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Preliminary investigation of mammographic density among women in Riyadh: association with breast cancer risk factors and implications for screening practices

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ABSTRACT

Purpose: Improved mammographic sensitivity is associated with reduced mammographic density. This study aims to: provide a preliminary report on mammographic density among women in Riyadh; identify risk factors associated with mammographic density; and consider the potential implications for screening practices.
Methods: Based on a cross-sectional design, we examined a total of 792 women using an area-based mammographic density method (LIBRA). Spearman's correlation, Mann-Whitney U, Kruskal–Wallis and binary logistic regression were used for analyses.
Results: The study population had a mean age of 49.6 years and a high proportion of participants were overweight or obese (90%). A large number of women had low mammographic density, with a mean dense breast area of 19.1 cm^2 and percent density of 10.3 cm^2. Slightly more than half of the variations in the dense breast area and percent density models were explained by BMI. In the adjusted analyses, BMI, menopausal status, age at menarche and number of children remained statistically significant predictors.
Conclusion: Given the high proportion of women with low mammographic density, our findings suggest that women living in Riyadh may not require additional imaging strategies beyond mammography to detect breast cancers. The high proportion of obese women reported here and across Saudi Arabia suggests that mammographic density is less likely to have an adverse impact on mammographic sensitivity. Thus and to improve clinical outcomes among Saudi women, annual mammography and commencing screening at a younger age are suggested. Additional studies are required to shed further light on our findings.

1. Introduction

Breast cancer is a major public health concern in Saudi Arabia accounting for 18.7% of the total cancer deaths among women in 2014 [1]. Approximately 56.5% of newly diagnosed breast cancer cases were classified with regional or metastatic disease which explain the poor disease prognosis reported among Saudi women [2]. This poor prognosis may also be attributable to delay in breast cancer diagnosis as a result of low mammography screening uptake reported across the country ranging from 0.6% to 18% [3].

Epidemiological studies have reported several risk factors associated with breast cancer aetiology within Saudi women [4,5]. However, mammographic density, a strong risk factor that has been recognised since the1970s [6–12], is not fully understood in this population. Mammographic density results from the different x-ray attenuation properties of breast tissue following a mammographic examination [13]. Adipose tissue appears dark (radio-lucent) and fibro-glandular tissue appears white (radio-opaque) [14]. An elevated risk of breast cancer ranging from factors of two to six has been reported among women with high mammographic density (75% dense breast tissue and

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over) compared to women with low mammographic density (25% dense breast tissue and less) [15]. Besides the increased risk associated with mammographic density, it has been reported particularly with film screen technology that an increase in the amount of dense breast tissue results in reduced mammographic sensitivity (a measure of the ability to detect cancer) increasing the likelihood of false negative findings [16–20]. Therefore, studying mammographic density offers valuable information about the modality of choice for screening and identification of women who could be targeted for a tailored screening [21].

Mammographic density has been reported to vary across racial backgrounds [22–25]. Previous studies have shown a high mammographic density in Vietnamese [26] and Mongolian [27] women whereas low mammographic density was observed among Indian [28] and Latin American women [29,30]. In addition, the first work to evaluate mammographic density in the Arab world was conducted among Lebanese women. The study concluded that mammographic density prevalence in Lebanon was similar to the Western population where 53% of the women had dense breast tissue compared with 46.9% to 79% in the West [31]. In contrast, our recent investigation among women living in Ras Al Khaimah, a northern emirate in the United Arab Emirates (UAE), revealed that 76% of Emirati participants had fatty breast tissue [32]. These variations highlight the importance of ethnic-dependent mammographic density studies.

While substantial efforts in creating a population-based breast cancer screening program is being established by the Saudi Arabian government [33], the aim of this study is to examine the distributions of mammographic density as represented by dense breast area and percent density (PD%) and to examine risk factors associated with mammographic density among Saudi women living in Riyadh, Saudi Arabia. The findings of this study would provide a preliminary evaluation of the aetiology and magnitude of mammographic density among Saudi women and would provide some potential clinical implications for screening practices.

2. Methods

2.1. Study population and data collection

The study was approved by the Human Ethics Committee at the University of Sydney (protocol number 2014/884). Informed written consent was obtained from all participants (including 38 consent forms obtained by thumb print from illiterate participants) prior to the interview and mammography screening.

Between December 2016 and May 2017, 902 women aged 30 years or over were enrolled in the study. Of these, 252 (27.9%) women were recruited from the following hospitals: Al-Eiman General Hospital (n = 115), Asser Central Hospital (n = 56) and King Salman Hospital (n = 81). The remaining 650 women (72.1%) were recruited from breast cancer screening centres provided by the Ministry of Health in Riyadh. Exclusion criteria included cases with previous history of breast cancer (n = 2), and to prevent any overestimation of mammographic density reading, cases with masses or calcifications were excluded (n = 25). Due to the absence of ethical approval, cases with oral consent forms were removed from the analysis (n = 31). Eleven other cases were excluded because the density measurement software was unable to accurately estimate mammographic density for unknown reasons. An additional 41 cases with missing mammography views at the time of data collection were also removed. Thus, a total of 792 women were included in our analysis.

Immediately before mammography screening, women who agreed to participate were interviewed by female radiographers using a structured questionnaire. The questionnaire included questions about age, occupation, income, education, menopause status, age at menarche, age at first pregnancy, number of deliveries, breast feeding, the use of oral contraceptives (OC) or hormone replacement therapy (HRT) and family history of breast cancer (having a first or second degree relative diagnosed with breast cancer). Anthropometric measures of height and weight were also taken for most women at the clinic visit and body mass index (BMI) was calculated, however 92 measures of height and weight were self-reported.

Each woman had the standard two view mammograms including craniocaudal (CC) and mediolateral oblique (MLO) of both breasts produced with full field digital mammography (Hologic and General Electric, GE units). Of the 792 participants, 179 had raw "For Processing" digital mammograms and 613 had post-processed "For Presentation" digital mammograms available at the time of the analysis.

2.2. Mammographic density estimation

The left CC view was used to estimate dense breast area and PD%. This projection is generally preferred over MLO view because CC view not affected by the superimposition of the pectoral muscle [34].

An area-based mammographic density measurement method using a fully automated software, the Laboratory for Individualized Breast Radiodensity Assessment (LIBRA) developed by the Computational Breast Imaging Group (CBIG) at the University of Pennsylvania, (version 1.0.4), was used to estimate dense breast area and PD % (all in cm2) for both raw and processed images. LIBRA has been applied to over 30,000 mammography screening examinations and it was developed to work with both raw and post-processed digital mammograms [21], and is being increasingly used in research studies [35–38].

Briefly, the software starts by defining the pectoral muscle (if present) and the breast boundaries through an edge-detection process [35]. It then applies an adaptive multi-class fuzzy c-means to split-up and classify the image gray levels (Fig. 1b) into clusters of similar X-ray attenuation (Fig. 1c). These clusters are then combined to form an absolute dense breast area segmentation (Fig. 1d). The PD% is then calculated by dividing the dense breast area by the total breast area.

2.3. Statistical analysis

The associations between mammographic density measurements (dense breast area and PD%) and items investigated with the questionnaire (see above) were examined by Spearman's rank correlation coefficient (r) for continuous variables and with Mann-Whitney U and Kruskal–Wallis tests used for categorical variables. The reliability of our mammographic density measurements between mammographic views (CC vs MLO) and sides (left/right) was examined by Spearman's rank correlation coefficient (r).

Before building the regression models for dense breast area and PD %, we first tried to normalise mammographic density measurements using either the square root or log10 transformations as dense breast area and PD% were found to be positively skewed (Fig. 2). However, the distributions remained non-normally distributed. Therefore, mammographic density measurements were divided into two categories based on the median value of each measure as suggested in previous research [25], and treated as categorical variables before being entered into the regression analyses.

Binary logistic regression using the "Enter" method was fitted to evaluate the independent association of the set of predictors (risk factors) that showed a significant association with the mammographic density measurements in the univariate analysis (Spearman's rank correlation coefficient or Mann-Whitney U or Kruskal–Wallis tests. Predictors were retained in the model if p values demonstrated to be below 0.05.

To explore the independent effect of each model, the prediction capability (Nagelkerke R^2) was compared between models. First, all significant predictors in the univariate analysis were entered into the model (baseline model). Predictors that showed significant associations were retained in the model (significant model). The last model (significant model) was then adjusted for age (continuous), breast feeding (categorical) and the use of OC (categorical) to provide a final fully

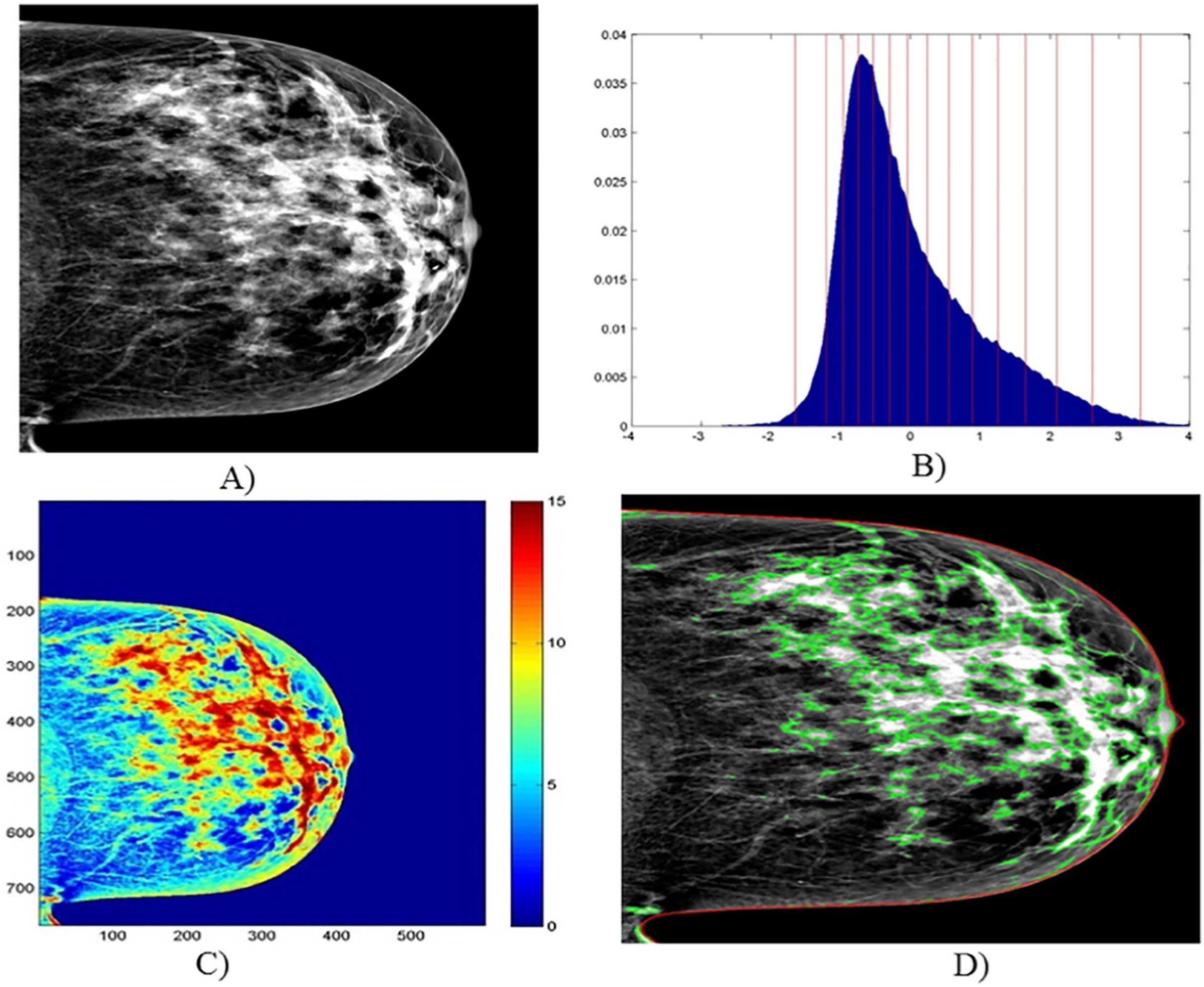

Fig. 1. a) Left craniocaudal (LCC) mammography view of a clinically free 49-year-old Saudi woman "For Presentation". b) Multi-class fuzzy c-means centroids (vertical lines) which use to provide a breast image intensity histogram. c) Intensity-clustered breast image. d) Final segmentation of breast and dense tissue [37], corresponding to a breast area of 312.6 cm^2, a dense breast area of 65.5 cm^2 and a percent density of 20.9% cm^2.

adjusted model. A two-sided significance level of $\alpha = 0.05$ was used. All analyses were performed using SPSS version 25.0 [IBM, USA].

3. Results

3.1. Baseline characteristics

The demographic characteristics of the study population are presented in Table 1. Overall, the mean age was 49.6 years and the majority of participants were married, homemakers and held Saudi citizenship. In relation to reproductive factors, the mean age at menarche was 13.3 years and 61% of participants were premenopausal. More than 90% were parous (having on average 6 children) and had previous breastfeeding experience. Nearly 60% of parous women delivered their first child at 20 years old or younger (mean age 20.9 years). More than half of participants had used OC whereas < 3% had used HRT through their life time.

The distributions of mammographic density measurements are presented in Fig. 2. Dense breast area and PD% were found to be positively skewed whereas breast area and non-dense area were found to be approximately normally distributed. In terms of the reliability of our mammographic density measurements, strong correlations were reported between different breast projections and sides. For the CC view, which was used in the current study, strong correlations were found between right and left CC views for breast area ($r = 0.91$, $p < 0.0001$), dense breast area ($r = 0.85$, $p < 0.0001$) and PD% ($r = 0.86$, $p < 0.0001$). Similarly, strong correlations were found between left CC and left MLO for breast area ($r = 0.93$, $p < 0.0001$), dense breast area ($r = 0.81$, $p < 0.0001$) and PD% ($r = 0.83$, $p < 0.0001$).

3.2. Univariate analyses

The results of the univariate analyses for the associations between dense breast area and PD% with risk factors are presented in Table 2. For continuous variables, negative correlations were observed for both density measures with age, weight, BMI and number of children ($p < 0.05$). In contrast, height, age at menarche and age at first child were positively correlated with dense breast area and PD% ($p < 0.05$).

For categorical variables, higher dense breast area and PD% were observed among pre-compared with post-menopausal women ($p < 0.0001$). Moreover, dense breast area and PD% were statistically different for varying educational levels and in particular the post-hoc analyses showed that dense breast area and PD% were statistically lower for women with no formal education compared with women in higher education group. No other statistically significant associations were observed.

3.3. Multivariable logistic regression analyses

The baseline model with all significant univariate risk factors

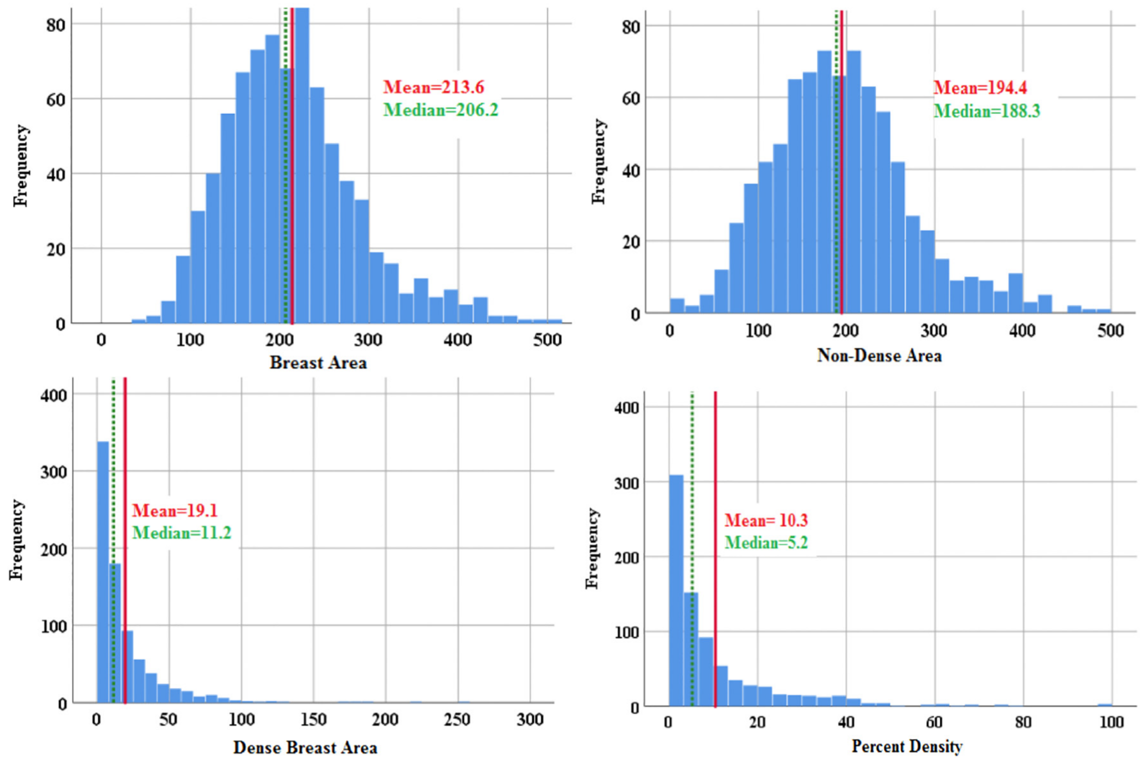

Fig. 2. Distributions of the breast area, non-dense area, dense breast area and percent density (PD%) among study participants.

explained 12.8% of the variance in dense breast area. With only the significant multivariable risk factors retained in the model (BMI, menopausal status, age at menarche and number of children), 12.4% of the variance in dense breast area was explained. When the significant model was then adjusted for age (continuous), breast feeding (categorical) and the use of OC (categorical), the model improved by only 0.1% and explained 12.5% of the variance in dense breast area. Only BMI ($B = -0.07$, $p \le 0.001$, OR = 0.93, 95% CI: 0.90, 0.95), menopausal status ($B = 0.46$, $p = 0.03$, OR = 1.59, 95% CI: 1.04, 2.42), number of children ($B = -0.06$, $p = 0.04$, OR = 0.93, 95% CI: 0.87, 0.99) and age at menarche ($B = 0.11$, $p = 0.01$, OR = 1.12, 95% CI:1.02, 1.23) remained statistically significant with dense breast area representing our final model shown in Table 3.

The PD% model showed a slightly better prediction than the dense breast area model. The baseline model with all the significant univariate risk factors explained 17.8% of the variance in PD%. With only the significant multivariable risk factors retained (BMI, menopausal, age at menarche and number of children), the model explained 17.2% of the variance in PD%. When the significant model was then adjusted for age (continuous), breast feeding (categorical) and the use of OC (categorical), the model decreased by 0.1% and explained 17.1% of the variance in PD%. Compared with fully adjusted dense breast area model, number of children was no longer a significate predictor for PD% (B = −0.06, p = 0.05, OR = 0.93, 95% CI: 0.87, 1.00). BMI (B = −0.09, $p \le 0.001$, OR = 0.90, 95% CI: 0.88, 0.93), menopausal status (B = 0.59, p = 0.007, OR = 1.80, 95% CI: 1.18, 2.77) and age at menarche (B = 0.10, p = 0.02, OR = 1.11, 95% CI: 1.01, 1.22) remained statistically significant with PD% in the representing our final model shown in Table 3.

4. Discussion

The aim of this study was to provide preliminary data on mammographic density patterns among Saudi women living in Riyadh, Saudi Arabia measured using an area-based mammographic density measurement method (LIBRA) which produces dense breast area and PD% values. It also aimed to highlight important risk factors associated with both density measures.

Consistent with previous studies, both density measures were inversely associated with BMI and number of children at the time of screening [35,39–41]. However, age at menarche was positively associated with both density measures which was in agreement with some but not all prior studies. Previous studies on the association between mammographic density and the age at menarche have led to conflicting findings. A number of studies have reported a null association [10,24,41–47], whereas one has reported a negative relationship [48]. In contrast and consistent with some previous reports [49–54], we found a statistically significant positive association between mammographic density and the age at menarche in both unadjusted and adjusted analyses. Our finding is supported by a recent, large population-based study that examined the mammographic density of > 24,000 American women aged between 20 and 74 years using a semi-automated thresholding technique, Cumulus, to estimate mammographic density. The study reported that the positive association remained statistically significant in both unadjusted and adjusted analyses [55]. It is worth noting that the strength of the association between age at menarche and mammographic density has been reported to vary across age groups and menopausal status [52]. Therefore, determining the strength of association stratified by age and menopausal status among Saudi females in future studies is recommended.

In relation to mammographic density distributions, our study showed that a large number of women had low mammographic density distributions compared with previous studies. The reported average dense breast area (19.1 cm^2) and PD% (10.3 cm^2) were lower than those previously reported among American women in two previous studies where dense breast area was 31.3 cm^2 and 22.3 cm^2 while PD% was 27.1 cm^2 and PD% = 17.1 cm^2 [25,35]. Singaporean Chinese women also displayed higher values with a dense breast area of 26.2 cm^2 and a PD% of 27.8 cm^2 [41]. Possible attributable factors for the reported low mammographic density among Saudi women will be discussed below.

It is well-established that increase in body weight is one of the most

Table 1
Characteristics of the study population

Characteristics		Characteristics	
Age at screening (years), mean (± SD)	49.6 (7.4)	Height (cm), mean (± SD)[h]	156.7 (6.8)
30–44	225 (28.4)	Weight (kg), mean (± SD)[h]	79.2 (15.3)
45–49	174 (22)	BMI (kg/cm²), mean (± SD)[h]	32.3 (6.3)
50–54	191 (24.1)	Normal and underweight (≤24.9)	65 (8.4)
55–59	126 (15.9)	Overweight (25–29.9)	233 (30.1)
≥60	76 (9.6)	Obese class I (30–34.9)	260 (33.6)
Ethnicity, n (%)[a]		Obese class II (35–39.9)	125 (16.1)
Saudi	764 (96.5)	Obese class III (≥40)	91 (11.8)
Non-Saudi	28 (3.5)	Age at menarche (years), mean (± SD)[i]	13.3 (1.7)
Marital status, n (%)[b]		≤13	444 (57.2)
Single	15 (1.9)	> 13	332 (42.8)
Married	638 (80.7)	Parity, n (%)[j]	
Divorced and widowed	138 (17.4)	Nulliparous	30 (3.9)
Working status, n (%)[c]		Parous	746 (96.1)
Full/part time	158 (20.2)	Number of children, mean (± SD)[k]	6.1 (2.6)
Homemakers	623 (79.8)	≤ 4	198 (27)
Education, n (%)[d]		5–7	324 (44.1)
No formal education	164 (20.8)	≥ 8	212 (28.9)
Literary, primary, secondary, high school	432 (54.9)	Age at first child (y), mean (± SD)[l]	20.9 (4.7)
Diploma, bachelor, postgraduate	191 (24.3)	≤20	428 (58.3)
Household monthly income, n (%)[e]		> 20	306 (41.7)
Less than 5000 (SAR)	183 (27.5)	Breast feeding, n (%)[m]	
From 5000 to 9000 (SAR)	229 (34.4)	Never	53 (7.2)
From 10,000 to 14,000 (ASR)	148 (22.2)	Ever	689 (92.8)
> 14,000 (SAR)	106 (15.9)	Oral contraceptive use, n (%)[n]	
Breast density Measurements, mean (± SD)[f]		Never	289 (37.4)
Breast Area (cm²)	213.6 (74.3)	Ever	483 (62.6)
Non-dense area (cm²)	194.4 (79.1)	Hormonal replacement therapy, n (%)[o]	
Dense breast area (cm²)	19.1 (23.8)	Never	754 (97.5)
Percent density (cm²)	10.3 (13.2)	Ever	19 (2.5)
Menopausal status, n (%)[g]		Family history of breast cancer, n (%)[p]	
Premenopausal	489 (61.9)	No	687 (87.4)
Postmenopausal	301 (38.1)	Yes	99 (12.6)

Abbreviations: n = number of participants; BMI = body mass index; SAR = Saudi Arabia Riyal.
[a] Non-Saudi participants were from: Syria (n = 13), Egypt (n = 4), Yemen (n = 3), Jordan (n = 2), India (n = 2), one participant from Sudan, Palestine, Pakistan and Philippines.
[b] One missing value.
[c] Part time workers (n = 8), full time student (n = 4), missing (n = 7).
[d] One refused and four missing values.
[e] Refused (n = 55), missing (n = 15), I do not know (n = 56).
[f] Left Cranio Caudal (LCC) view was used to calculate mammographic density measurements.
[g] One refused and one missing value.
[h] Missing (n = 18).
[i] Missing (n = 10), I do not know (n = 6).
[j] Among parous women only (One missing value).
[k] Among parous women only (One I do not know, and 12 missing values).
[l] Among parous women only (4 I do not know, and 9 missing values).
[m] Among parous women only (Four missing values).
[n] Among parous women only (One refused, 2 I do not know and 3 missing values), 30 participants were current users.
[o] Among parous women only (One refused, 2 I do not know and one missing values), one participant was current user.
[p] 5 I do not know and one missing value.

important factors associated with reduction in mammographic density [56]. In our study, a considerable proportion of women were overweight (30.1%) or obese (61.5%) as shown in Table 1. The confounding effect of BMI in our study can be illustrated by comparing the final adjusted dense breast area and PD% regression models with the model having only BMI as the main predictor. Approximately more than half of the variance in the dense breast area model (12% compared with 17.1% in the fully adjusted model) and PD% model (7.7% compared with12.5% in the fully adjusted model) were explained by BMI when it was used as the only predictor in both models.

Another possible explanation of the low mammographic density measures reported in the current investigation may relate to the reproductive characteristics of our sample (Table 1). In the present study, 96% of women were parous, 73.2% had 5 children or more and only 2.6% had used HRT during their life time, all of which have been reported to be associated to reduce mammographic density [57,58]. While the reproductive and hormonal factors may explain only 20–30% of variations in mammographic density [58], it could also help to focus on genetic and environmental factors for better understand the aetiology of mammographic density among Saudi population.

In relation to the regression analysis, a somewhat similar predictive pattern was reported for the dense breast area and PD% models indicating that similar agents were key to the final model. However, the factors associated with the PD% model had a better predictive capacity (R^2 = 17.2%) than they had with dense breast area (R^2 = 12.4%, Table 3). This slightly higher performance of the PD% measurement may be partially due to the contribution of both non-dense and dense tissue of the breast compared with dense breast area, which only takes the dense breast tissue into account. Additionally, non-dense area reflects the quantity of fatty tissue in the breast and 40% of the variation in non-dense area has been shown to be explained by BMI [59]. Women with high BMI tend to have large breast with increased amounts of

Table 2
Univariate analyses of risk factors associated with dense breast area and percent density

	Dense breast area (cm^2)		Percent density (cm^2)	
Risk factors	Correlation (r)	p-Value[a]	Correlation (r)	p-Value[a]
Age (years)	(−) 0.21	< 0.0001	(−) 0.24	< 0.0001
Height (cm)	0.13	< 0.0001	0.12	0.001
Weight (kg)	(−) 0.23	< 0.0001	(−) 0.34	< 0.0001
BMI (kg/cm^2)	(−) 0.28	< 0.0001	(−) 0.39	< 0.0001
Age at menarche (years)	0.10	0.003	0.09	0.006
Number of children	(−) 0.17	< 0.0001	(−) 0.17	< 0.0001
Age at first child (years)	0.11	0.002	0.12	0.001
Education	Median	p-Value[b]	Median	p-Value[b]
No formal education	8.3		3.6	
Literary, primary, secondary, high school	11.1	0.02	5.3	0.03
Diploma, bachelor, postgraduate	12.3		6.0	
Menopausal status				
Premenopausal	13.6		6.6	
Postmenopausal	7.5	< 0.0001	3.1	< 0.0001

Abbreviations: BMI = Body Mass Index.
[a] Obtained from Spearman's rank correlation coefficient for continuous variables.
[b] Obtained from Mann-Whitney U and Kruskal–Wallis tests for categorical variables.

adipose (non-dense) tissue [25,56]. This was evident in our study in that the non-dense area mean (194 cm^2) was close to total breast area mean (213 cm^2). While 91.6% of our participants were overweight and obese, this might explain the higher performance of PD% model compared with dense area model.

4.1. Clinical implications

Mammography is the only proven and validated clinical tool for breast cancer screening [60]. However, the clinical benefits for women undergoing mammography screening largely depend on their mammographic density, with improved screening sensitivity associated with lower levels of mammographic density [16–19]. Sensitivity of 85% was reported among women with fatty breast tissue [61]. Therefore, mammography screening is probably of most benefit in women with low breast density since masses are more easily detected and better outcomes are more likely.

Our study showed that a large number of women had low mammographic density when measured as dense breast area and PD%. This low-density observation is supported by the density distributions using the Breast Imaging and Reporting and Data System, 4th edition (BI-RADS). Our results showed that 53% and 28% of women were assigned to either BI-RADS 1 or BI-RADS 2, categories respectively, whereas 14% and 5% of participants were assigned to BI-RADS 3 and BI-RADS 4, respectively (Supplementary file 1). The relative proportion of BI-RADS distributions observed in our study were approximately similar to those reported among women living in the Eastern province of Saudi Arabia [62]. Although the authors did not report all distributions across all mammographic density categories, the study showed that 77% of the women were categorised as BI-RADS 1 while only 4.0% were assigned to BI-RADS 3 and BI-RADS 4 [62]. Therefore, in the light of the current and previously reported low mammographic density, one potential clinical implication is that women living in Riyadh may not be targeted for additional screening and that mammography would be a sufficiently sensitive breast imaging modality for early detection of breast cancer in this population.

It should be borne in mind that a proportion of women with dense breast tissue, particularly those with other breast cancer risk factors, may benefit from additional screening to aid early cancer detection. Improvement in the breast cancer detection rates have been reported when Magnetic Resonance Imaging (MRI), breast ultrasound, Automated Breast Ultrasound (ABU), Digital Breast Tomosynthesis (DBT) and molecular imaging are used in addition to normal mammography screening [63,64]. Women at high-risk of breast cancer might benefit the most from MRI and breast ultrasound screening, which have a reported sensitivity of 78% and 80%, respectively, when combined with mammography screening [65]. However, any improvements in detection of breast cancers come at the expense of increased recall rates, false-positives, costs and patient anxiety [63]. Although some studies have suggested that DBT or breast ultrasound be added for average risk women, reports from various international organisations and evidence-based review studies do not recommend supplemental screening for women at average or low risk of breast cancer who have increased mammographic density [66]. This highlights the importance of breast cancer risk assessment to assist radiologists to identify women who might derive the greatest benefit from additional screenings [65].

It is well established that high BMI has consistently been reported as a major contributor to mammographic density reduction [56], an effect that seen in the current study. The obesity profile reported here is in line with previous studies in different regions in Saudi Arabia [67–69], and with recent large household survey by the Ministry of Health showed that 28% and 33.5% of all Saudi women were overweight or obese, respectively [70]. Notably, the obesity prevalence seen in the current study is also consistent with that reported by Al Mulhim, F. A., et al., 2015 among women resident in Eastern province of Saudi Arabia in which comparable low BI-RADS density distributions were observed [62]. Therefore, given the consistent finding of low mammographic density between women living in Riyadh and Eastern regions, along with the increased BMI recorded across the country, it could be suggested that low mammographic density would be more common among Saudi women. If this was found to be true, our conclusion regarding the use of mammography as a primary screening modality might be able to be generalised to the wider Saudi female population. Further studies with larger sample are needed to report mammographic density levels across Saudi Arabia, which would shed more light on our conclusion.

One might think that increased BMI would be advantageous as mammographic density will be lower among those individuals. However, this comes at the cost of increased risk, particularly among obese postmenopausal women [71]. Moreover, data showed that, compared with women of normal weight, women with BMI of 28 kg/cm^2 had an 80% increased risk not only of advanced stages at diagnosis of breast cancer (stages III and IV) but also of poorly differentiated grade ($p = 0.014$, OR = 1.80, 95% CI = 1.1–2.8) [72], both of which are common among Saudi women [2,67,73,74]. Therefore, to facilitate early detection of breast cancer and to reduce the number of women presenting at advanced stages, there may be a need to revise recommended mammography screening intervals and the appropriate age to start screening particularly if mammographic density is not likely to be the main obstacle to the detection of breast masses using mammography [23].

Recent work carried out in Sweden suggested that shorter screening intervals (a12-month screening interval) might be considered for women with high BMI [75]. The study reported that for cancers diagnosed within 24 months of a negative mammogram, which are known as interval cancers, women with higher BMI had larger cancers than women with lower BMI. While the current practice in Saudi Arabia recommends screening intervals of 24 months [60], and in the light of high prevalence of obesity observed in our study and in the country, it might be worthwhile exploring the advantages to women with high BMI having a 12-month screening interval particularly women belonging to high-risk groups.

Table 3
Multivariable regression analyses for factors associated with dense breast area and percent density.

Covariate	Baseline model				Significate model				Fully adjusted model[a]				BMI model			
	B	Wald	P	OR (95% CI)	B	Wald	P	OR (95% CI)	B	Wald	P	OR (95% CI)	B	Wald	P	OR (95% CI)
Dense breast area																
BMI (kg/cm^2)	−0.07	25.8	< 0.001	0.93 (0.90,0.95)	−0.07	27.9	< 0.001	0.93 (0.90, 0.95)	−0.07	26.7	< 0.001	0.93 (0.90, 0.95)	−0.08	40.7	< 0.001	0.92 (0.89, 0.94)
Age at menarche (years)	0.13	7.5	0.006	1.14 (1.03,1.25)	0.12	6.8	0.009	1.13 (1.03, 1.24)	0.11	5.8	0.01	1.12 (1.02, 1.23)				
Number of children	−0.10	7.1	0.007	0.90 (0.83, 0.97)	−0.09	8.2	0.004	0.91 (0.85, 0.97)	−0.06	4.0	0.04	0.93 (0.87, 0.99)				
Premenopausal	0.50	5.5	0.01	1.65 (1.08, 2.52)	0.58	12.2	< 0.001	1.80 (1.29, 2.50)	0.46	4.7	0.03	1.59 (1.04, 2.42)				
Postmenopausal	1.0 (ref)	–	–	–	–	–	–	–	–	–	–	–				
Age at first child (years)	−0.01	0.4	0.52	0.98 (0.95, 1.02)												
Age (years)	−0.009	0.3	0.56	0.99 (0.96, 1.02)												
Education (1)	1.0 (ref)	–	–	–												
Education (2)	−0.009	0.002	0.96	0.99 (0.64, 1.52)												
Education (3)	0.08	0.09	0.75	1.08 (0.63, 1.86)												
Nagelkerke R^2%		12.8%				12.4%				12.5%				7.7%		
PD%																
BMI (kg/cm^2)	−0.09	43.8	< 0.001	0.90 (0.87, 0.93)	−0.09	44.9	< 0.001	0.90 (0.88, 0.93)	−0.09	43.6	< 0.001	0.90 (0.88, 0.93)	−0.10	61.1	< 0.001	0.89 (0.87, 0.92)
Age at menarche (years)	0.12	6.1	0.01	1.13 (1.02, 1.24)	0.11	5.9	0.01	1.12 (1.02, 1.23)	0.10	4.9	0.02	1.11 (1.01, 1.22)				
Number of children	−0.10	6.9	0.008	0.90 (0.83, 0.97)	−0.08	7.5	0.006	0.91 (0.86, 0.97)	−0.06	3.6	0.05	0.93 (0.87, 1.00)				
Premenopausal	0.63	8.3	0.004	1.87 (1.22, 2.88)	0.73	18.3	< 0.001	2.08 (1.49, 2.92)	0.59	7.6	0.007	1.80 (1.18, 2.77)				
Postmenopausal	1.0 (ref)	–	–	–	–		–	–	–	–	–	–				
Age at first child (years)	−0.007	0.1	0.71	0.99 (0.95, 1.03)												
Age (years)	−0.01	0.6	0.40	0.98 (0.95, 1.10)												
Education (1)	1.0 (ref)		–	–												
Education (2)	−0.003	0.00	0.98	0.99 (0.64, 1.55)												
Education (3)	−0.13	0.2	0.63	0.87 (0.50, 1.51)												
Nagelkerke R^2%		17.8%				17.2%				17.1%				12%		

Abbreviations: OR = Odds ratios; CI = Confidence Interval; BMI = Body Mass Index; PD = Percent Density; Ref = reference category.
Note: Education categories literary, primary, secondary or high school (2) and diploma, bachelor or postgraduate (3) were compared with no formal education (reference category).
[a] Adjusted for age (continuous), breast feeding (Ever vs Never) and the use of OC (Ever vs Never).

In terms of appropriate age to start mammography screening, age has been used as a clinical metric to decide when a woman needs to start and stop breast cancer screening; this is referred to as the "age-based breast screening" approach [65,76]. Even though most breast cancer screening recommendations were established based on information derived from Western women, there is a lack of agreement between international organisations about the optimal age to commence screening [63]. Thus, it is not necessary to implement Westernised recommendations in Saudi Arabia, where breast cancer epidemiology differs, particularly in terms of tumour biology, age at first presentation and mammographic density.

Existing data showed that a significant number of Saudi women tend to develop breast cancer before they reach the recommended age to start mammography screening (40 years) [23]. Early studies among Saudi women showed that between 26 and 35% of all breast cancers were reported among women younger than 40 years old [74,77]. A recent report from the Ministry of Health showed that 18.89% (n = 354) of newly developed breast cancer was detected before the age of 40 years [2]. Of those breast cancers, 176 (51%) were seen in the age group 35–39 years. Therefore, a meaningful proportion of women with breast cancer will not be diagnosed until the first round of screening at 40 years. While it has been suggested that the recommended age for initial breast screening should be 5 to 10 years before the age at which breast cancer is most frequently diagnosed [78], it would seem reasonable to revise the starting age for screening and explore the use of 35 years as a cut-off point for breast cancer screening in Saudi Arabia. This approach of recruiting younger women has been previously recommended for African American and Ugandan women, although no cut-off point was proposed [23,79].

We acknowledge that recruiting younger women might necessitate the use of other imaging modalities, mainly breast ultrasound, as the accuracy of mammography screening is arguably low among younger women. However, this argument was based on mammographic density data mainly derived from Western women [65]. Therefore, until more data about mammographic density levels across Saudi Arabia become available, particularly for younger individuals, it is believed that offering mammography screening at an earlier age might improve clinical outcomes and reduce the breast cancer burden among young Saudi women by detecting breast cancers before they become symptomatic.

4.2. Strengths and limitations

To the best of our knowledge, this is the first study that has examined mammographic density among Saudi women and identified risk factors associated with dense breast area and PD%. The findings are strengthened by the use of a fully automated area-based mammographic density measurement method (LIBRA) which has been reported to have a moderate to strong correlations not only with both BI-RADS (5th version) and Cumulus mammographic density measurements, all of which are widely used in clinical and screening settings, but also with volumetric density measurements [21,34,80].

Some limitations should also be noted. The cross-sectional design and small sample size may limit the generalizability of our findings to the wider Saudi population. Another likely limitation is the use of post-processed "For Presentation" digital mammograms which may slightly improve our LIBRA outputs (dense breast area and PD%) as a result of increased contrast and presence of a relatively sharp, well-defined air-tissue boundary compared with raw digital mammograms [21]. In addition, the study population was predominantly from Riyadh, the capital of Saudi Arabia and as such, our observation needs to be validated in a larger study including all regions of Saudi Arabia, particularly since breast cancer incidence has been reported to vary across the country [81].

5. Conclusion

Higher dense breast area and PD% were observed among pre-menopausal women compared with post-menopausal women, and mammographic density was found to be inversely associated with BMI and positively associated with age at menarche. A large number of women had low mammographic density, which was found to be mainly explained by increased BMI. Consequently, the study suggested that Saudi women living in Riyadh may not require additional breast screenings beyond mammography to detect cancers. However, individuals with increased dense breast tissue, who are at high risk of developing breast cancer, may benefit from additional screenings, particularly MRI and breast ultrasound. Given the substantial increase in obesity observed in the present study and across Saudi Arabia, it is recommended that mammography screening be offered for women at 35 years, along with a shorter interval between mammograms (12 months instead of 24 months), in order to improve the poor breast cancer prognoses reported among Saudi women through earlier detection of the disease. These recommendations were based on the consistently reported association between reduced mammographic density and increased BMI, which suggests that mammographic density is less likely to impair earlier detection. Further studies of the impact of obesity on mammographic density involving women of different age groups, particularly under-researched Saudi women are needed to shed further light on the study's findings and implications.

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Conflict of interests

The authors have no conflict of interest to declare.

Research data for this article

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared. Data not available/The data that has been used is confidential.

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