World Cancer Research Journal WCRJ 2022; 9: e2451

RELATIONSHIP OF BREAST CANCER TYPES WITH TISSUE DENSITY AND PATIENT AGE, RIYADH, SAUDI ARABIA, 2012-2020

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Abstract – *Objective:* *This study aims to characterize the types of breast cancer among women in Riyadh and evaluate the association between breast cancer types, breast tissue density, and age.*

Patients and Methods: *This cross-sectional study included 524 female cancer patients aged 18 years with histologically or radiologically confirmed diagnoses from 2012 to 2020. Age, breast density, cancer type, TNM staging, radiographic grade, presence or absence of calcification, histological grading, and surgery type were extracted from the cancer program's electronic reporting system. .*

Results: *We observed a significant association between type of cancer and age (p=0.006), stage of cancer (p<0.0001), histologic grade (p=0.004), and presence of calcifications (p=0.000). While the younger patients aged <50 had heterogeneously dense breasts, scattered areas of fibro glandular density were common among older patients (p=0.004). Multinomial logistic regression analysis showed that the odds of patients having ductal carcinoma were 11 times higher in patients with Grade I cancer (p=0.011) and three times higher in those with Grade II cancer (p=0.021). The absence of calcifications decreased the odds of ductal carcinoma in situ (p=0.000).*

Conclusions: *We observed a significant relationship between breast cancer type with age and stage of cancer. Although breast density was associated with age, it was independent of cancer type.*

KEYWORDS: *Breast cancer, Calcifications, Cancer type, Density, Tumor grade.*

INTRODUCTION

Breast cancer is amongst the most frequent neoplasms affecting women worldwide. In 2020, with an estimated incidence of 2.3 million cases, breast cancer surpassed the worldwide lung cancer rates. It is the seventh leading cause of cancer-related deaths, with 685,000 new deaths in 2020[1]. In Saudi Arabia in 2020, with 3954 new cases, breast cancer accounted for 29% of all cancers reported among women of all ages and 14.2% of all cancers recorded among Saudi citizens. According to the International Agency for Research on Cancer, the age-standardized incidence rate and mortality rate of breast cancer were 28.8 and 8.9 per 100,000 women, respectively[2,3].

Cancer incidence adversely affects the physical, social, and mental well-being of patients and their family members. Most incidences affect women, mostly in less developed countries. Breast cancer incidence varies significantly over the world, ranging from 27 incidences per 100,000 people in East Asia and the center of Africa to 96 instances per 100,000 people in Western Europe[4]. With the advent of sophisticated and effective therapies in recent years, the success rate of breast cancer is relatively high. Early cancer detection plays a significant factor in successful treatment. Amongst the various cancer detection projects, the Breast Cancer Early Detection Project of Saudi Arabia focuses on educating women about the risk factors of breast

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DOI: 10.32113/wcrj_202212_2451

cancer and encourages women aged 40 and above to undergo regular yearly cancer screening[5].

Although breast cancer was perceived to be common in postmenopausal women, an increasing trend is reported in women below 40 years of age. The increased occurrence in the younger population is related to endogenous hormonal changes, exogenous hormone exposure, dietary changes, and late pregnancy[6]. A positive relationship between increased breast size, breast density, and breast cancer risk has also been reported. Also, breast cancer prevalence and mortality rate are significantly dependent on Human Development Index (HDI) globally. Reports also show the incidence of breast cancer and risk of death are related to the obesity[7]. Females with large breasts are four to six times more likely to get breast cancer. A heterogeneously thick and highly dense breast has a higher relative risk of 1.2 and 2.1 times, respectively, than a breast with an average density[8]. However, previous studies have suggested that most of the missed cancer diagnosis is in patients with dense breasts.

In addition to thorough clinical examination, ultrasound and mammography are recommended as the gold standard procedures for breast cancer screening. However, in women with increased breast density and larger breasts, tumors on radiographs can be masked, while they may appear as cancer on mammography. Therefore, the association between increased breast density and increased cancer risk is yet to be elucidated. The Breast Imaging Reporting and Data System (BI-RADS) is widely used to categorize breast lesions based on density as observed on mammography, ultrasound, and MRI[9]. This allows early referral of suspicious lesions for further investigations and aids in early diagnosis.

Although studies on the relationship between breast density, age, and mammographic type of lesion have been conducted in western countries[10] and some parts of Asia[11,12], limited studies have been conducted in Saudi Arabia. Therefore, the present study was conducted to characterize the types of breast cancer among women in Riyadh and to evaluate the association between breast cancer types, breast tissue density, and age. The findings of the present study may help identify risk factors of breast cancer, support early detection of breast lesions in high-risk patients in Saudi Arabia, and facilitate the identification of reasons for missed mammographic diagnosis.

MATERIALS AND METHODS

This was a cross-sectional descriptive study of data collected from the Breast Cancer Program, General Administration of Health Programs and Chronic Diseases, and Ministry of health between 2012 and 2020 in Riyadh city. Data of patients from King Fahad Medical City, Riyadh, were collected. All female patients (Saudi and non-Saudi) aged ≥18 years treated in MOH hospitals in Riyadh with histologically or radiologically confirmed breast cancer diagnoses between 2012 and 2020 were included. Patients of <18 years of age without both histologic and radiographically confirmed breast cancer diagnosis were excluded.

Ethical Approval

The study was approved by the Central Institutional Review Board, Ministry of Health. IRB Log No: 22- 16 M. Since this was a retrospective data analysis, patients' informed consent was deemed unnecessary and was omitted.

Data Collection

All data were anonymized, and the following data were extracted; age, the size of the lesion (≤5 mm to >50 mm), presence or absence of calcification, breast density based on BI-RADS classification (A: Almost entirely fatty, B: Scattered areas of fibro glandular density, C: Heterogeneously dense, and D: Extremely dense), diagnosis based on BI-RADS classification (category 0: incomplete diagnosis, 1: negative 2: benign, 3: probably benign, 4: suspicious abnormality, 5: highly suspicious of malignancy, and 6: known biopsy-proven malignancy), TNM staging, histological grading (Grade I: well differentiated, Grade II: moderately differentiated, and Grade III: poorly differentiated), cancer type (Ductal carcinoma *in situ*, Lobular carcinoma *in situ*, Invasive ductal carcinoma, Invasive lobular carcinoma, and combination tumors), and type of surgery (lumpectomy, mastectomy, or both).

Statistical Analysis

The recorded data were compiled and entered in Microsoft Excel 2010 and then exported to the data editor page of IBM SPSS version 23 (SPSS Inc., Armonk, NY, USA). The Chi-square test was applied to compare the proportions of categories among the groups. Multinomial logistic regression analysis was applied with the type of cancer as the dependent variable. For all tests, the confidence interval and p-value were set at 95% and ≤ 0.05, respectively.

RESULTS

A total of 524 patients were included in the study. The majority (97%) were Saudi nationals. Overall, the mean (SD) age of patients was 53.51(8.89) years, with a majority in the age group of 41-60

TABLE 1. Baseline characteristics of study participants.

Demographic Parameters		**Cases**	**%**
Nationality	Saudi	510	97%
	Non-Saudi	3	1%
	Not-Mention	11	2%
Age Group	= < 40	26	5%
	41-50	185	35%
	51-60	207	40%
	61-70	88	17%
	71 and above	18	3%
Breast Density	A	151	29%
	B	175	33%
	C	151	29%
	D	20	5%
	Not Examined	27	5%
Breast Cancer Type	Ductal carcinoma in situ (DCIS)	64	12%
	Invasive ductal carcinoma (IDC)	173	33%
	Invasive lobular carcinoma (ILC)	21	4%
	IDC + DCIS	201	38%
	ILC + LCIS	22	4%
	OTHERS	15	3%
	Missing	28	5%
Grade	I	39	39%
	II	251	48%
	III	141	27%
	Not-Examined	93	18%

years (75%). Type B breast density, characterized by scattered areas of fibro glandular density, was the most common type reported in 33% of patients, followed by type C (heterogeneously dense) and type A (almost entirely fatty) in 29% of patients each. Invasive ductal carcinoma and ductal carcinoma were reported in 33% and 12% of patients, respectively. Around 38% of patients had a combination of DCIS and IDC. Almost half of the patients (48%) had grade II breast cancer. Baseline characteristics are summarized in Table 1.

Table 2 shows a comparative assessment between age and type of cancer among different age groups. A combination of ductal carcinoma *in situ* and inva-

TABLE 2. Comparative assessment of the type of cancer according to age.

Type of cancer	***Age groups (years) n (%)***					***p-value***	***Total n (%)***
	<40	***41-50***	***51-60***	***61-70***	***71 and above***		
Ductal carcinoma in situ	3 (12.5)	26 (14.8)	25 (12.8)	9 (11.1)	1 (5.6)		64 (12.9)
Lobular carcinoma in situ	0	0	0	0	0		0
Invasive ductal carcinoma	10 (41.7)	60 (34.1)	75 (38.3)	23 (28.4)	5 (27.8)		173 (34.9)
Invasive lobular carcinoma	0	7 (4)	9 (4.6)	4 (4.9)	1 (5.6)		21 (4.2)
IDC + DCIS	11 (45.8)	71 (40.3)	74 (37.8)	35 (43.2)	9 (50)		200 (40.4)
ILC + DCIS	0	0	2 (1)	0	1 (5.6)	0.006*	3 (0.6)
ILC + IDC	0	0	1 (0.5)	0	0		1 (0.2)
ILC +LCIS	0	5 (2.8)	8 (4.1)	9 (11.1)	0		22 (4.4)
IDC + ILC + DCIS	0	0	0	0	1 (5.6)		1 (0.2)
ILC + LCIS + DCIS	0	1 (0.6)	0	0	0		1 (0.2)
Others	0	6 (3.4)	2 (1)	1 (1.2)	0		9 (1.8)
Total	24 (4.8)	176 (35.6)	196 (39.6)	81 (16.4)	18 (3.6)		495 (100)

Test applied: Chi-square test, *indicates statistically significant association; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*.

TABLE 3. Comparative assessment of the type of cancer according to breast density.

Type of cancer	Breast density n (%)				p-value	Total n (%)
	Almost entirely fatty	Scattered areas of fibroglandular density	Hetero-geneously dense	Extremely dense		
Ductal carcinoma in situ	24 (16)	21 (12.7)	11 (7.9)	4 (21.1)	0.804	60 (12.6)
Lobular carcinoma in situ	0	0	0	0		0
Invasive ductal carcinoma	49 (32.7)	60 (36.1)	50 (35.7)	8 (42.1)		168 (35.3)
Invasive lobular carcinoma	4 (2.7)	8 (4.8)	6 (4.3)	3 (15.8)		21 (4.4)
IDC + DCIS	61 (40.7)	65 (39.2)	62 (44.3)	4 (21.1)		192 (40.3)
ILC + DCIS	2 (1.3)	0	1 (0.7)	0		3 (0.6)
ILC + IDC	0	1 (0.6)	0	0		1 (0.2)
ILC +LCIS	8 (5.3)	7 (4.2)	6 (4.3)	0		21 (4.4)
IDC + ILC + DCIS	0	0	0	0		0
ILC + LCIS + DCIS	0	0	1 (0.7)	0		1 (0.2)
Others	2 (1.3)	4 (2.4)	3 (2.1)	0		9 (1.9)
Total	150 (31.5)	166 (34.9)	140 (29.4)	19 (4)		476 (100)

Test applied: Chi-square test; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*.

sive ductal carcinoma was the common breast cancer type observed in approximately 40-50% of patients in individual age categories. The association between age and type of cancer was statistically significant (p=0.006). The density of breast tissue was extremely dense in invasive ductal carcinoma (42.1%), whereas fatty (40.7%), scattered areas of fibro glandular density (39.2%), and heterogeneous density (44.3%) were common among patients with combinations of ductal carcinoma *in situ* and invasive ductal carcinoma. The association was not significant (p=0.804; Table 3). Table 4 summarizes the association between the cancer type and cancer stage. At stage 0, all cancers (100%) were Ductal carcinoma *in situ*. Approximately half of the patients with stages I, IIA, IIIC, and IV had a combination of IDC and DCIS. The association was significant (p<0.0001).

During an ultrasound examination, the size of the breast lesion was 21 to 50 mm in diameter for most of the patients (53%), followed by 11-20 mm in

TABLE 4. Comparative assessment of the type of cancer according to the stage of cancer.

Type of cancer	Stage of cancer n (%)								p-value	Total n (%)
	0	I	IIA	IIB	IIIA	IIIB	IIIC	IV		
Ductal carcinoma *in situ*	5 (100)	12 (12.5)	3 (3.4)	2 (2.1)	1 (1.6)	0	0	0	<0.0001*	23 (5.9)
Lobular carcinoma *in situ*	0	0	0	0	0	0	0	0		0
Invasive ductal carcinoma	0	22 (22.9)	32 (36.4)	44 (46.8)	24 (38.1)	10 (43.5)	3 (27.3)	6 (50)		141 (36)
Invasive lobular carcinoma	0	3 (3.1)	4 (4.5)	3 (3.2)	6 (9.5)	1 (4.3)	0	0		17 (4.3)
IDC + DCIS	0	55 (57.3)	40 (45.5)	37 (39.4)	26 (41.3)	9 (39.1)	6 (54.5)	6 (50)		179 (45.7)
ILC + DCIS	0	1 (1)	1 (1.1)	1 (1.1)	0	0	0	0		3 (0.8)
ILC + IDC	0	0	0	1 (1.1)	0	0	0	0		1 (0.2)
ILC +LCIS	0	2 (2.1)	5 (5.7)	6 (6.4)	4 (6.3)	2 (8.7)	2 (18.2)	0		21 (5.4)
IDC + ILC + DCIS	0	0	1 (1.1)	0	0	0	0	0		1 (0.3)
ILC + LCIS + DCIS	0	0	0	0	1 (1.6)	0	0	0		1 (0.3)
Others	0	1 (1)	2 (2.3)	0	1 (1.6)	1 (4.3)	0	0		5 (1.3)
Total	5 (1.3)	96 (24.5)	88 (22.4)	94 (24)	63 (16.1)	23 (5.9)	11 (2.8)	12 (3.1)		392 (100)

Test applied: Chi-square test, *indicates statistically significant association; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*.

TABLE 5. Comparative assessment of the type of cancer according to size US.

Type of cancer	*Size US (mm) n (%)*					*p-value*	*Total n (%)*
	< 5	*5-10*	*11-20*	*21-50*	*>50*		
Ductal carcinoma in situ	6 (50)	7 (16.3)	9 (7.3)	20 (8.5)	1 (3)	0.804	43 (9.6)
Lobular carcinoma in situ	0	0	0	0	0		0
Invasive ductal carcinoma	3 (25)	12 (27.9)	37 (30.1)	96 (40.9)	13 (39.4)		161 (36.1)
Invasive lobular carcinoma	0	0	6 (4.9)	9 (3.8)	4 (12.1)		19 (4.3)
IDC + DCIS	3 (25)	18 (41.9)	62 (50.4)	96 (40.9)	11 (33.3)		190 (42.6)
ILC + DCIS	0	0	1 (0.8)	2 (0.9)	0		3 (0.7)
ILC + IDC	0	0	0	1 (0.4)	0		1 (0.2)
ILC +LCIS	0	5 (11.6)	6 (4.9)	7 (3)	2 (6.1)		20 (4.5)
IDC + ILC + DCIS	0	0	0	0	1 (3)		1 (0.2)
ILC + LCIS + DCIS	0	0	1 (0.8)	0	0		1 (0.2)
Others	0	1 (2.3)	1 (0.8)	4 (1.7)	1 (3)		7 (1.6)
Total	12 (31.5)	43 (34.9)	123 (29.4)	235 (52.7)	33 (7.4)		446 (100)

Test applied: Chi-square test; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*.

diameter (27%). The size of invasive ductal carcinoma in different types of breast cancers was comparable (p=0.804; Table 5, Figure 1, and Figure 2).

Moderately differentiated cancer (Grade II) was common among all types of cancers, followed by poorly differentiated cancer (Grade III; p=0.004; Table 6). Positive calcifications were commonly reported in patients with ductal carcinoma *in situ* (22.6%) and a combination of ductal carcinoma *in situ* and invasive ductal carcinoma (48.9%). There was a significant difference between the presence and absence of calcifications among different cancer types (p=0.000; Table 7).

Overall, very few participants (4%) had extremely dense breasts. Heterogeneously dense breasts were common (53%) among younger patients up to the age of 50. In older age groups, the majority of cancer patients (67%) had scattered areas of fibro glandular density. The difference was statistically significant (p=0.004; Table 8, Figure 3). We graded the patients according to BI-RADS category 0 to 6, as shown in Table 9. Over half of the patients (53%) were graded as 0 (incomplete diagnosis), and 42% were categorized as grade 5, suggestive of highly suspicious malignancy.

Table 10 shows multinomial logistic regression with the type of cancer as the dependent variable and grade and calcification as independent variables. To achieve a model fit, predictor variables age and stage needed to be removed. The analysis revealed that those with Grade I cancer had 10.9 times significantly (p=0.011) greater odds of having ductal

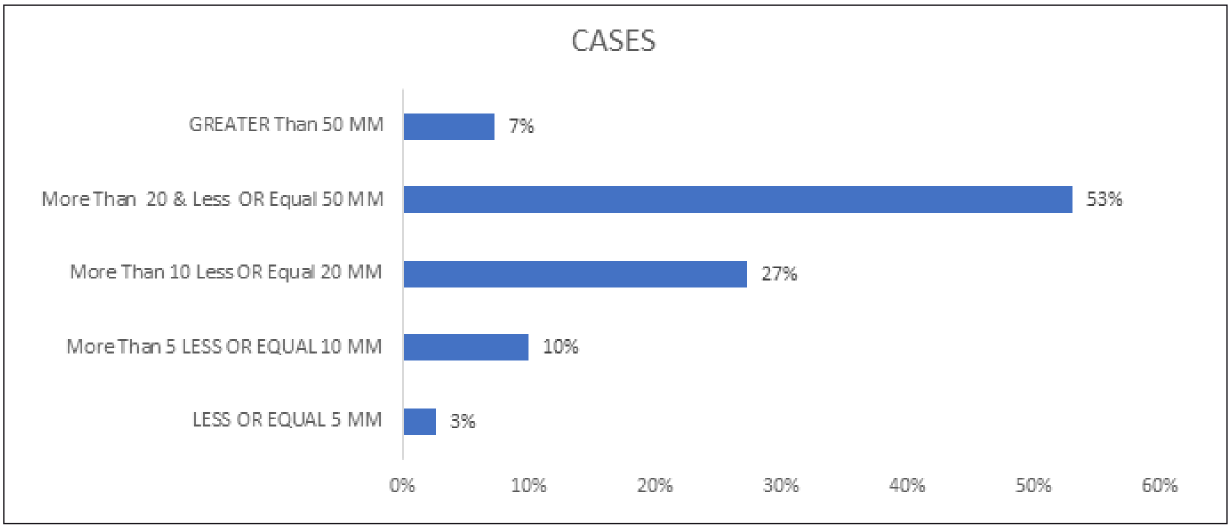

Fig. 1. Distribution of breast cancer cases according to the size of lesion in ultrasound.

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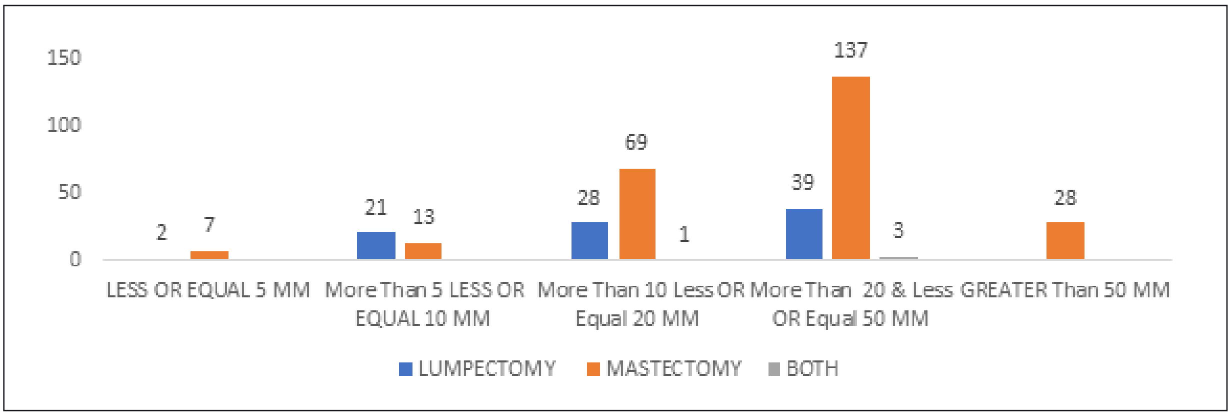

Fig. 2. Distribution of breast cancer cases according to the size of cancer and type of surgery.

carcinoma *in situ* than those with Grade III cancer compared to other cancer types. Those with Grade II cancer had 3.2 times significantly (p=0.021) greater odds of having ductal carcinoma *in situ* than those with Grade III cancer compared to other cancer types. Those with no calcification had 0.1 times significantly (p=0.000) lesser odds of having ductal carcinoma *in situ* than those with calcification compared to other cancer types. Also, those with no calcification had 0.4 times significantly (p=0.019) lesser odds of having IDC+DCIS than those with calcification compared to other cancer types.

DISCUSSION

This limited nationwide study in Saudi Arabia assessed the relationship between breast cancer types, age, and breast tissue density. Our study comprised majorly of Saudi nationals over 40 years of age. Moderately differentiated invasive ductal carcinoma with scattered areas of fibroglandular density was the most common type of cancer observed in approximately one-third of the patients. A significant relationship between breast cancer types with age and cancer stage was observed. Although breast density was associated with age, it was independent of cancer type.

Additionally, we observed a significant association between TNM staging and the type of cancer. TNM Stage IIB was common among patients with invasive ductal carcinomas. Stage I was common among patients with ductal carcinoma *in situ*, a combination of ductal carcinoma *in situ*, and invasive ductal carcinoma. Grade I and Grade II cancer had 11 and 3 times greater odds of having Ductal Carcinoma *in situ*, respectively. Compared to well-differentiated tumors, moderately-poorly differentiated tumors had lower odds of high breast density. While a positive association

TABLE 6. Comparative assessment of the type of cancer according to grade.

Type of cancer	*Grade n (%)*			*p-value*	*Total n (%)*
	I	*II*	*III*		
Ductal carcinoma in situ	2 (5.1)	16 (6.4)	4 (2.8)	0.001*	22 (5.1)
Lobular carcinoma in situ	0	0	0		0
Invasive ductal carcinoma	11 (28.2)	79 (31.5)	77 (54.6)		167 (38.7)
Invasive lobular carcinoma	4 (10.3)	11 (4.4)	4 (2.8)		19 (4.4)
IDC + DCIS	16 (41)	121 (48.2)	54 (38.3)		191 (44.3)
ILC + DCIS	0	3 (1.2)	0		3 (0.7)
ILC + IDC	0	1 (0.4)	0		1 (0.2)
ILC +LCIS	4 (10.3)	17 (6.8)	0		21 (4.9)
IDC + ILC + DCIS	0	1 (0.4)	0		1 (0.2)
ILC + LCIS + DCIS	0	1 (0.4)	0		1 (0.2)
Others	2 (5.1)	1 (0.4)	2 (1.4)		5 (1.2)
Total	39 (9)	251 (58.2)	141 (32.7)		431 (100)

Test applied: Chi-square test, *indicates statistically significant association; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*.
Grade I: well-differentiated, Grade II: moderately differentiated, Grade III: poorly differentiated.

TABLE 7. Comparative assessment of type of cancer according to calcification.

Type of cancer	*Calcification n (%)*		*p-value*	*Total n (%)*
	Negative	*Positive*		
Ductal carcinoma in situ	7 (3)	53 (22.6)	0.000*	60 (12.7)
Lobular carcinoma in situ	0	0		0
Invasive ductal carcinoma	110 (46.4)	53 (22.6)		163 (34.5)
Invasive lobular carcinoma	15 (6.3)	3 (1.3)		18 (3.8)
IDC + DCIS	80 (33.8)	115 (48.9)		200 (40.4)
ILC + DCIS	1 (0.4)	2 (0.9)		3 (0.6)
ILC + IDC	1 (0.4)	0		1 (0.2)
ILC +LCIS	15 (6.3)	6 (2.6)		21 (4.4)
IDC + ILC + DCIS	0	1 (0.4)		1 (0.2)
ILC + LCIS + DCIS	0	1 (0.4)		1 (0.2)
Others	8 (3.4)	1 (0.4)		9 (1.9)
Total	237 (50.2)	235 (49.8)		472 (100)

Test applied: Chi square test, *indicates statistically significant association; IDC-Invasive Ductal Carcinomas; ILC-Invasive Lobular Carcinoma; DCIS-Ductal carcinoma *in situ*; LCIS-Lobular carcinoma *in situ*. Grade I: well-differentiated, Grade II: moderately differentiated, Grade III: poorly differentiated.

TABLE 8. Distribution of mammographic density by age groups.

Age group (years)	*Breast density n (%)*				*p-value*	*Total n (%)*
	Almost entirely fatty	*Scattered areas of fibroglandular density*	*Hetero-geneously dense*	*Extremely dense*		
< 40	5 (21.7)	3 (13)	14 (60.9)	1 (4.3)	0.004*	23 (4.6)
41-50	44 (25)	54 (30.7)	67 (38.1)	11 (6.2)		176 (35.4)
51-60	65 (33.5)	75 (38.7)	45 (23.2)	8 (4.1)		194 (39.03)
61-70	31 (35.6)	33 (37.9)	23 (26.4)	0		87 (17.5)
71 and above	6 (33.3)	10 (55.6)	2 (11.1)	0		18 (3.6)
Total	151 (30.3)	175 (35.1)	151 (30.3)	20 (4)		497 (100)

Test applied: Chi-square test, *indicates statistically significant difference.

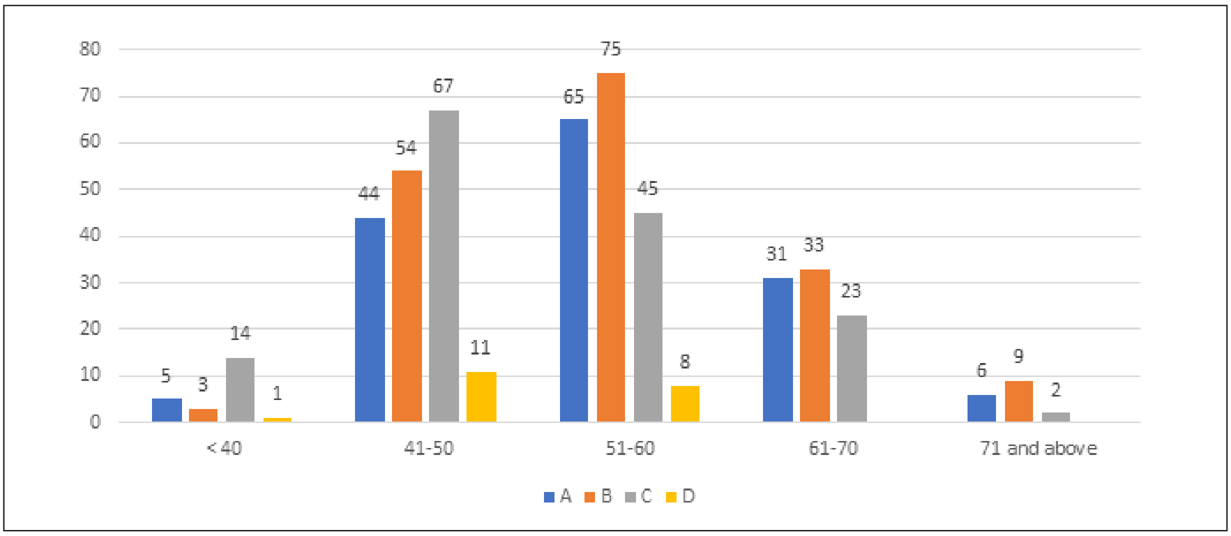

Fig. 3. Frequency of breast cancer cases according to breast density and age groups. A, B, C, and D denote the Breast Density.

TABLE 9. Distribution of breast cancer according to BI-RADS categories.

Category	Number of cases (%)	Diagnosis	Recommendations
0	272(53)	Incomplete	Your mammogram or ultrasound didn't give the radiologist enough information to make a clear diagnosis; follow-up imaging is necessary.
1	1(0)	Negative	There is nothing to comment on; routine screening is recommended.
2	4(1)	Benign	A definite benign finding; routine screening is recommended.
3	2(0)	Probably benign	Findings have a high probability of being benign, or noncancerous (>98%); six-month follow-up is recommended.
4	10(2)	Suspicious abnormality	Finding is not characteristic of breast cancer, but there is a possibility of malignancy, or cancer (3%–94%); biopsy should be considered.
5	214(42)	Highly suspicious of malignancy	Lesion that has a high probability of being malignant (>= 95%) is detected; take appropriate action as recommended by your healthcare provider.
6	7(1)	Known biopsy proven malignancy	Lesions known to be malignant are being imaged prior to definitive treatment; assure that treatment is completed.

between large tumors of over 2 cm with breast density has been reported previously[13], the results of our study did not show an association between the lesion size and breast cancer type. Mastectomy was the preferred procedure, followed by lumpectomy for larger lesions of >10 mm diameter and smaller diameter lesions, respectively, across all cancer types.

According to the results of a study by Bertnard *et al*[13], an increased risk of ductal carcinoma *in situ* is seen amongst younger age groups compared to patients of over 55 years of age. Although one-third of our study population comprised patients with invasive ductal carcinoma, a combination of ductal carcinoma and invasive ductal carcinoma was predominant among all age groups. Salem *et al*[14] reported 3.3% increased odds of breast cancer with age and 1.4% with increased breast density. In our study, very few participants (4%) had extremely dense breasts. Younger age groups up to 50 years old had the maximum proportion of heterogeneously dense breasts. In older age groups, the majority of cancer patients had scattered areas of fibro glandular density.

It is interesting to note that breast density and age are inversely related to each other, while age is positively related to breast cancer incidence. Boyd *et al*[15], in their model, explained the importance of breast tissue exposure than chronologic age as a measure to define breast cancer incidence. Breast tissue exposure is the area that is exposed to cumulative hormonal changes, risk factor exposures, and lifestyle changes throughout life[15]. Studies have suggested that breast cancer is more

TABLE 10. Multinomial logistic regression with type of cancer as a dependent variable.

	Ductal carcinoma in situ		Invasive Ductal Carcinoma		IDC+DCIS	
Independent variables	Odds ratio (95% Confidence Interval)	p-value	Odds ratio (95% Confidence Interval)	p-value	Odds ratio (95% Confidence Interval)	p-value
Grade						
I	10.861 (1.712-68.887)	0.011*	3.341 (0.693-16.099)	0.133	1.594 (0.317-8.021)	0.572
II	3.222 (1.197-8.678)	0.021*	1.781 (0.868-3.651)	0.115	1.053 (0.519-2.137)	0.886
III@	—		—		—	
Calcification						
Negative	0.059 (0.020-0.173)	0.000*	0.867 (0.420-1.791)	0.700	0.424 (0.207-0.866)	0.019*
Positive@	—		—		—	

@Reference category (Independent variables), others: Reference category (Dependent variable). *indicates statistically significant difference.

aggressive and associated with increased mortality in younger women[16,17]. These findings suggest that breast density and age are independent predictors of breast cancer, and they predict the accuracy of mammography screening[18].

Albeshan *et al*[19] reported low mammographic density in the majority of patients living in Riyadh, eliminating the need for additional imaging to detect breast cancers in Saudi women. On the contrary, the results of our study indicate that heterogeneous breast density is common in younger age groups, and densities scatter and become fibro glandular in nature as age advances. A similar inverse relationship between age and breast density is reported by Ji *et al*[12] in the Chinese population. Breast density decreases with increasing age, and hence, the identification of changes in breast tissues is optimal[10]. Interestingly we observed extremely dense breast tissues in patients with invasive ductal carcinoma (42.1%), whereas in patients with a combination of ductal carcinoma and invasive ductal carcinoma, heterogeneous (44.3%), fatty (40.7%), and scattered areas of fibro glandular density (39.2%) were predominant. Despite the categorization of density, based on BI-RADS's classification, over half of the patients' mammograms or ultrasounds did not give enough information to make a clear diagnosis suggesting an incomplete diagnosis, and only 42% of imaging was highly suspicious of malignancy.

Calcification of the breast is another important parameter of breast cancer screening. Previous studies have reported a positive correlation between dense breasts and calcification and a negative correlation with age[13,20]. In our study, positive calcifications were commonly reported in patients with ductal carcinoma *in situ* (22.6%) and a combination of IDC and DCIS (48.9%), suggesting a positive relationship between calcifications and breast cancer. However, the sensitivity of mammography and ultrasound in detecting microcalcifications is still debatable[21]. Further studies should be warranted to optimize the best screening modality for breast cancer screening.

Mammography has decreased sensitivity in cancer diagnosis, particularly in large breasts with dense tissues where the signs of cancer can be missed[11]. These heterogeneous dense patterns should be depicted in the mammographic findings for better clarity so that further investigations can be performed. Therefore, we believe, in this part of the country, mammography must be additionally supplemented with other screening modalities in younger women with heterogonous and extremely dense breast tissues. Digital breast tomosynthesis and magnetic resonance imaging modalities are beneficial screening modalities in patients with dense breasts[12].

BI-RADS categorization based on density is a widely accepted approach to reporting breast tissue using mammography, ultrasound, or MRI. Although grades 3 and 4 suggest low-risk breast lesions, uncertainty in the diagnosis often leads to biopsies leading to additional cost and psychological burdens on patients and their families. Therefore, a better imaging modality that clearly differentiates between benign and malignant lesions must be incorporated into screening programs. The dynamic contrast-enhanced, diffusion-weighted, short inversion recovery and T2-weighted sequences of magnetic resonance imaging have shown better sensitivity in breast cancer detection[12]. Aloufi *et al*[23] and Duffy *et al*[24] compared the efficacy of mammography and automated methods in measuring the density of breast tissues during screening. The studies reported a strong association between increased mammographic densities with breast cancer which declined with age. They further suggested using automated breast density methods in high-risk patients which may act as a personalized screening method in coming years.

Since the sensitivity of mammography is low and advanced imaging modalities are not feasible for screening procedures, it is advisable to incorporate risk-based models for breast cancer screening programs. One such model is the most widely used Gain model with components including age, age at first menstruation, first pregnancy, live birth, family history of breast cancer, and previous history of benign breast biopsies[15]. This should be further supplemented with advanced imaging and ultrasound-guided biopsy for definitive diagnosis. According to MA-BREAST criteria, women with over 20% lifetime risk must be subjected to further imaging and investigations. Women with 15-20% lifetime risk must be adequately counseled and, if required, examined with advanced imaging to identify subclinical cancers, including ductal and lobular carcinoma, *in situ*. For patients with <15% of lifetime risk, routine advanced imaging must not be prescribed; however, regular follow-up is essential[25]. Additionally, patients with high-density breasts must be adequately counseled on weight loss and lifestyle modifications, including smoking cessation, decreased alcohol consumption, and regular exercise[26].

The Breast Cancer Early Detection (BCED) Project, rolled out by the Ministry of Health, Saudi Arabia, aims to promote primary prevention against breast cancer through health education and frequent screening programs with mammography examinations once in two years in all women over 40 years of age. Results of our study indicate that breast cancer screening should be implemented in a younger age group in Saudi patients. It further emphasizes the need for imaging modalities with high sensitivity and specificity for cancer detection, particularly in patients with increased breast density. With the increased predicted incidence of breast cancer in Saudi[27], there is an unmet need to develop and implement policies on breast cancer screening and education programs to reduce the burden of breast cancer.

Our study has certain limitations. Risk factors of breast cancer, including weight, nutritional status, menopausal status, age, and pregnancy, were not recorded in the study. Furthermore, due to the nature of the study, data were gathered retrospectively from patients' records and registries of the non-communicable disease directorate. As a result, some data were missing. Furthermore, as the sample was limited to one center hospital, generalizing the findings to other regions of Saudi Arabia may be skewed. Also, because a large number of cancer patients were Saudis, and expatriates are not entitled to free treatment, extrapolating the findings to all female residents in Saudi Arabia might be biased.

CONCLUSIONS

There is a relationship between age, breast density, and type of cancer. The absence of calcifications decreases the odds of breast cancer, particularly a combination of ductal carcinoma *in situ* and invasive ductal carcinoma. Breast density is strongly associated with the age of the patient and independent of cancer type. The results of our study highlight the importance of early detection of breast cancer with the implementation of screening programs in high-risk breast cancer populations.

Ethical Approval:

The study was approved by the Central Institutional Review Board, Ministry of Health. IRB Log No: 22- 16 M. Since this was a retrospective data analysis, patients' informed consent was deemed unnecessary and omitted.

Funding:

None

Conflicts of Interest:

None

Data availability statement:

The data that support the findings of this study are available on request from the corresponding author, [FA]. The data are not publicly available.

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