Original Article

Dense breast tissue in screened postmenopausal women

Prevalence and determinants

Ibrahem H. Kanbayti, *MSc, PhD.*

ABSTRACT

الأهداف: استكشاف انتشار أنسجة الثدي الكثيفة بين النساء بعد انقطاع الطمث اللواتي خضعن للفحص، وتحديد العوامل المؤثرة على كثافة الثدي في هذه الفئة.

المنهجية: أجرينا تحليل بأثر رجعي لبيانات النساء بعد انقطاع الطمث اللواتي خضعن لفحص سرطان الثدي في جدة، المملكة العربية السعودية، خلال الفترة من أبريل 2017م ويونيو 2021م. تم تقييم كثافة الثدي بشكل وصفي، وتم الحصول على العوامل المؤثرة من نظام معلومات المستشفى. تم استخدام النسب لتحليل البيانات الوصفية، واستخدم الانحدار اللوجستي الثنائي لتحديد العوامل المؤثرة في أنسجة الثدي الكثيفة.

النتائج: فقط 12.7% من النساء بعد انقطاع الطمث كان لديهن أنسجة ثدي كثيفة. كانت النساء غير السعوديات (نسبة الأرجحية=1.95، 95% فترة الثقة=1.07-3.54، p=0.02)، واللواتي لم يحملن أبدًا (نسبة الأرجحية=2.75، 95% فترة الثقة=1.33-5.53، p=0.006)، و اللواتي لديهن عدد أقل من الأطفال كان لديهن فرصة أكبر لامتلاك أنسجة ثدي كثيفة (نسبة الأرجحية=2.58، 95% فترة الثقة=1.23-5.40، p=0.01).

الخلاصة: كان انتشار أنسجة الثدي الكثيفة بين النساء بعد انقطاع الطمث اللواتي خضعن للفحص منخفضًا. ومع ذلك، فإن بعض العوامل تزيد من خطر وجود أنسجة كثيفة في هذه الفئة، بما في ذلك عدم كونها سعودية، عدم الرضاعة الطبيعية، عدم الحمل، وقلة عدد الأطفال.

Objectives: To explore the prevalence of dense breast tissue among screened postmenopausal women and identify the factors influencing breast density in this population.

Methods: A retrospective analysis of data from postmenopausal women screened for breast cancer in Jeddah, Saudi Arabia, between April 2017 and June 2021 was carried out. Breast density was subjectively assessed, and influencing factors were retrieved from the hospital information system. Proportions were used for descriptive analysis, and binary logistic regression was used to identify the determinants of dense breast tissue.

Results: Only 12.7% of the postmenopausal women had dense breast tissue. Non-Saudi women (odds ratio [OR]=1.95, 95% confidence interval [CI]: [1.07-3.54], p=0.02) and those who did not breastfeed (OR=2.75, 95% CI: [1.33-5.53], p=0.006) had a greater likelihood of having dense breast tissue. Women who had never been pregnant (nulliparous) were 4 times more likely to have dense breast tissue than those who had been pregnant (parous; p<0.001). Additionally, women with fewer children had a higher chance of dense breast tissue (OR=2.58, 95% CI: [1.23-5.40], p=0.01).

Conclusion: The prevalence of dense breast tissue among screened postmenopausal women was low. However, certain factors increase the risk of having dense tissue in this population, including not being Saudi Arabian, never having breastfed, being nulliparous, and having fewer children.

Keywords: postmenopausal women, mammographic density, mammography, reproductive factors

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From the Department of Radiologic Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Ibrahem H. Kanbayti, Radiologic Sciences Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.
E-mail: Ikanbayti@kau.edu.sa
ORCID ID: https://orcid.org/0009-0002-3730-9880

Globally, breast cancer (BC) is the most prevalent cancer in women, with 2.3 million new cases and more than half a million deaths reported in 2020.[1] It accounts for less than one-third of cancers diagnosed in Saudi Arabia.[2] Early identification facilitated by mammography expands the array of available treatment options, enhances treatment success rates, and improves overall survival rates.[3] However, the accuracy of mammography in detecting lesions can be influenced by breast density.

Among the various factors influencing BC risk, breast density, which is the relative amount of fibrous and glandular tissue compared with fatty tissue within a woman's breasts, has emerged as a crucial indicator,

with higher density being linked to a higher risk of BC.[4] Breast density is a dynamic trait that changes over time, particularly with age.[5] Typically, older women have lower breast density than younger women, with the most significant changes occurring during menopausal transition. Despite this trend, a subset of postmenopausal women may experience persistently high breast densities. Studies have shown that BC found in postmenopausal women with dense breasts tends to be more aggressive.[6,7] Since dense breast tissue can hinder mammography accuracy and increase the risk of BC, it is vital to understand its prevalence among postmenopausal-screened women. Additionally, identifying the factors that contribute to denser breasts in this population and using this knowledge to assess patients with these risk factors are essential for early BC detection.

The influence of reproductive, demographic, and anthropometric factors on mammographic density has been a major area of investigation, with specific emphasis on premenopausal women. Existing research has consistently revealed associations between certain factors and breast density. Specifically, skipping breastfeeding, having a lower parity and pregnancy count, and increased age have been linked to higher breast density, whereas body mass index (BMI) and age tend to exhibit an inverse relationship with breast density.[8-10] Despite extensive evidence being available in this area, the correlation between these factors and mammographic density among postmenopausal women remains relatively unexplored. To date, only one study carried out among the Turkish population, has specifically investigated the associations of anthropometric and reproductive factors with breast density in postmenopausal women.[11] It revealed that lower BMI and a lower number of pregnancies serve as potential predictors of dense breast tissues in postmenopausal women. These results highlight the need for further research to better understand the complex interplay between reproductive history, demographic characteristics, anthropometric measures, and breast density in postmenopausal women.

This study aimed to explore the prevalence of dense breast tissue among postmenopausal-screened women and the factors influencing its density. Investigating breast density in postmenopausal women may reveal important implications for identifying women at a high risk of developing BC.

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Methods. At the Sheikh Mohammed Hussien ALAmoudi Center of Excellence in Breast Cancer, King Abdulaziz University, Jeddah, Saudi Arabia, 908 women were screened for BC between April 2017 and June 2021. Among them, 410 fulfilled the eligibility criteria for inclusion, including postmenopausal status and bilateral mammographic density assessment. The exclusion criteria were premenopausal women (n=80), individuals without recorded mammographic density readings (n=175) as indicated in radiology reports, and women with a history of BC, breast surgery, benign breast conditions, or radiotherapy (n=243; **Figure 1**). The participants completed a questionnaire that collected details regarding their background and health, including nationality, age, weight, and height (used to calculate BMI); menstruation history (age at first period and menopause); childbirth history (age at first pregnancy, number of children, and breastfeeding); any family history of BC; and administration of hormone replacement therapy (HRT). The mammographic density profile of each woman was retrieved from the radiology report.

This study was approved by the Institutional Review Board of King Abdulaziz University Hospital, Jeddah, Saudi Arabia (reference No: 449-18).

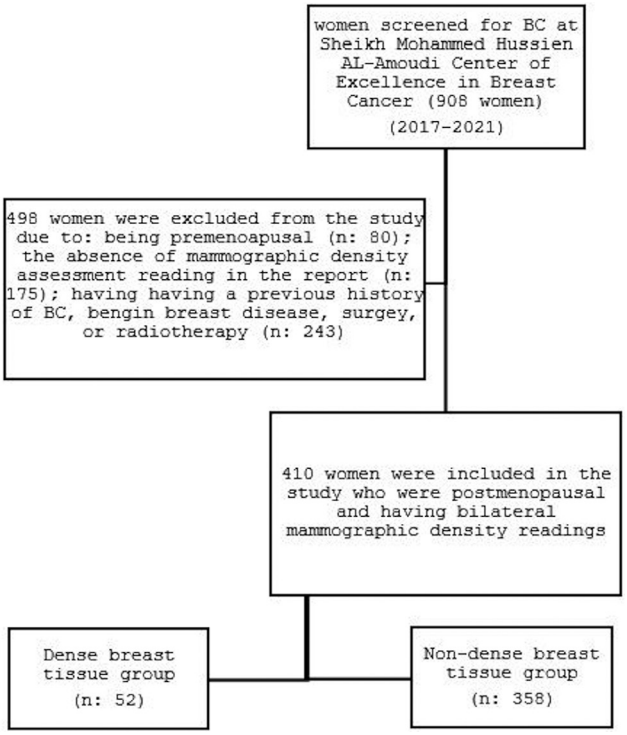

Figure 1 - Flowchart outlining the eligibility requirements for study participants.

Categorization of mammographic density in women was carried out according to the Breast Imaging Reporting and Data System (BI-RADS, 4th edition scheme), which divides breast density into 4 categories: BI-RADS A (almost entirely fatty), BI-RADS B (scattered fibroglandular tissue), BI-RADS C (heterogeneously dense), and BI-RADS D (extremely dense; Figure 2). A dual review process was instituted to ensure the accuracy of breast density assessment. Initially, a radiology resident interpreted the mammography findings, which were then reviewed and verified in detail by a female imaging consultant. This dual review procedure aims to improve the reliability and precision of interpretations, thus ensuring the accuracy of mammographic density assessment. The BI-RADS scale was categorized into low (BI-RADS A and B) and high (BI-RADS C and D) categories to simplify the interpretation of the study findings.

Statistical analysis. Differences in population characteristics, including age at screening, menopause, menarche, first birth, BMI, parity, live children, hormonal replacement therapy, family history of BC, and breastfeeding were analyzed between the dense and non-dense groups using the Chi-square test (X^2). Unadjusted logistic regression models were used to explore the association between mammographic density and the population features that exhibited a significant relationship ($p \leq 0.05$) with mammographic density. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to describe the analyses. All statistical tests were carried out using the Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA). A significance level of $p<0.05$ was used to determine statistical significance.

Results. Table 1 shows the demographic characteristics of the screened women included in the study. On average, their mean age was approximately 55±5.72 years. The mean age at first childbirth was approximately 22±4.94 years, with an average age at menarche of 12.9±1.74 years and menopause of 49.07±5.04 years. The participants had an average BMI of approximately 31±12.04 kg/m². Most of the population (68.5%) consisted of Saudi women, with nearly half (46.3%) falling into the 50-60 age group. Notably, half of the women (51.6%) had their first child before the age of 20, and 65.3% experienced menarche between the ages of 12-14 years. Most participants (91.9%) had given birth, with a small percentage (9%) reporting more than 8 children. Breastfeeding was prevalent, as reported by 87.3% of participants, whereas a minority (21%) had undergone HRT. A family history of BC was reported in 19.5% of screened women. The distribution of BMI revealed a higher prevalence of overweight (33.2%) and obesity (53.5%) among the participants. A minority of the women (12.7%) had dense breasts (Figure 3).

Table 2 displays variations in breast density across different population characteristics. Among the screened women, those with dense breasts were more likely to be

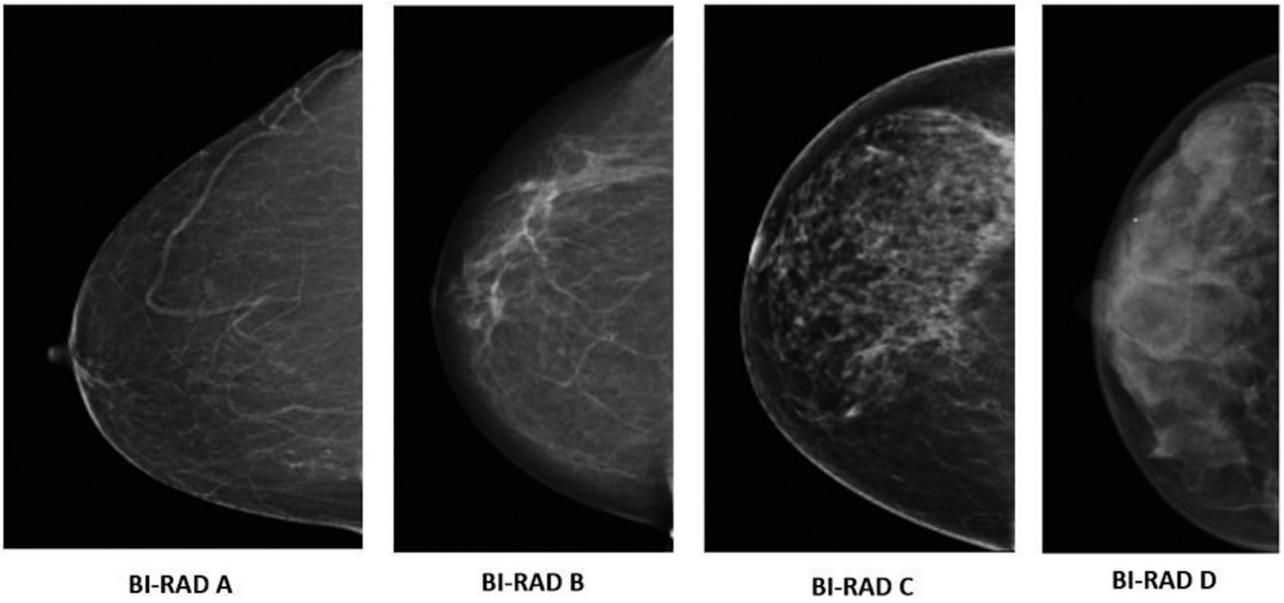

Figure 2 - The Breast Imaging Reporting and Data System (BI-RADS 4th edition scheme).

Table 1 - Population characteristics.

Characteristics	n (%)
Nationality	
Saudi	280 (68.5)
Non-Saudi	129 (31.5)
Age at screening	
≤49 years	17 (4.1)
50-54 years	190 (46.3)
55-59 years	114 (27.8)
≥60 years	89 (21.7)
Age at first pregnancy	
≤21 years	194 (51.6)
>21 years	182 (48.4)
Age at menarche	
<12 years	62 (15.8)
12-14 years	256 (65.3)
>14 years	74 (18.9)
Age at menopause	
<45 years	40 (14.3)
≥45 years	240 (85.7)
Number of children	
≤4	175 (46.5)
5-7	167 (44.4)
≥8	34 (9.0)
Breastfeeding	
No	52 (12.7)
Yes	357 (87.3)
Hormonal replacement therapy	
No	320 (79.0)
Yes	85 (21.0)
Family history of BC	
No	327 (80.5)
Yes	79 (19.5)
Body mass index	
Underweight	2 (0.6)
Normal weight	43 (12.6)
Obese	182 (53.5)
Overweight	113 (33.2)
Parity	
No	33 (8.1)
Yes	376 (91.9)
Age (years), mean±SD	55.71±5.72
Age at first pregnancy (years), mean±SD	21.8±4.94
Age at menarche (years), mean±SD	12.9±1.74
Age at menopause (years), mean±SD	49.07±5.04
Body mass index (kg/m^2), mean±SD	31.11±12.04

Values are presented as numbers and percentages (%) or mean ± standard deviation (SD). BC: breast cancer

non-Saudi (p=0.02), nulliparous (p<0.001), have fewer children (p=0.03), skip breastfeeding (p=0.004), and have a lower BMI (p=0.03). However, factors such as age, HRT administration, and family history of BC did not seem to influence breast density (p≥0.08).

Table 3 illustrates the determinants of dense breast tissue in postmenopausal women. Compared with

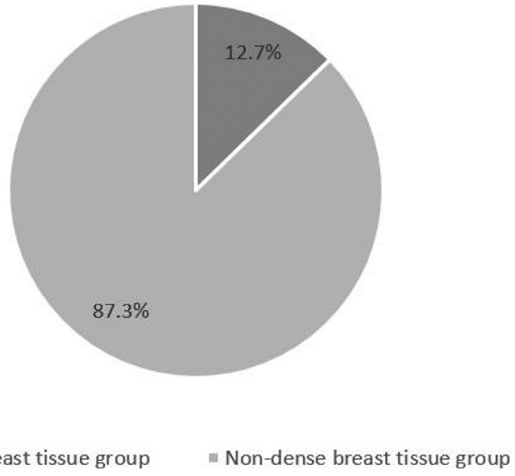

Figure 3 - Breast density distribution (dense and non-dense breast tissue groups).

Saudi women and those who breastfed, non-Saudi women (OR=1.95; 95% CI: [1.07-3.54]; p=0.02) and those who did not breastfeed (OR=2.75; 95% CI: [1.33-5.53]; p=0.006) had an increased likelihood of dense breast tissue. Compared with parous women, nulliparous individuals exhibited a 4-fold higher probability of having dense breast tissue (p<0.001). Additionally, those with fewer children (OR=2.58; 95% CI: [1.23-5.40]; p=0.01) showed higher odds of dense breast tissue. Notably, no significant variation was observed between breast density and BMI classifications (p≥0.07).

Discussion. The findings of the current study indicate that screened postmenopausal women in Saudi Arabia typically demonstrate low breast density. However, a minority of women exhibit dense breast tissue, notably, those who are non-Saudi, nulliparous, have lower parity, and abstain from breastfeeding.

The unexpected finding of dense breasts in some postmenopausal women highlights the complexity of breast density and the need for further research. Although age and menopause typically lead to a decrease in density, other factors may influence this trend. For example, HRT influences breast density. Although not statistically significant in our study, there was a slight increase in the number of women using HRT who exhibited denser breasts. The use of HRT among postmenopausal women potentially impedes the natural process of breast involution that typically occurs with aging, consequently leading to a sustained high breast density. Although this finding implies a potential association between HRT and increased breast density, further research is required to validate this observation.

Table 2 - Differences in population characteristics by mammographic density status.

Population features	Dense breast tissue	Non-dense breast tissue	*P*-values
Nationality			
Saudi	28 (54.9)	252 (70.4)	0.02
Non-Saudi	23 (45.1)	106 (29.6)	
Age			
≤49 years	3 (5.8)	14 (3.9)	
50-54 years	31 (59.6)	159 (44.4)	0.15
55-59 years	10 (19.2)	104 (29.0)	
≥60 years	8 (15.4)	81 (22.6)	
Age at first pregnancy			
≤21 years	20 (47.6)	174 (52.1)	0.58
>21 years	22 (52.3)	160 (47.9)	
Age at menarche			
<12 years	7 (14.0)	55 (16.1)	
12-14 years	33 (66.0)	223 (65.2)	0.9
>14 years	10 (20.0)	64 (18.7)	
Age at menopause			
<45 years	7 (25.0)	33 (13.1)	0.08
≥45 years	21 (75.0)	219 (86.9)	
Parity			
No	11 (21.1)	22 (6.2)	<0.001
Yes	41 (78.8)	335 (93.8)	
Number of children			
≤4	27 (65.8)	148 (44.2)	
5-7	11 (26.8)	156 (46.5)	0.03
≥8	3 (7.31)	31 (9.2)	
Breastfeeding			
No	13 (25.0)	39 (10.9)	0.004
Yes	39 (75.0)	318 (89.1)	
Hormonal replacement therapy			
No	40 (76.9)	280 (79.3)	0.6
Yes	12 (23.1)	73 (20.7)	
Family history of BC			
No	41 (78.8)	286 (80.7)	0.7
Yes	11 (21.1)	68 (19.2)	
Body mass index			
Normal weight	11 (25.5)	32 (10.8)	
Obese	17 (39.5)	165 (55.5)	0.03
Overweight	15 (34.8)	98 (32.9)	
Underweight	0 (0.0)	2 (0.6)	

Values are presented as numbers and percentages (%). BC: breast cancer

Table 3 - Predictors of dense breast tissue among postmenopausal women.

Population features	Dense breast tissue		
	OR	95% CI	*P*-values
Nationality			
Saudi	Reference	Reference	0.02
Non-Saudi	1.95	1.07-3.54	
Breastfeeding			
Yes	Reference	Reference	0.006
No	2.71	1.33-5.53	
Parity			
Yes	Reference	Reference	<0.001
No	4.08	1.84-9.03	
Body mass index			
Overweight	Reference	Reference	
Obese	0.67	0.32-1.40	0.29
Normal weight	2.24	0.93-5.38	0.07
Number of children			
5-7	Reference	Reference	
≤4	2.58	1.23-5.40	0.01
≥8	1.37	0.36-5.20	0.64

OR: odds ratio, CI: confidence interval

Genetic predisposition and inflammation may increase breast density in postmenopausal women. Variations or mutations in genes such as *BRCA1* and *BRCA2*, which are involved in estrogen metabolism, potentially contribute to sustained breast density.[12] These genetic alterations may disrupt estrogen breakdown processes, leading to prolonged exposure of breast tissue to active estrogen postmenopausally and facilitating the development of denser tissue. Furthermore, elevated levels of inflammatory markers, such as interleukin-6 (IL-6), in the breasts of postmenopausal women have been linked to greater breast density.[13,14] This link may be explained by the connection between inflammation and local estrogen production. The IL-6 may stimulate the production of an enzyme called aromatase, which converts other hormones into estrogen within the breast tissue. This potential pathway suggests a possible explanation for how inflammation contributes to higher breast density in postmenopausal women, although the overall estrogen levels typically decline post-menopause. Unfortunately, the current study had limited data regarding genetic factors and inflammatory markers. Therefore, further research is required to gain a deeper understanding of the complex interplay between genetic factors and breast density in postmenopausal women.

To date, only a single study focusing on Turkish postmenopausal women has explored dense breast tissue among postmenopausal women.[11] The results of that study support the current study's observation that postmenopausal women with dense breast tissue tend to have had fewer pregnancies and live births. Despite this correlation, the mechanisms underlying higher breast density observed in postmenopausal women with these reproductive characteristics remain largely unknown. One potential explanation for this phenomenon is related to hormonal changes associated with reproductive history. For instance, nulliparity, skipping breastfeeding, and delayed childbearing may lead to prolonged exposure of postmenopausal women to endogenous estrogen and progesterone, because

these hormones are known to influence breast tissue composition and density.[15] Therefore, it is plausible that extended exposure to estrogen and progesterone due to reproductive factors could contribute to the higher mammographic density observed in postmenopausal women with these reproductive characteristics. Further studies are required to elucidate the precise mechanisms underlying this relationship.

Our findings validate previous research indicating that Saudi women, as a group, tend to exhibit low levels of breast density.[16,17] The current study also reveals significant national differences in mammographic density among postmenopausal women undergoing screening. Variations in mammographic density between Saudi women and individuals of other nationalities were observed, which is consistent with the findings of Albeshan et al.[18] Their research indicated that Arab women, including Saudis, generally exhibit a lower mammographic density than women of Asian and African nations. These national variations in mammographic density underscore the necessity of considering national differences in BC screening and risk assessments in the Saudi population. Understanding these differences can inform personalized screening strategies and risk assessment models tailored to specific racial and ethnic groups. Further investigation into the underlying factors contributing to these disparities may provide valuable insights into BC risk and prevention strategies across diverse populations.

Our study findings align with prior research indicating that postmenopausal women with lower BMI often exhibit denser breast tissue.[11] Although the precise mechanism remains unclear, one potential explanation lies in the association between BMI and fatty tissue within the breasts. Studies have consistently shown a positive relationship between BMI and the presence of fatty breast tissue.[19-21] Consequently, higher BMI levels are typically linked to increased non-dense breast tissue. Thus, the observed reduction in breast density among our study participants, particularly among those classified as obese, may be attributed to the direct relationship between BMI and non-dense breast tissue.

Our findings hold significant promise for improving the detection and prevention of BC in postmenopausal Saudi Arabian women. First, identifying factors associated with higher breast density can help tailor screening strategies. Currently, mammography is less effective in women with dense breast tissue. Knowing who might fall into this category may allow us to consider additional methods such as ultrasonography or MRI in combination with mammography for these women, potentially leading to earlier and more accurate cancer detection. Secondly, these findings lay the groundwork for future research on lifestyle modifications as a potential preventive strategy. While more research, particularly large-scale longitudinal studies, is needed to confirm these links, our findings suggest a possible correlation of factors such as childbirth, breastfeeding, and birth control use with breast density. Understanding these relationships could inform future recommendations for women when considering these choices. This knowledge can empower healthcare professionals to tailor strategies based on individual risk factors, ultimately contributing to improved patient outcomes.

Our investigation offers distinct advantages that may guide personalized BC tactics in Saudi Arabia. Additionally, detailed data on potential influencing factors such as demographics, reproductive history, and body measurements play a role in revealing the predictors of dense breast tissue among postmenopausal individuals.

Study limitations. While the BI-RADS 4th edition scheme is typically used by radiologists for breast density assessment, this method can be subjective and prone to variations between observers. However, the dual review process used in this study may address the potential benefits of breast density assessment. Another limitation is the lack of genetic and breast tissue inflammation marker data, which have been linked to a higher density in postmenopausal women.[13,14,22]

In conclusion, our findings revealed a very low prevalence of dense breast tissue among screened postmenopausal women. Furthermore, the study revealed that being non-Saudi, being nulliparous, having fewer children, and skipping breastfeeding were correlated with increased breast density in this population. Although these results hold promise for the development of personalized BC screening and prevention strategies in postmenopausal women in Saudi Arabia, further research is required to confirm these findings in larger and more diverse populations.

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