a significant positive correlation with MBD while height showed no correlation with MBD. Furthermore, no significant differences in MBD were identified between right and left breast as well as parous and nulliparous patients. A significantly higher MBD was observed in premenopausal patients than that of postmenopausal patients. In conclusion, we attempted to describe the association of the MBD with certain selected factors which were believed to affect the BD for the Sri Lankan population. However, further studies should be carried out to completely understand the factors affecting the BD of an individual to predict it without radiation exposure.

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Conflict of Interest

There are no conflicts of interest.

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