ORIGINAL ARTICLE

BREAST DENSITY AS AN INDIVIDUAL RISK FACTOR FOR DEVELOPMENT OF BREAST CANCER IN OUR POPULATION A STUDY CARRIED OUT AT TERTIARY CARE HOSPITAL, KARACHI

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ABSTRACT

BACKGROUND: According on the proportion of fibroglandular tissue to fatty tissue, the Breast Imaging Reporting and Data System (BI-RADS) divides breast density into 4 groups and offers radiologists standardized communication tools. **OBJECTIVE:** To determine the association of breast density with development of breast cancer in local Asian population. **MATERIAL AND METHODS:** Total 108 female patients were included in the cross-sectional study. A full-field digital mammography equipment was used for the mammograms. For bilateral breasts, four mediolateral oblique and craniocaudal images were acquired. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) was used to guide the interpretation of mammogram. The categories were recorded as follows: 1) Almost entirely fat (≤25% fibroglandular tissue); 2) Scattered fibroglandular (26%-50%); 3) Heterogeneously dense (51%-75%); and 4) Extremely dense (>75%). Stratification was done and post stratification Chi square test or Fisher s exact test was applied. P-value ≤0.05 was considered statistically significant. **RESULTS:** The categories of BI-RADS were found as 16(14.8%) had category A, 48(44.4%) had category B, 38(35.2%) had category C and 6(5.6%) had category D. The breast cancer was noted in 5(31.3%) cases of category A, 24(50%) of cases of category B, 30(78.9%) of cases of category C and 5(83.3%) cases of category D, the breast cancer was significantly associated with the categories of BI-RADS (p=0.002). **CONCLUSION:** There is a significant association between the risk of breast cancer inour population with mammographic breast tissue density categorized by BI-RADS.
Key Words: Breast Density, Breast Cancer, Breast Imaging Reporting AndData System

Introduction

Among all malignancies in females, breast cancer is the major malignancy with approximately 25% of all cancers in women worldwide.[1,2] As compared to West, the incidence of breast cancer is increasing more quickly in Asia.[3] Reproductive factors (age at first birth and parity), menstrual factors (age at menarche and menopausal status), breast density, and factors for modifiable lifestyle such as hormone replacement therapy (HRT), body mass index (BMI), alcohol consumption[4-6] and family history[7] are well established multiple risk factors for breast cancer.

The proportion of fibroglandular tissue to fatty breast tissue shown on a mammography is known as breast density.[7] Breast cancer mostly arises from this fibroglandular tissue because it contains the epithelial structures of the breast, such as the glandular lobes and ducts. The quantity of fibroglandular tissue relies on hormone stimulation and is mostly genetically

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determined. It often gets smaller over time, especially after menopause. On mammography, the fibroglandular tissue appears white after absorbing ionising radiation (X-rays). It is therefore frequently referred to as "dense" tissue. Therefore, malignancies that are also thick (white) in mammograms might be hidden by the dense (white) tissue. In other words, thick tissue may mask tumours on mammography, preventing the identification of them.[8,9]

When referring to high breast density as a cancer risk, there is a lot of uncertainty because there is much debate about its relevance. Some researchers contend that other risk factors and the high breast density masking effect confuse the association between breast density and breast cancer. However, the most recent research claims that breast cancer and high breast density are significantly related. The risk of breast cancer may thus be influenced by breast density.[7]

Breast cancer screening is extremely important for identifying asymptomatic cancer, which leads to less intrusive therapies and better outcomes since the disease will be found in its early stages before the tumour grows. Be familiar with the guidelines for which categories of women should be tested, how frequently, and with which imaging modalities.[10,11] The majority of research looking at the association between mammographic density and breast cancer employed just one density measurement at one point with a long interval between the last negative mammography and the diagnosis of breast cancer.[12,13] The best imaging method for screening breast cancer in all women is still mammography, which is dependent on a mutual choice between the patient and her doctor based on risk factors and competing co-morbidities.[11] On the other hand, mammographic density is a characteristic that is continually changing and often declines with ageing, particularly during menopause.[14] Body mass index (BMI),[15] exogenous hormone usage,[16] diet[17,18] and reproductive history are other factors that have been shown to have an effect on breast density.[19]

The American College of Radiology's (ACR's) Breast Imaging Reporting and Data System (BI-RADS) divides breast density into 4 groups based on the proportion of fibroglandular tissue to fatty tissue and offers radiologists standardized communication tools, i.e.category-A (entirely fatty); category-B (scattered fibroglandular); category-C (heterogeneously dense); and category-D (extremely dense).[8,9] Breast with low-density are those that fall under BI-RADS categories A or B, whereas breast with high-density are those that fall under categories C or D.[9]

In one research, ACR-A made up 23%, ACR-B 49%, ACR-C 25%, and ACR-D 3% among all study cases. All positive breast cancer cases occurred at an incidence of 2.2% in the ACR-A density group, 2.7% in the ACR-B density group, 3.3% in the ACR-C density group, and 13.7% in the ACR-D density group. High breast densities (ACRC- and ACR-D) were significantly associated with an increased risk of breast cancer.[10] In another research, 54.0% of the 107 patients had been given a breast cancer diagnosis. As many as 66% of the participants in this study had breasts that were "heterogeneously dense" according to BI-RADS C, followed by 22% and 11% of individuals who had breasts that were thick according to BI-RADS B and A, respectively. One participant only that met the BI-RADS D criteria for "extremely dense". Therefore, for the sake of statistical analysis in this study, BI-RADS C and BI-RADS D were merged into a single group referred to as "dense" breasts.[7] The total distributions of mammographic density (MD) were 11% (nearly exclusively fat), 37% (scattered fibroglandular densities), 50% (heterogeneously dense), and 3% (very dense) in another investigation. As a result, the most prevalent MD category in this research was very dense, or C and D combined.[20]

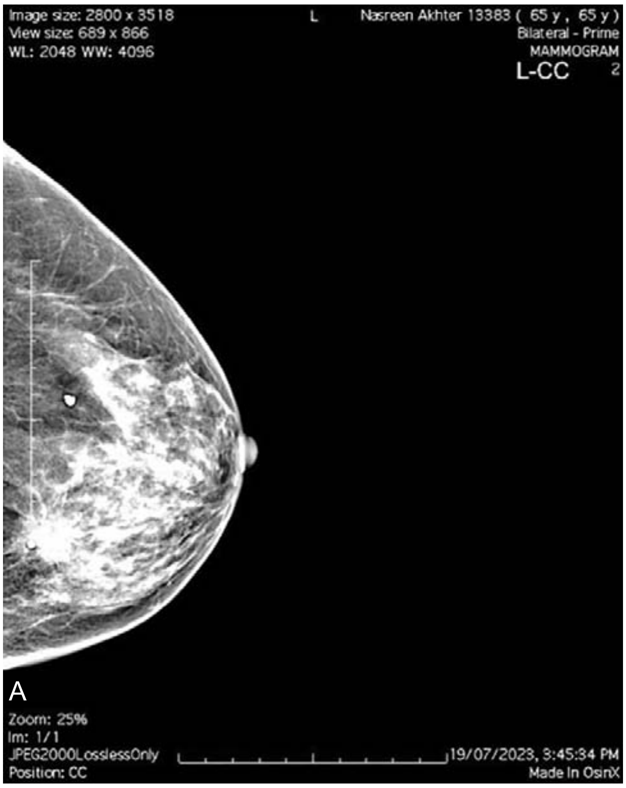
A local investigation on the relationship between breast density and breast cancer has not been located in the literature search. In order for women to make wise health decisions, there is a need to increase knowledge of the possibility that breast density may be a risk factor. This study aims to evaluate the level of cancer risk that high breast density poses in the local environment. In order to ascertain if mammographic breast density is related to the risk of breast cancer, this study is being prepared.

Material and Methods

Female patients with symptoms suggestive of breast cancer and those who were asymptomatic and between the ages of 15 and 65, but qualified for screening mammography were taken into account. Females with mammograms suspicious for malignancy underwent tissue biopsy, and were referred to the radiology department at Liaquat National Hospital Karachi were included in the cross-sectional study. After receiving acceptance of the study proposal from the institutional ethical review committee, the study was carried out. Before enrolling the patient in the study, the patient's informed permission was acquired. The sample size was calculated through Sample Size Calculator using Wan Nor Arifin (available at https://wnarifin.github.io/ssc/sssnsp.html) by taking incidence of ACR-D (d)=13.7%[10] margin of error (d)=6.5%, and 95% confidence level. The calculated sample size came out was 108 patients.

The researcher conducted a clinical evaluation on each study participant. Data regarding age, race, height, weight, BMI, DM, HTN, Obesity, smoking, parity, family history, menopausal status, alcohol use, were noted by principal investigator before going to mammography. Breast cancer was identified through self-reporting of physician-diagnosed breast cancer using standardized, self-administered questionnaires at the time of follow-up visits. When compared with confirmed invasive breast cancer (International Classification of Diseases, Tenth Revision [ICD-10] codes C50.0-C50. A full-field digital mammography equipment (Selenia Dimensions [Hologic, Marlborough, Massachusetts] or Senographe 2000D/DMR/DS [General Electric Company, Milwaukee, Wisconsin]) was used for the mammograms, which were conducted by a consultant radiologist. For bilateral breasts, four mediolateral oblique and craniocaudal images were acquired. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) was used to guide the interpretation of every mammogram which was done by experienced breast imaging radiologists. The categories of breast density were recorded as follows: 1) Almost entirely fat (≤25% fibroglandular tissue); 2) Scattered fibroglandular (26%-50%); 3) Heterogeneously dense (51%-75%) (Fig. 1-4); and 4) Extremely dense (>75%). For the analysis of the changes in dense breasts, dense breast tissue was defined as breasts that were heterogeneously dense or extremely dense .

With the help of the statistical package for social science (SPSS) software, version 25, data were compiled and analyzed. Mean and standard deviation were calculated for quantitative variables i.e. age, duration of disease, parity, alcohol consumption, height, weight, BMI, SBP, DBP, FBS, and BI-RADS. Frequency and percentages were calculated for qualitative variables i.e. place of residence, HTN, DM, Obesity, Smoking, ethnicity, family history of breast cancer, menopausal status, breastfeeding, breast cancer, and categories of BI-RADS. The Kolmogorov-Smirnov test was applied to quantitative variables to test for normality of the distribution. If data were skewed, median and interquartile range were used to present quantitative variables. Pearson Chi-square test was conducted for test of association for qualitative variables. Chi-square test was used to test for homogeneity for categorical data. Whenever assumptions will not be met, Fisher's exact test was used. Effect modifiers were controlled through stratification of age, duration of disease, parity, alcohol consumption, place of residence, HTN, DM, Obesity, Smoking, ethnicity, family history of breast cancer, menopausal status, breastfeeding. Post stratification Chi square test or Fisher s exact test was applied to see the effect of these modifies on outcome. P-value ≤0.05 was considered statistically significant in all analysis.



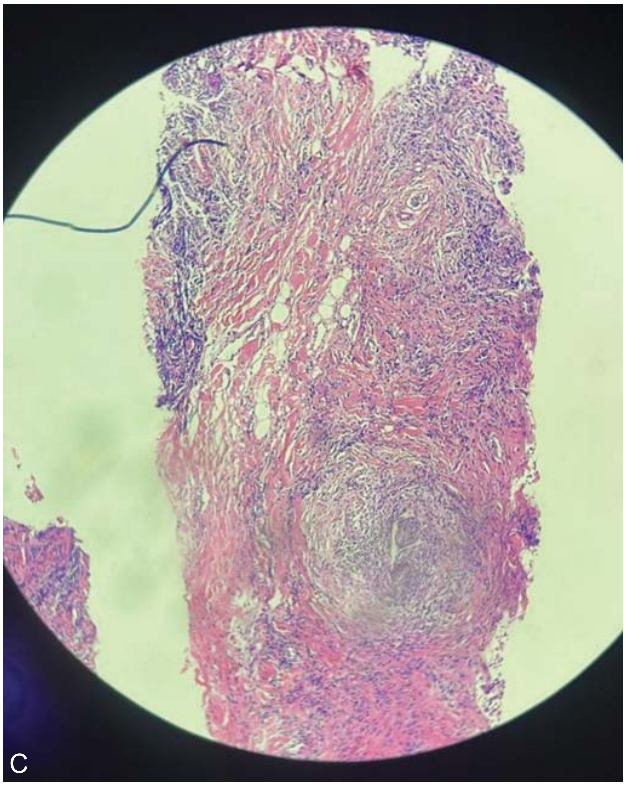
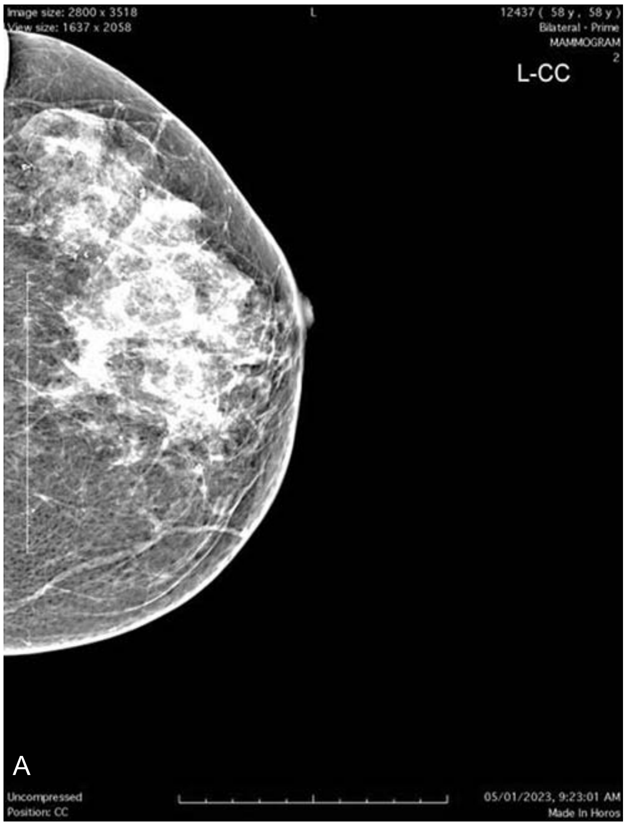
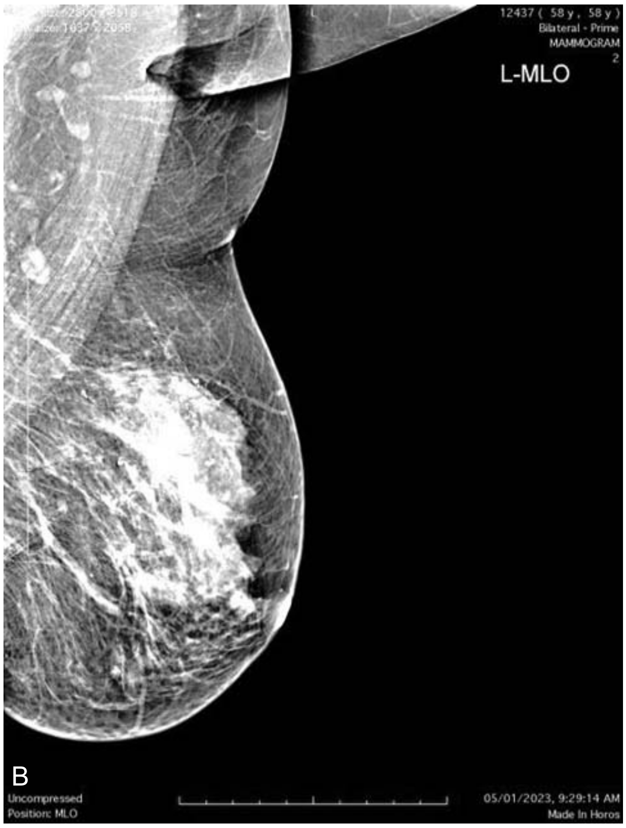


Figure-1: A & B Mammogram CC and MLO views.Heterogeneously dense breast parenechyma (Density score=3) with a soft tissue density mass with speculated margins and surrounding architectural distortion in upper inner quadrant near retromammary space. Foci of micro calcification is also noted. **C.** Biopsy showed invasive carcinoma.





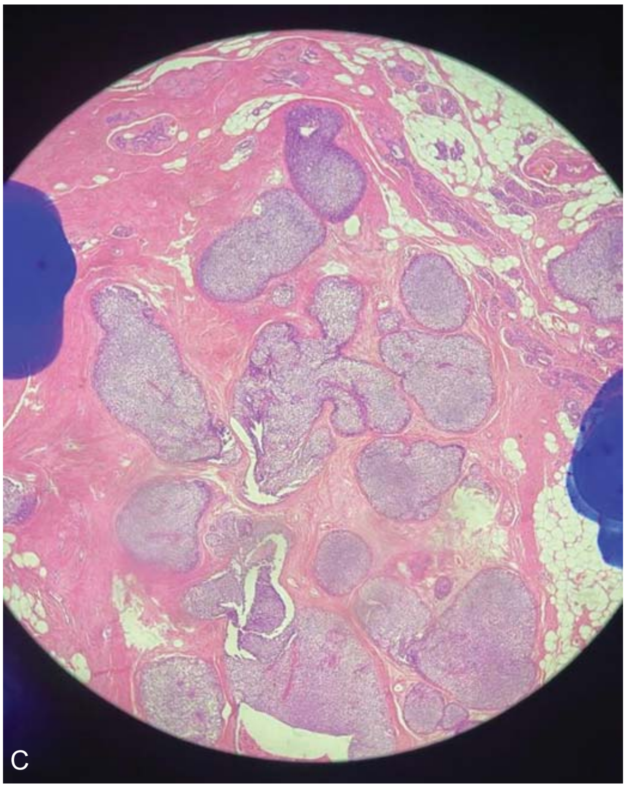
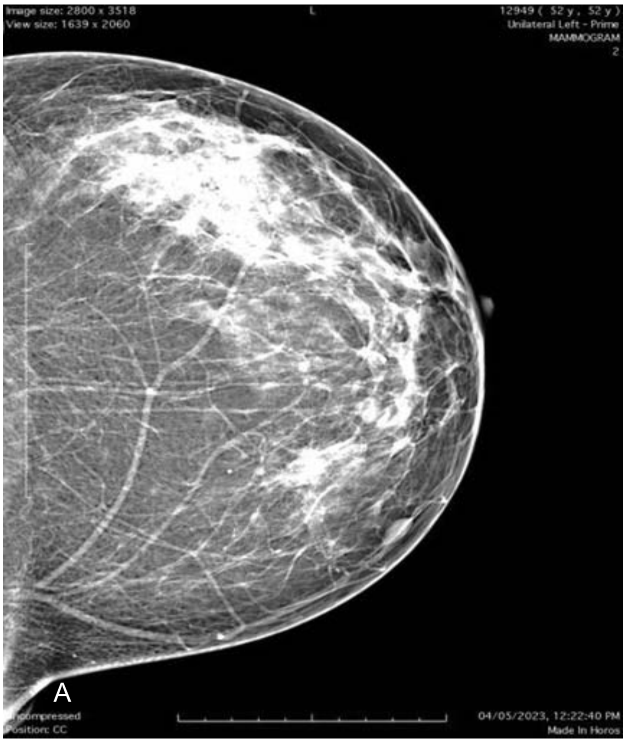


Figure 2: A & B Mammogram CC and MLO views. Heterogeneously dense breast parenchyma is noted (Density score=3). Area of asymmetric parenchymal density is seen in upper outer quadrant with few clusters of macro and micro calcification. **C.** Biopsy showed low grade ductal carcinoma in situ.



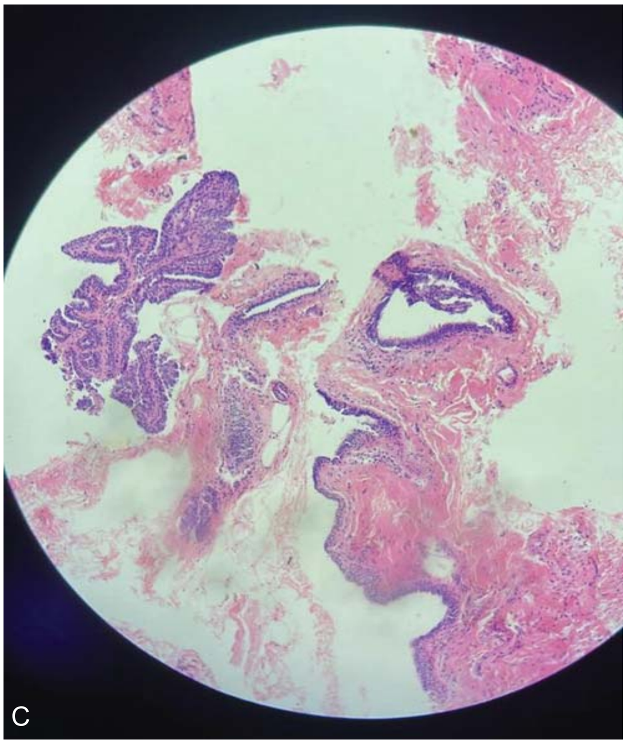
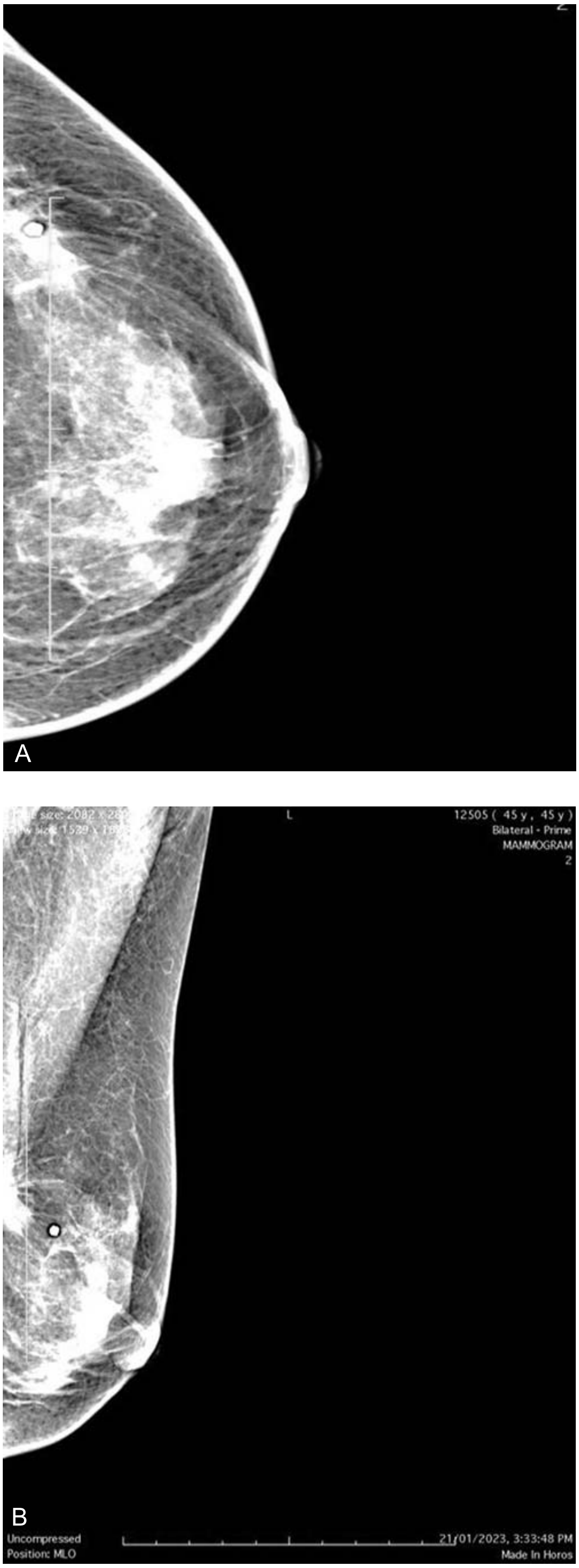


Figure 3: A & B Mammogram CC and MLO views. Heterogeneously dense breast parenechyma is noted (Density score=3) with a soft tissue density mass with speculated margins in upper outer quadrant near retromammary space. Another seen in retroareolar region. Few rounded axillary lymph nodes with loss of fatty hila are seen. Some of them show irregular margins. **C.** Biopsy showed intraductal papilloma.



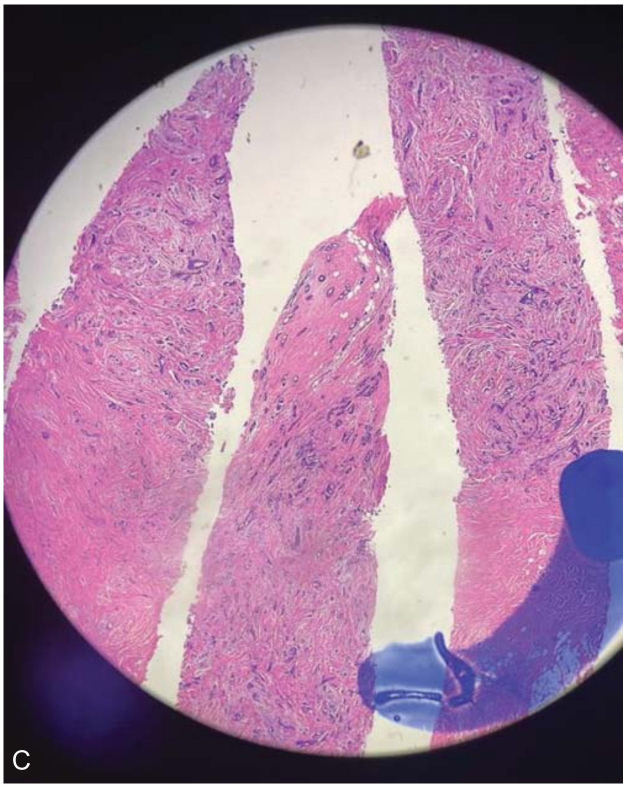


Figure 4: A & B Mammogram CC and MLO views.Heterogeneously dense breast parenchyma in noted (Density score=3) with a soft tissue density in lower inner quadrant. **C.** Biopsy showed invasive breast carcinoma.

Results

To check normality of quantitative variables The Kolmogorov-Smirnov test was applied. The study results showed that age, parity, duration of disease, height, weight, BMI, systolic blood pressure, and diastolic blood pressure, were not follow normal distribution so median with interquartile range were reported. Hence the median (IQR) with range of age, parity, duration of disease, height, weight, BMI, systolic blood pressure, and diastolic blood pressure were 47(13) with (27-83) years, 2(2) with (1-6), 15(15) with (3-36) weeks, 5.8(0.4) with (5.1-6.0) meters, 71.5(28) with (50-99) kg, 23.2(5.7) with (19.1-33.7) kg/m^2, 110(20) with (90-130) mmHg, and 65(10) with (50-91) mmHg. The results are also presented in (Tab.1).

The ethnicity was found as 32(29.6%) sindhi, 36 (33.3%) punjabi, 21(19.4%) Pashto, and 19(17.6%) balochi. The place of residence of the patients were found as 58(53.7%) lives in urban areas while 50(46.3%)

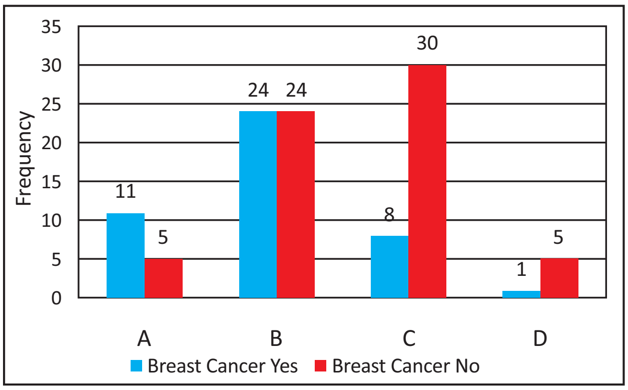
	Median (IQR)	Minimum	Maximum	Range
Age in years	47(13)	27	83	56
Parity	2(2)	1	6	5
Duration of disease (weeks)	15(15)	3	36	33
Height (meters)	5.8(0.4)	5.1	6	0.9
Weight (Kg)	71.5(28)	50	99	49
Body Mass Index (Kg/m^2)	23.2(5.75)	19.1	33.7	14.5
Systolic Blood Pressure (mmHg)	110(20)	90	130	40
Diastolic Blood Pressure (mmHg)	65(10)	50	91	41

Table 1: Descriptive statistics of demographic characteristics.

were lives in rural areas. There were 68(63%) females who had pre menopause and 40(37%) had post menopause. The comorbidities were noted as 42(38.9%) were obese, 24(22.2%) were diabetic, 16(14.8%) were hypertensive and 7(6.5%) were smokers. Those women who were on breast feeding were 41(38%). The history of breast cancer was found in 28(25.9%) cases. The breast cancer was found in 44(40.7%) females. The categories of BI-RADS were found as 16(14.8%) had category A, 48(44.4%) had category B, 38(35.2%) had category C and 6(5.6%) had category D, as presented in (Tab.2). The frequency distribution of breast cancer according to BI-RADS categories are presented in (Graph 1).

	n(%)		n(%)
Ethnicity		**Breastfeeding**	
Sindhi	32(29.6)	Yes	41(38)
Punjabi	36(33.3)	No	67(62)
Pushto	21(19.4)	**History of Breast Cancer**	
Balochi	19(17.6)	Yes	28(25.9)
Residence		No	80(74.1)
Urban	58(53.7)	**Breast Cancer**	
Rural	50(46.3)	Yes	44(40.7)
Menopausal status		No	64(59.3)
Pre	68(63)	**Categories of BIRADS**	
Post	40(37)	A	16(14.8)
Comorbids		B	48(44.4)
Diabetes	24(22.2)	C	38(35.2)
Hypertension	16(14.8)	D	6(5.6)
Obesity	42(38.9)		
Smoking	7(6.5)		

Table 2: Frequency distribution of demographic, comorbidies, and clinical characteristics.



Graph 1: Frequency distribution of breast cancer with the BI-RADS categories.

The study results found statistically insignificant differences of age (p=0.550), body mass index (p=0.891), duration of disease (p=0.966), systolic blood pressure (p=0.713) and diastolic blood pressure (p=0.207) with respect to categories of BI-RADS. However, statistically significant difference was observed in parity (p=0.005). More than 50% patients lives in urban areas who had category A, category B and category C of BI-RADS. Most of the women in all four categoryof BI-RADS had pre menopause as compared to post menopause. The history of breast cancer was found in 3(18.8%) cases of category A, 16(33.3%) of cases of category B, 6(15.8%) of category C and 3(50%) cases of category D. We found statistically insignificant association of residence (p=0.734), menopausal status (p=0.828), obesity (p=0.481), breast feeding (p=0.685) and history of breast feeding (p=0.119) with categories of BI-RADS. The breast cancer was noted in 5(31.3%) cases of category A, 24(50%) of cases of category B, 30(78.9%) of cases of category C and 5(83.3%) cases of category D, the breast cancer was significantly associated with the categories of BI-RADS. (p=0.002), as presented in (Tab.3).

Discussion

Early detection has a major impact on the likelihood of a complete recovery from breast cancer, which is why yearly mammography screening is essential.[21] Annual breast cancer screening is crucial for identifying people with asymptomatic breast cancer and improving outcomes.[10] Women with an increasing percentage

	Category of B-Irads				P-value
	A	B	C	D	
Median (IQR)					
Age in years	49.5(6)	46(15)	45.5(8)	48(17)	0.550**
Parity	3(2)	2(1)	2.50(2)	2(3)	0.005*
Body Mass Index (Kg/m^2)	21.8(9.8)	23.2(6.18)	23.1(5.7)	23.1(9.2)	0.891**
Duration of disease (weeks)	16(24)	15(12)	14.5(17)	11(22)	0.966**
Systolic Blood Pressure (mmHg)	110(27.5)	110(20)	110(20)	110(15.5)	0.713**
Diastolic Blood Pressure (mmHg)	65(17.5)	70(10)	70(12.5)	60(13)	0.207**
Frequency (%)					
Ethnicity					
Sindhi	5(31.3)	13(27.1)	13(34.2)	1(16.7)	0.611**
Punjabi	4(25)	20(41.7)	11(28.9)	1(16.7)	
Pushto	4(25)	7(14.6)	9(23.7)	1(16.7)	
Balochi	3(18.8)	8(16.7)	5(13.2)	3(50)	
Residence					
Urban	9(56.3)	25(52.1)	22(57.9)	2(33.3)	0.734**
Rural	7(43.8)	23(47.9)	16(42.1)	4(66.7)	
Menopausal status					
Pre	10(62.5)	28(58.3)	26(68.4)	4(66.7)	0.828**
Post	6(37.5)	20(41.7)	12(31.6)	2(33.3)	
Diabetes					
Yes	4(25)	12(25)	7(18.4)	1(16.7)	0.910**
No	12(75)	36(75)	31(81.6)	5(83.3)	
Hypertension					
Yes	1(6.3)	8(16.7)	7(18.4)	0(0)	0.660**
No	15(93.8)	40(83.3)	31(81.6)	6(100)	
Smoking					
Yes	1(6.3)	3(6.3)	1(2.6)	2(33.3)	0.090**
No	15(93.8)	45(93.8)	37(97.4)	4(66.7)	
Obesity					
Yes	9(56.3)	18(37.5)	13(34.2)	2(33.3)	0.481**
No	7(43.8)	30(62.5)	25(65.8)	4(66.7)	
Breastfeeding					
Yes	4(25)	19(39.6)	16(42.1)	2(33.3)	0.685**
No	12(75)	29(60.4)	22(57.9)	4(66.9)	
History of Breast Cancer					
Yes	3(18.8)	16(33.3)	6(15.8)	3(50)	0.119**
No	13(81.3)	32(66.7)	32(84.2)	3(50)	
Breast Cancer					
Yes	5(31.3)	24(50)	30(78.9)	5(83.3)	0.002*
No	11(68.8)	24(50)	8(21.1)	1(16.7)	

Kruskal Wallis test was used for comparison of median (IQR).
Chi-square test is used for categorical variables.
P-values <0.05 is considered as significant.

Table 3: Association of demographic and clinical factors with categories of BI-RADS.

of fibroglandular tissue of 75% or more typically show a higher risk of developing breast cancer by 4 to 6 folds compared to those with an increasing fatty component in mammograms because mammogram films typically combine both non-radiolucent areas and radiolucent areas representing a mixture of both fibroglandular tissue and fat.[22] This study was conducted to ascertain if mammographic breast density is related to the risk of breast cancer.

The US Food and Drug Administration proposed modifications to the Mammography Quality Standards Act in March 2019 to make it required to inform patients' physicians about their breast density.[23,24] As more sophisticated and modern methods of measuring breast density are created.[24] In particular, among women aged 75 or older, for whom screening mammography standards are still uncertain, examination of the proliferation of such advances among older women with a goal of developing individualised screening techniques would be crucial. Implementing life expectancy-based screening strategies that take breast cancer risk into account is becoming more crucial as the population in the US and around the world ages. This will allow older women who are likely to benefit from screening to continue, and the risk of harms like overdiagnosis and overtreatment can be reduced among those unlikely to benefit.[26,27]

According to a research of the Vermont population from the BCSC registry that used the BI-RADS density classifications, premenopausal women have a higher relative risk of breast cancer than women in the post-menopausal stage if they have exceptionally dense breasts.[28] According to Ahmadinjad et al.,[29] patients with thick breasts are more likely to develop cancer (61.2%) than those with low breast densities (37.3%). (P= 0.007) asstated in another study, as compared to groups ACR A and ACR B, groups ACR C and ACR D have a higher frequency of breast cancer.[29]

One study included 1500 cases of breast cancer that had been pathologically confirmed. Depending on the frequency of instances that tested positive for carcinoma, the cases were arranged as follows: D (13.7%), C (3.3%), B (2.7%), and A (2.2%).[23] Numerous cohort studies have noted the correlation between rising breast mammographic density and a higher risk of breast cancer in women.[30] According to Byrne et al., women with breast densities of 75% or above had a four-fold increased chance of developing breast cancer compared to those with mammographic densities of 0%.[31]

A study by Advani SM et al.[23] adds to the body of research by demonstrating that, among women aged 65 to 74 and those aged 75 or older, density remained related with a slight increase in breast cancer risk despite a decline in breast density associated with ageing. After adjustment for BMI and other variables, the author found that the link between the BI-RADS breast density categories and breast cancer was statistically significant. Breast density was associated with increased breast cancer risk among women aged 65 and older, regardless of BMI, and among those aged 75 and older with a BMI of 25 or higher, according to a cohort study of the relationship between BI-RADS breast density categories and the risk of invasive breast cancer by BMI level and age.[10]

The results are in line with those of a prior study[32] of women between the ages of 40 and 74 that showed relationships between age and the majority of the breast cancer risk variables examined, with the relationship between age and BI-RADS breast density falling with age.[33,34] Given that higher breast density, as defined by the BI-RADS, continues to be a risk factor for breast cancer in older women,[32,35] information on breast density and life expectancy may be useful in clinical decision-making when determining whether screening should continue after age 75.[34]

After adjusting for a patient's BMI, Lam et al.[36] discovered that the risk of breast cancer increased in association with increased breast density and vice versa. However, the study only included a small number of women aged 75 or older, and the estimates did not account for factors linked to breast cancer. Similar to this, Vacek et al.37 detected an increased risk of breast cancer in conjunction with increasing breast density in a cohort of 61,844 women, of whom 4137 (6.7%) were 75 years or older, but did not stratify findings based on age. Maskarinec et al. also found that women with breast densities greater than 50% are 3.6 times more likely to get breast cancer than women with densities less than 10%.[38]

According to research results, having thick breasts at birth and having them endure throughout time are both independent risk factors for developing breast cancer.[39] The same study's conclusion that mammographic density at baseline is highly related to breast cancer risk is consistent with the findings of numerous earlier investigations.[40,41]

Age, menopausal state, and changes in body weight would have had an impact on mammographic density during the interval between the baseline mammography and the cancer diagnosis, with subsequent effects on the risk of breast cancer.[42] In one study,[39] when changes in dense breasts, BMI, and other covariates during follow-up were added as time-varying covariates, the relationships between dense breasts and breast cancer risk were consistently detected and were even slightly greater.

Additionally, several studies found no link between variations in mammographic density and the risk of breast cancer.[43-45] Azam et al.'s cohort study of 43,810 Swedish women, aged 30 to 79, found no correlation between mammographic density changes and breast cancer risk, but they did observe a non-significant tendency towards a difference in risk among perimenopausal women (those aged 40 to 49).[9] In two case-control investigations, conducted on predominantly postmenopausal women, Maskarinec et al.[44] and Vachon et al.[45] found no correlations between variations in the % mammographic density with the risk of breast cancer. Additionally, breast density varied with age in premenopausal women without increasing breast size, whereas postmenopausal women's breast size also increased with age.[46] As a result, premeno-pausal and postmenopausal women may experience various variations in percentage density and their underlying causes.[39]

Conclusion

According to this study, identifying breast cancer risk factors can be done by using the BI-RADS classification of rising breast density. The study's findings lead us to the conclusion that mammography-detected greater breast tissue density is significantly associated with our population's increased risk of breast cancer.

Conflict of Interest: None

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