Association between mammographic breast density and breast carcinoma – a unit based experience

Dilini Nanayakkara[1], Chathurika Batuwitage[1], Pubudu Chulasiri[2], Dilupani Abeywardhana[1], Subhashini Samaraweera[1]

Abstract

Introduction: Breast cancer has a high incidence and is showing a rising trend in Sri Lanka. Mammographic breast density is a radiologically measurable risk factor which has been found to be significantly associated with breast cancer risk in women, with minor variations between ethnicities. However, the Asian populations studied in previous international studies were of Japanese, Chinese and Filipino ethnicities and not Sri Lankan or other South Asian ethnicities. Also, a previous Sri Lankan study found no significant association between breast density and breast cancer. Therefore it is of interest to study whether there is actually an association between breast density and breast cancer in Sri Lankan women.

Objectives: This study aimed to assess whether there is a significant association between mammographic breast density and breast cancer in Sri Lankan women and also to assess factors affecting breast density.

Methodology: We conducted a retrospective unmatched case control study of 110 women (22 cases of breast cancer and 88 controls) aged between 40 and 75 years who came for mammography to Sri Jayewardenepura General Hospital. Breast density was categorized in to two, as lower density (BIRADS type a and b compositions) and higher density (type c and d compositions) for the analysis.

Results: Contrary to most international research findings and similar to the previous Sri Lankan study, no significant association was found between breast density and breast cancer. Additionally, out of multiple factors, only age, menopausal state and BMI were found to be significantly associated with breast density.

Conclusion: These findings may indicate that there is a true difference in the Sri Lankan population from the previously studied international populations suggesting that there is no association between breast density and breast cancer in Sri Lankan women. A further multicenter research is necessary to prove or disprove this theory.

Introduction

Breast carcinoma is one of the leading cancers in terms of incidence worldwide with the number of incident cases standing at almost 2.1 million in 2020 (24.2% of the total cancer burden) according to the "WHO report on cancer" published in 2020 [1]. It is also the most common cancer among women. In Sri Lanka, there has been a rising trend in the incidence of breast cancer and this is due to a combination of factors such as the rising number of post-menopausal women and better screening and detection of cancers according to a study done by Fernando *et al* [2].

Fortunately, although it has high incidence, breast cancer is also one of the most treatable cancers with a lower mortality rate of only 6.6% compared to mortality rates of lung (18.4%) and colorectal (9.2%) cancer which are also two types of cancers with high incidence rates [1]. Therefore it is a worthwhile endeavor to detect and treat breast cancer early and also to identify women at higher risk of breast cancer in order to provide more vigilant screening for this sub category of women.

There are many factors that increase the risk of breast cancer such as advanced age, BMI, race/ ethnicity, dense breasts, early menarche and late menopause, older maternal age at birth of first child, nulliparity, lack of breast feeding, hormonal contraceptives, prior benign breast disease, atypical hyperplasia, radiation exposure, smoking, alcohol, obesity, low physical activity, personal history of breast cancer, personal history of uterine, ovarian and colon cancer, first degree relatives with breast cancer,

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[1]*Sri Jayawardenapura General Hospital, Sri Lanka,* [2]*Anti Malaria Campaign.*

Correspondence: DNN, *e-mail: <dilininpn@yahoo.com>.* *Received 13 May 2022 and revised version 01 September 2022 accepted 05 September 2022*

BRCA 1 and 2 gene mutations and familial syndromes such as Cowden, Li Fraumeni, Peutz Jegher etc.

Out of the above mentioned risk factors, a radiologically assessable factor is, breast density as seen in mammography. Higher breast density is currently identified as a risk factor for breast cancer worldwide [3-5].

Breast density can be assessed in mammograms in many ways based on the amount of glandular tissue in comparison to the surrounding fatty tissue of the breast. Given below are four such methods of breast density measurement. 3 and 4 below are the most commonly used methods currently.

1. Wolfe classification of breast density [9]
2. Visual estimation of percentage breast density – Boyd *et al* [3] proposed a system of 6 categories to classify percentage breast density
3. Breast Imaging Reporting and Data System (BI-RADS) density classification [7]
4. Computer assisted measurements of breast density

Additionally, the degree of risk of breast cancer in dense breasts has been found vary among different ethnicities such as Japanese, Filipino, Chinese, Hawaiian and Caucasians (although not statistically significant) [8,12]. However, neither Sri Lankan nor South Asian populations were included in these studies. Therefore it is of interest to assess whether this increased cancer risk in denser breasts holds true for Sri Lankan women as well. Interestingly, a descriptive study done by Perera *et al* in the Central Province of Sri Lanka published in 2016 found no significant association between mammographic breast density and invasive ductal carcinoma [13]. This study is more likely to represent patients from the central province, whereas our current study is more likely to represent patients from the Western province as the database consists of patients coming to Sri Jayewardenepura General Hospital. However, since neither of these samples are representative of the entire Sri Lankan population, more multicenter data analysis would be required to confidently comment on the relationship between mammographic breast density and breast carcinoma in the Sri Lankan population.

It is also known that breast density is influenced by many factors such as age, parity, breast feeding, ethnicity, smoking, BMI, and diet [6-10]. Physical activity was shown to affect annual change in breast density in a study done by Azam *et al* [10] but physical activity has not been shown to affect breast density in other studies although low physical activity is a risk factor for breast cancer [11].

Research regarding the association between breast density and these risk factors has not been done in the Sri Lankan population.

Therefore this study aims to assess the association between mammographic breast density and breast carcinoma in Sri Lankan women as well as to assess association between breast cancer and modifiable and non-modifiable factors mentioned above. This data in turn could help to modify breast cancer screening programmes within the country as needed as well as used to possibly modify breast density and in-turn reduce breast cancer risk. (The current recommendation for screening mammogram varies between countries. The guidelines published by the National Cancer Control Programme in Sri Lanka in 2020 recommends screening mammogram every 2-3 years for women aged 50-69 years with more intensive screening in women with one or two first degree relatives with breast cancer, women with history of breast biopsy showing atypical hyperplasia or lobular carcinoma in situ, women with known mutations (eg- BRCA 1 and BRCA 2) and women with history with chest wall radiation at 30 years of age or younger.)

Main objective:To assess the association between mammographic breast density and breast carcinoma.

Specific objectives:

1. To assess the association between breast density and modifiable risk factors for breast carcinoma.
2. To evaluate the association between breast density and non-modifiable risk factors.
3. To assess association between mammographic breast density and breast carcinoma

Methodology

The study was undertaken at the Sri Jayewardenepura General Hospital (SJGH) after ERC approval from both the hospital and PGIM (Post Graduate Institute of Medicine).

The design of this study was an unmatched retrospective case control study. Sample size was calculated using the formula given by Kelsey *et al*, (Methods in Observational Epidemiology – 2nd edition). Open Epi software was used for the calculation and based on this, a total sample size of 110 was decided upon comprising of 22 cases and 88 controls from women aged between 40 years to 75 years undergoing mammographic breast examination at SJGH. Women who have undergone previous breast surgeries and women who have previously been diagnosed with breast carcinoma and are undergoing follow up mammography were excluded from the study.

Case – A woman aged 40 years or above who underwent a mammographic breast examination and found to have histologically proven breast carcinoma.

Control – A woman aged 40 years or above with no clinically and radiologically detectable breast mass who undergoes a mammogram purely for screening purposes or a woman with a histologically benign breast lesion who underwent mammographic breast examination.

Informed consent was obtained prior to use of patient data. Data collection commenced on 1st of June 2021. Both archived and new patient data from July 2017 to 31st of December 2021 was used for the study.

A systematic random sampling method was used as follows. For each histologically proven cancer positive case, the next 10 cancer negative women were selected. Then out of these 10 cancer negative women, 4 were selected randomly (by a random number generator) as controls.

Data were collected using a questionnaire administered by two trained medical officers from the Department of Radiology, SJGH. Mammographic breast density was assessed solely by the principal researcher to avoid inter observer variability. Also breast density was assessed without obtaining prior knowledge regarding the histological findings of the patients to avoid bias. 3D mammogram images obtained by tomosynthesis (which is known to improve image quality and detection of pathologies were used). Mammographic breast density was categorized in to the following groups based on the 5th edition of BI-RADS classification published by the American College of Radiology in 2013.

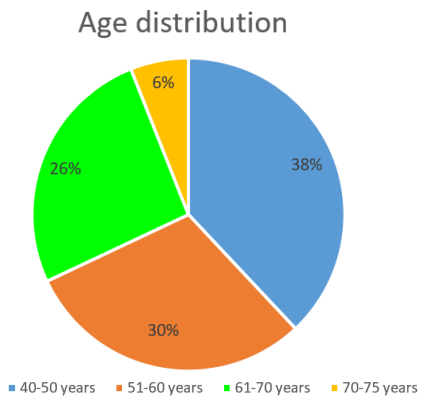
- **a:** the breasts are almost entirely fatty
- **b:** there are scattered areas of fibroglandular density
- **c:** the breasts are heterogeneously dense, which may obscure small masses
- **d:** the breasts are extremely dense, which lowers the sensitivity of mammography

The interviewer administered questionnaire collected information on non-modifiable variables such as age, age at menarche, age at menopause, age at birth of first child, personal history of uterine/endometrial/colon carcinoma and family history of carcinoma as well as modifiable variables such as BMI, exercise, duration of breast feeding, hormonal contraceptive use, smoking and alcohol consumption.

Statistical significance between association of mammographic breast density and breast cancer and also between risk factors assessed and breast density were determined by Chi square test. P value less than 0.05 were considered statistically significant. Statistical analysis was done using SPSS version 24.

Results

Age distribution of the 110 study participants was categorized as illustrated in below pie chart.

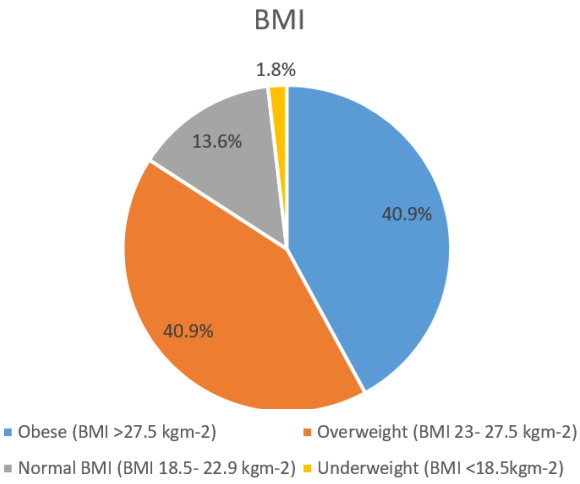


Out of these, a majority of 85 (77.3%) were post-menopausal. These 85 women were categorized as premature menopause (<40y), early menopause (<45y), normal age of menopause (45y - 55y) and late menopause (>55y). Most had reached menopause at the normal age (83.7%) while a combined 16.3% had premature and early menopause with no one having late menopause.

13 women (11.8%) had a history of early menarche. (Menarche < 12 years).

The study population consisted of 103 parous women (93.6%). Out of the 103 parous women, most women (37.9%) had their first child between the ages of 26 - 30 years. There were 5 (4.8%) geriatric mothers (>35 years) in this sample which was the lowest percentage. Young mothers less than 20 years of age made up 12.7% of the sample.

Majority of the women in this study were found to be obese or overweight as shown below.

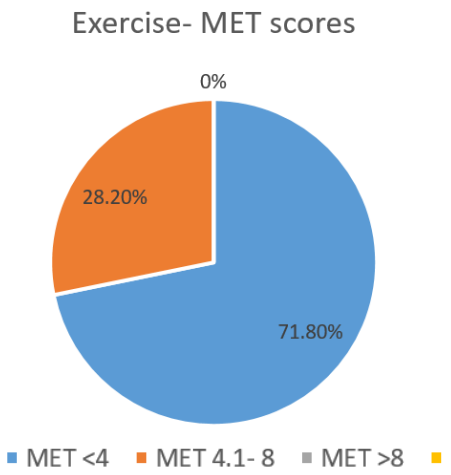


Breast density in the study population showed that most women had lower density breasts as shown below.

Breast density

	Frequency	*Percent*
Low density (types a & b)	78	70.9
High density (types c & d)	32	29.1
Total	110	100.0

MET values of exercise performed by study participants was categorized as low (MET <4), moderate (MET 4.1 - 8) and high (MET >8) as illustrated below. Weekly MET min/week scores were also calculated which found that the percentage of women meeting the amount of weekly exercise recommended by the American Heart Association (500 - 1000 MET min/week) was 22.7% while 3.6% surpassed this with a MET min/ week value above 1000. The remaining majority were below the recommended exercise level.



In this sample of women, a majority of 77.3% had no history of use of hormonal contraceptives.

There were no active smokers in this sample of women. 9 women (8.2%) were exposed to cigarette smoke by passive smoking.

A percentage of 6.4% consumed alcohol in small amounts. (Between 0.1 to 10g/day) while the rest (93.6%) did not consume alcohol.

13 women (11.8%) had a family history of breast cancer while 5 of those were in first degree relatives and the remaining 8 in other relatives (Non first degree). One woman was unaware regarding the presence or absence of a family history of breast cancer.

Only one woman (0.9%) had a known personal history of uterine/ ovarian or colonic carcinoma.

As shown in the below table, a significant association was shown between mammographic breast density and age. Menopausal state was also significantly associated with breast density ($p<0.001$). Among the modifiable risk factors, only BMI was found to have a significant association with breast density. The rest of the modifiable and non-modifiable factors were not shown to be significantly associated with breast density.

Discussion

Our study was a retrospective unmatched case control study using a sample of 110 women (22 cases of histologically proven breast cancer and 88 controls). We analysed association between breast cancer and mammographic breast density by dividing breast density in to two groups of lower density (BIRADS type a and b composition) and higher density breasts (BIRADS type c and d composition). It showed similar findings to the previously mentioned Sri Lankan study by Perera *et al* [13] with no significant association found between breast density and breast cancer. (p value- 0.462). This is in contrast to the international consensus of increased cancer risk in denser breasts.

Furthermore, this study also assessed the association between breast density and other modifiable and non modifiable factors (stated above) which could possibly affect breast density. Out of these, only age, menopausal

Table 1. Association between variables assessed and mammographic breast density

	Chi square value (χ2)	*Degree of freedom (DF)*	*p value*
Risk of breast carcinoma	0.540	1	0.462
Age	23.633	4	0.001
Early menarche	0.258	1	0.611
Menopausal state (pre or post-menopausal)	28.877	1	0.001
Age at menopause	0.727	2	0.695*
Parous/ Nulliparous	0.002	1	0.962 *
Age at birth of first child	2.046	2	0.360 *
Family history of breast carcinoma	1.236	1	0.266
Personal history of uterine/ ovarian/ colon carcinoma	0.401	1	0.527*
BMI	8.693	3	0.035
Exercise – MET min/ week	4.420	2	0.110
Duration of breast feeding	3.15	4	0.532
Hormonal contraceptive use	0.092	1	0.762
Smoking	0.224	1	0.636
Alcohol consumption	0.001	1	0.975*

*Fishers exact test used

state and BMI were found to have significant association with breast density with p values of 0.001, 0.001 and 0.035 respectively; with only BMI being a modifiable risk factor.

In conclusion, no significant association was found between mammographic breast density and breast cancer while factors significantly affecting breast density were found to be age, menopausal state and BMI.

The findings of this study warrant further advanced and widespread multicenter research into this topic to further assess whether there is truly no association between mammographic breast density and breast cancer in Sri Lankan women which would be a significant change from the current worldwide findings.

Limitations

We have identified two limitations in this study. The first is the unavailability of a computerized method to assess breast density which has been shown to further increase the association between breast cancer risk and breast density in some studies. Also, this study was done in a sample population of women who came for mammographic breast examination at SJGH and this sample does not represent the entire at risk Sri Lankan female population.

Acknowledgement

Department of Histopathology , Sri Jayewardenepura General Hospital, Sri Lanka.

Conflicts of interest

None.

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