International Journal of Drug Research in Clinics

Int J Drug Res Clin, 2024, 2, e3
10.34172/ijdrc.2024.e3
http://ijdrug.com

Original Article

The Relationship Between Breast Cancer Risk Factors and Mammographic Density

Mahnaz Ranjkesh[1], Somayeh Shaker[1], Saba Mehrtabar[2,3], Mahya Ahmadpour Youshanlui[2], Samin Alihosseini[1*]

[1]Medical Radiation Sciences Research Group, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Article History:
Received: November 22, 2023
Accepted: January 12, 2024
ePublished: April 3, 2024

***Corresponding Author:**
Samin Alihosseini,
Email: samin.alihosseini@gmail.com

Abstract

Background: Mammography is the most important evaluation technique for breast cancer screening. The importance of understanding mammographic density becomes evident when considering its relationship with breast cancer risk. There exists a positive correlation between high mammographic density and an increased susceptibility to breast cancer. Therefore, knowing the prevalence of breast density and its associated factors helps consider possible interventions and medical management to alter the density and properly follow up with the patients.

Methods: A total of 350 women in Azerbaijan enrolled in this cross-sectional study. Patient's questionnaires included demographic data such as age, weight, height, education, menarche age, menopause status and age, oophorectomy history, marital status, number of successful deliveries, age of first delivery, number of breast-feeding times, duration of breastfeeding, oral contraceptives/ hormone replacement therapy (HRT) usage, menstrual status, familial history of cancer, history of benign breast lesion biopsy, and alcohol/smoking status. The evaluation of breast density was done according to the American College of Radiology grading A to D.

Results: The average age of the studied patients was 45.68±6.96 years with a median of 44.5 years. The population of women with breast density above 50% was higher compared to those with low breast density (51.4% versus 48.6%). In women without a history of breastfeeding, the frequency of breast density above 50% was observed in 76.4% of women. Significantly, lower densities were observed during menopause, and higher densities were observed during non-menopause ($P=0.001$). Furthermore, no relationship was observed between breast composition and nulliparity, history of oophorectomy, duration of breastfeeding, marital status, menstrual status, and oral contraceptive pill (OCP) consumption.

Conclusion: The main risk factors of high breast density include young age, menstrual status (non-menopausal patients), lack of breastfeeding after childbirth, older age of first delivery, and lower body mass index.

Keywords: Breast density, Screening mammography, Breast cancer, Risk factors, Cross-sectional

Please cite this article as follows: Ranjkesh M, Shaker S, Mehrtabar S, Ahmadpour Youshanlui M, Samin Alihosseini S. The relationship between breast cancer risk factors and mammographic density. Int J Drug Res Clin. 2024; 3: e3. doi: 10.34172/ijdrc.2024.e3

Introduction

Breast cancer is a major public health issue worldwide, and the implementation of breast screening programs is crucial in reducing death rates and improving patient outcomes by enabling early detection.[1-3] Mammography, being widely recognized as the main technique for breast cancer screening, has played a crucial role in the early detection of tumors, enabling timely intervention and treatment. Furthermore, mammographic density, which refers to the proportion of dense, fibroglandular tissue relative to the overall breast composition, has attracted increasing attention as a characteristic of mammographic images.[4-7] The importance of understanding mammographic density becomes evident when considering its relationship with breast cancer risk. There exists a positive correlation between high mammographic density and an increased susceptibility to breast cancer, hence presenting obstacles in the process of cancer identification.[8]

The significance of investigating mammographic density resides in its potential as a biomarker for the evaluation of breast cancer risk. There exists a notable association between elevated mammographic density in women and a substantially heightened susceptibility to the development of breast cancer when contrasted with those with breast tissue characterized by low density.[6,9,10] Additionally, there may exist a correlation between breast density and the chance of developing ovarian cancer, hence suggesting the potential use of breast density as a predictive factor for assessing future risk.[11]

Gaining insight into the factors that contribute to the

© 2024 The Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

variability in mammographic density can provide valuable knowledge on the fundamental mechanisms involved in the progression of breast cancer. Several variables contribute to this condition, including age, the effect of drugs and hormones, genetic predisposition, parity, body mass index (BMI), lifestyle decisions, environmental exposures, dietary patterns, regional and ethnic variations, and past medical records.[12-20] Furthermore, it can facilitate the recognition of individuals at a heightened risk level who could potentially get greater advantages from stricter screening and preventative approaches.[21-24] The unique genetic, behavioral, and environmental variables present in this particular location may exert differential effects on breast density and the risk of developing breast cancer compared to other communities.[25-27]

Mammographic density has been widely studied in many populations, but there is limited information about its characterization and consequences in Northwest Iran. This cross-sectional study aimed to investigate mammographic density among women who were undergoing breast screening assessment in the region. The study sought to fill the knowledge gap regarding the prevalence, distribution, and potential risk factors associated with mammographic density in this specific population. The research not only contributes to the global understanding of breast cancer risk factors, but it also has the potential to inform more effective and region-specific screening strategies, improving breast cancer outcomes in Northwest Iran.

Methods

This cross-sectional study encompasses 350 women in Azerbaijan who underwent screening mammography at Al-Zahra hospital (obstetrics and gynecology tertiary referral hospital of Tabriz University of Medical Sciences) between May 2018 and May 2019. Patients with a history of breast cancer, metabolic diseases, or undergoing infertility treatment were excluded. The subjects were informed that no additional interventions, costs, or risks would be imposed on them, and their information would be kept confidential. The patients were given a questionnaire that included questions about their age, weight, height, education, age of first menstruation, menopause status and age, history of ovary removal, marital status, number of successful deliveries, age of first delivery, number of times breastfed, duration of breastfeeding, usage of oral contraceptive pill (OCP) or hormone replacement therapy (HRT), menstrual status, familial history of cancer, history of benign breast lesion biopsy, and alcohol/smoking habits. The breast density was evaluated based on the proportion of radiolucent and radiodense tissue seen in the mammography, which was graded according to the American College of Radiology (ACR) scale - A to D[28]:

- ACR A: A breast that is almost entirely fat;
- ACR B: The presence of scattered fibroglandular densities;
- ACR C: Breast tissue that is heterogeneously dense and may lower the sensitivity of mammography;
- ACR D: Extremely dense breast tissue that could obscure a lesion on mammography.

The data were analyzed using SPSS software (SPSS Version 22, Chicago, USA). Mean and dispersion indices were used for quantitative variables, and frequency and percentage were used for qualitative variables. Student's *t* test investigated the relationship between quantitative variables, while the chi-square test investigated the relationship between qualitative variables. A *P* value less than 0.05 was considered significant.

Results

In this cross-sectional study, 350 women referred for screening mammography were examined. The average age of the studied patients was 45.68 ± 6.96 years, with a median of 44.5 years. The minimum age of the patients was 30 years, and the maximum was 68 years. The average weight of the studied patients was 73.98 ± 11.97 kg with a median of 72 kg. The lowest weight of the patients was 50 kg, and the highest was 118 kg. The average height of the studied patients was 159.99 ± 6.09 cm with a median of 160 cm. The minimum height of the patients was 140 cm, and the maximum height was 180 cm. The average BMI of the studied patients was 28.91 ± 4.32 kg/m^2, with a median of 28.28 kg/m^2, the lowest BMI of the patients was equal to 19 kg/m^2, and the highest was equal to 42.8 kg/m^2. All three variables of weight, height, and BMI in the studied patients had a normal distribution.

Regarding education, the highest frequency was related to primary education, with a frequency of 25%. The average age of menarche in the studied patients was 13.08 ± 1.25 years, with a median of 13 years. The minimum age of menarche was 11 years, and the maximum age was 19 years. Of the 350 studied patients, 94 (26.9%) were menopausal, and the average age of menarche in these patients was 47.26 ± 5.52 years, with a median of 48.5 years. The minimum age of menopause was 28 years, and the maximum was 55 years. Out of 350 studied patients, 10 (2.9%) had a history of oophorectomy, and the average age of oophorectomy was 41.2 ± 13.55 years, with a median of 47 years. Furthermore, the minimum age for oophorectomy was 17, and the maximum age was 48 years.

Regarding marital status, 18 (1.5%) were single, and 332 (94.9%) were married. The average number of successful deliveries in the studied patients was 2.32 ± 1.18 times, with a median of 2 times. The lowest number of successful births was 0, and the highest was 8. The average age of the patients at their first delivery was 23.66 ± 5.62 years, with a median of 22 years. Moreover, the minimum age of the patients at their first delivery was 14 years, and the maximum was 42 years.

The average number of breastfeeding cases of the studied patients was 2.30 ± 1.17 times with a median of 2 times. The lowest number of breastfeeding patients was 0 times,

and the highest was eight times. The average breastfeeding duration of the studied patients was 18.87 ± 6.44 months, with a mean of 21 months. Additionally, the minimum duration of breastfeeding was two months, and the maximum was 36 months.

In terms of OCP use by patients, in general, 222 patients (63.4%) used OCP in the past in the form of monthly and annual periods. The average monthly periods of OCP consumption in the studied patients was 5.31 ± 5.2, with a median of 3 months, and the average annual periods of OCP consumption in the studied patients was 4.4 ± 3.1 years, with a median of 3 years. In contrast, there was no history of HRT in any of the patients.

Menstrual status was reported as regular in 202 patients (57.7%), irregular in 98 patients (28%), and not reported in 50 patients (14.3%). The average duration of the menstrual cycle in patients with regular menstruation was 26.37 ± 3.09 days and 22.38 ± 3.75 days in patients with irregular menstruation. Moreover, the duration of the menstrual cycle was significantly longer in patients with regular menstruation ($P = 0.001$).

Examining the family history of cancer in the studied patients showed that in 42 cases (12%), there was a positive family history, the frequency of which is shown in Table 1.

A history of breast biopsy with benign results was reported in 18 patients (1.5%), which included 12 cases of fibrocystic changes, 4 cases of fibroadenoma, and 2 cases of granulomatous mastitis. Moreover, a history of endometrial cancer was reported in 2 patients. Meanwhile, no atypical papilloma or lobar carcinoma in situ was reported.

In the case of alcohol and tobacco consumption, only 2 cases of daily alcohol consumption were reported, and the patients had no history of smoking.

Table 1. Frequency of Cancer Family History in the Studied Patients

Family History of Cancer	Number (%)
Breast cancer in the mother and prostate cancer in the father at the same time	2 (4.75%)
Breast cancer in mother	8 (19%)
Breast cancer in sister	18 (43%)
Breast cancer in the mother and simultaneously in the sister	2 (4.75%)
Prostate cancer in father	12 (28.5%)
Total	42 (12%)

Table 2. Frequency of Bra Size in the Studied Patients

Bra Size	Number (%)
65	8 (2.3)
70	58 (16.6)
75	94 (26.9)
80	62 (17.7)
85	104 (29.7)
90	8 (2.3)
95	10 (2.9)
100	6 (1.7)
Total	350 (100)

Table 2 presents the frequency of Bra size in the studied patients. As can be seen, the highest frequency is related to size 85, with a frequency of 104 cases (29.7%).

Table 3 illustrates the frequency of breast composition in the screening mammography of the studied patients. It can be seen that the highest frequency is related to type B, with a frequency of 154 cases (44%), and then Type C, with a frequency of 152 cases (43.4%).

Significantly, the results showed that higher densities are most frequently found in the younger age group of patients (between 30-50 years old), while lower densities are most frequent in the older age group (between 51-68 years old, $P = 0.003$). Significantly, lower densities were observed during menopause, and higher densities were observed during non-menopause ($P = 0.001$). Furthermore, there was no relationship between breast composition and the history of oophorectomy ($P = 0.373$), marital status ($P = 0.230$), menstrual status ($P = 0.176$), and OCP consumption ($P = 0.119$).

In the present study, the frequency of nulliparous patients was equal to 12 cases (6.9%). In these patients, the highest density frequency was related to type C, with a frequency of 6 cases (50%), but no statistically significant relationship was observed ($P = 0.061$).

It is evident that higher densities are significantly seen when there is no history of breastfeeding ($P = 0.028$). In addition, there was no relationship between the duration of breastfeeding and breast composition status in the studied patients (Table 4).

The results of the present study indicated that patients with a higher age at first delivery have a significantly higher density in breast composition ($P = 0.034$). Furthermore, patients with lower BMI have significantly higher densities ($P = 0.001$), as depicted in Table 5.

Discussion

The patients examined in the present study had an average age of 45.68. Factors associated with higher breast density in this study include younger age (between 30 and 50 years old), menstrual status (non-menopausal patients), nulliparity, lack of breastfeeding after childbirth, higher age at first delivery, and low BMI.

In women without a history of breastfeeding, the frequency of breast density above 50% was observed in 76.4% of women. Significantly, lower densities were observed during menopause, and higher densities were

Table 3. Frequency of Breast Composition in the Screening Mammography of the Studied Patients

Breast Composition	Number (%)
Type A	16 (4.6)
Type B	154 (44)
Type C	152 (43.4)
Type D	28 (8)
Total	350 (100)

Table 4. The Relationship Between Risk Factors and Breast Composition Status

	Type A (%)	Type B (%)	Type C (%)	Type D (%)	Total (%)
Age group					
30-50	6 (2.2)	114 (41)	134 (48.2)	24 (8.6)	278 (79.4)
51-68	10 (13.9)	40 (55.6)	18 (25)	4 (5.6)	72 (20.6)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
Menstrual status					
Menopaused	14 (14.9)	60 (63.8)	18 (19.1)	2 (2.1)	94 (26.9)
Non-menopaused	2 (8.0)	94 (36.7)	134 (52.3)	26 (10.2)	256 (73.1)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
History of oophorectomy					
Positive	2 (20)	4 (40)	4 (40)	0	10 (2.9)
Negative	14 (4.1)	150 (44.1)	148 (43.5)	28 (8.2)	340 (97.1)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
Marital status					
Single	2 (11.1)	4 (22.2)	8 (44.4)	4 (22.2)	18 (5.1)
Married	14 (4.2)	150 (45.2)	144 (43.4)	24 (7.2)	332 (94.9)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
Delivery status					
Nulliparous	2 (8.3)	4 (16.7)	12 (50)	6 (25)	24 (6.9)
Others	14 (4.3)	150 (46)	140 (42.9)	22 (6.7)	326 (93.1)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
Breastfeeding history					
No breastfeeding	2 (5.9)	6 (17.6)	18 (52.9)	8 (23.5)	34 (9.7)
Breastfeeding	14 (4.4)	148 (46.8)	134 (42.4)	20 (6.3)	316 (90.3)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)
OCP consumption					
Yes	8 (3.6)	114 (50.9)	84 (38.2)	16 (7.3)	222 (63.4)
No	8 (6.2)	42 (32.3)	68 (52.3)	12 (9.2)	128 (36.6)
Total	16 (4.6)	154 (44)	152 (43.4)	28 (8)	350 (100)

Note. OCP: Oral contraceptive pill.

Table 5. Relationship between the Age of First Delivery and BMI with Breast Composition

Breast Composition	The Average Age of First Delivery (years)	Average BMI (kg/m^2)
Type A	21.85 ± 4.05	33.17 ± 6.01
Type B	22.56 ± 5.08	29.65 ± 3.99
Type C	24.54 ± 6.05	28.28 ± 3.97
Type D	26.72 ± 5.67	25.70 ± 4.26

Note. BMI: Body mass index.

observed during non-menopause ($P = 0.001$). Additionally, no relationship was observed between breast composition and nulliparity, history of oophorectomy, duration of breastfeeding, marital status, menstrual status, and OCP consumption.

In the present study, most of the patients were in the classification of B and C according to ACR-Breast Imaging Reporting and Data System (ACR-BIRADS). According to the findings, it seems that breast density in Iranian women is higher than that in other studies in this field. In the study by Wolf et al, the frequency of high density in the case group was 66%, while it was 37% in the control group.[29] According to the results of case-control research done by Saftlas et al, the proportion of mammographic densities in the breast has a higher level of accuracy in predicting the risk of breast cancer compared to a qualitative evaluation of mammographic patterns.[30] According to the results obtained in the present study, age, menstrual status, breastfeeding status, age at first delivery, and BMI had a statistically significant relationship with breast density. Studies suggest that women under the age of 50 are more likely to have high breast density. As women age, the density of breast tissue tends to decrease, which is consistent with recent research in this field. Recent studies have found that women between the ages of 30-50 have the highest density of breast tissue, which is believed to be associated with their hormonal status.[30-35]

Unlike parity and menstrual status, patients' age was unrelated to breast density. It seems that parity and menstrual status led to the masking of the effect of age on breast density, which was also mentioned in the study by Modugno et al.[35] In a study by Moradi et al, no relationship

was observed between age and breast density by adjusting the effect of parity and BMI.[36]

The present study found that women without a history of breastfeeding have a significantly higher frequency of breast density above 50% (76.4%) in contrast to a study conducted in the United States by Modugno et al which found no relationship between breastfeeding and high breast density. This suggests that breastfeeding may lead to a change in the rate of cancer through altering breast density. It is important to note that the average rate of parity in developing countries is higher than that in the United States, and this may explain the difference observed compared to the Modugno et al study. Therefore, it is recommended that future studies investigate the relationship between breastfeeding duration and breast density in women. This study found that breast density in pre-menopausal women is higher than that in menopausal women, possibly due to hormonal changes. Although the use of OCP is expected to affect breast density, the present study did not find any statistical significance. However, unlike our study, other studies have reported a relationship between OCP use and breast density.[31,33,37] This difference could be due to the inaccuracy of the history of OCP use in our study.

The present study reported only two cases of alcohol and tobacco use, but it is suspected that the amount was not reported accurately due to cultural factors. Other studies have found a significant correlation between smoking and breast density.[38,39]

In contrast to our study, other studies have found a significant relationship between higher parity and a decrease in breast density. It appears that low parity is associated with young age and increased breast density, likely due to hormonal changes in the body after pregnancy, and this leads to changes in breast density.[40-42] On the other hand, our study found that low parity is associated with young age and increased breast density. Furthermore, a statistically significant relationship was observed between breast density and the age of the first delivery in our study, which is consistent with the known effect of the age of the first delivery on the risk of breast cancer. Other studies have also supported our findings.[29,30,32,33] For example, it was found in a study that nulliparity and the age of the first delivery at an advanced age were significantly related to the increase in breast density during menopause and pre-menopause.[31] However, some studies have reported contradicting results, with no observed correlation between the age of first delivery and breast density.[29,43] Some studies, however, reported an inverse relationship between BMI and breast density. Likewise, our study found that women with low breast densities have a BMI above 30 kg/m^2, while those with high breast densities have a BMI below 26 kg/m^2.[30,31,37]

Based on the findings of the current study, it can be concluded that the majority of patients had B and C breast density according to mammography classification. The main risk factors for high breast density in women who underwent mammography screening include young age (30-50 years), non-menopausal status, nulliparity, lack of breastfeeding after childbirth, older age at first delivery, and lower BMI. In Iran, breast cancer is the most common cancer among women, and studies have documented a prevalence rate of 24.4% among all neoplasms for breast cancer.[34,35] Its prevalence is increasing, and despite different diagnostic methods, many patients are diagnosed with higher cancer stages.[36] For this reason, a quick and timely diagnosis of breast cancer can be beneficial in the treatment efficiency and reducing the mortality rate.

Some studies suggest that certain factors such as medication use, underlying disorders (e.g., diabetes mellitus), and metabolic status (e.g., lipid profile) that are common in society may influence the study's outcome. Unfortunately, this study did not examine these factors which is one of its limitations.[44-46] Therefore, it is recommended to conduct larger population studies and compare previous mammograms of patients with and without a cancer history to obtain more valuable information

Conclusion

Breast density is a significant risk factor for breast cancer, and it can be influenced by various factors such as young age, menstrual status (non-menopausal patients), lack of breastfeeding after childbirth, older age of first delivery, and lower BMI. By altering these factors, we can manipulate the risk of breast cancer prevalence. Accordingly, future studies should focus on the pharmaceutical and medical interventions that can alter the density of breasts in high-risk patients, hence reducing the likelihood of breast cancer development.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tabriz University of Medical Sciences with code IR.TBZMED.REC.1397.321. Informed consent was also obtained from all individual participants included in the study.

Disclosure of funding source

None.

Conflict of interests declaration

None.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to individual privacy but are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: Mahnaz Ranjkesh.
Data curation: Somayeh Shaker.
Formal analysis: Somayeh Shaker, Mahya Ahmadpour Youshanlui.
Investigation: Mahnaz Ranjkesh, Somayeh Shaker.
Methodology: Somayeh Shaker, Saba Mehrtabar.
Project administration: Mahnaz Ranjkesh.
Resources: Mahnaz Ranjkesh.

Software: Saba Mehrtabar.
Supervision: Saba Mehrtabar.
Validation: Samin Alihosseini.
Visualization: Samin Alihosseini.
Writing–original draft: Samin Alihosseini, Saba Mehrtabar, Mahya Ahmadpour Youshanlui.
Writing–review & editing: Samin Alihosseini, Saba Mehrtabar, Mahya Ahmadpour Youshanlui.

Consent for publication

Not applicable.

References

1. Azamjah N, Soltan-Zadeh Y, Zayeri F. Global trend of breast cancer mortality rate: a 25-year study. Asian Pac J Cancer Prev. 2019;20(7):2015-20. doi: 10.31557/apjcp.2019.20.7.2015.
2. Suwankhong D, Liamputtong P, Boonrod T, Simla W, Khunpol S, Thanapop S. Breast cancer and screening prevention programmes: perceptions of women in a multicultural community in southern Thailand. Int J Environ Res Public Health. 2023;20(6):4990. doi: 10.3390/ijerph20064990.
3. Nayyar S, Chakole S, Taksande AB, Prasad R, Munjewar PK, Wanjari MB. From awareness to action: a review of efforts to reduce disparities in breast cancer screening. Cureus. 2023;15(6):e40674. doi: 10.7759/cureus.40674.
4. Sankatsing VDV, van Ravesteyn NT, Heijnsdijk EA, Looman CW, van Luijt PA, Fracheboud J, et al. The effect of population-based mammography screening in Dutch municipalities on breast cancer mortality: 20 years of follow-up. Int J Cancer. 2017;141(4):671-7. doi: 10.1002/ijc.30754.
5. Al-Mousa DS, Alakhras M, Spuur KM, Alewaidat H, Abdelrahman M, Rawashdeh M, et al. The implications of increased mammographic breast density for breast screening in Jordan. J Med Radiat Sci. 2020;67(4):277-83. doi: 10.1002/jmrs.414.
6. Shaghayeq Nazari S, Mukherjee P. An overview of mammographic density and its association with breast cancer. Breast Cancer. 2018;25(3):259-67. doi: 10.1007/s12282-018-0857-5.
7. Tarchi SM, Pernia Marin M, Hossain MM, Salvatore M. Breast stiffness, a risk factor for cancer and the role of radiology for diagnosis. J Transl Med. 2023;21(1):582. doi: 10.1186/s12967-023-04457-0.
8. Brown AL, Vijapura C, Patel M, De La Cruz A, Wahab R. Breast cancer in dense breasts: detection challenges and supplemental screening opportunities. Radiographics. 2023;43(10):e230024. doi: 10.1148/rg.230024.
9. Duffy SW, Morrish OW, Allgood PC, Black R, Gillan MGC, Willsher P, et al. Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. Eur J Cancer. 2018;88:48-56. doi: 10.1016/j.ejca.2017.10.022.
10. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res. 2011;13(6):223. doi: 10.1186/bcr2942.
11. Tran TX, Kim S, Park B. Mammographic breast density and risk of ovarian cancer in Korean women. Cancer Epidemiol Biomarkers Prev. 2023;32(12):1690-8. doi: 10.1158/1055-9965.epi-23-0494.
12. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5(2):77-106. doi: 10.1016/j.gendis.2018.05.001.
13. Boyd NF, Martin LJ, Rommens JM, Paterson AD, Minkin S, Yaffe MJ, et al. Mammographic density: a heritable risk factor for breast cancer. Methods Mol Biol. 2009;472:343-60. doi: 10.1007/978-1-60327-492-0_15.
14. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol. 2005;6(10):798-808. doi: 10.1016/s1470-2045(05)70390-9.
15. Holowko N, Eriksson M, Kuja-Halkola R, Azam S, He W, Hall P, et al. Heritability of mammographic breast density, density change, microcalcifications, and masses. Cancer Res. 2020;80(7):1590-600. doi: 10.1158/0008-5472.can-19-2455.
16. Moran O, Eisen A, Demsky R, Blackmore K, Knight JA, Panchal S, et al. Predictors of mammographic density among women with a strong family history of breast cancer. BMC Cancer. 2019;19(1):631. doi: 10.1186/s12885-019-5855-2.
17. Pastore E, Caini S, Bendinelli B, Palli D, Ermini I, de Bonfioli Cavalcabo N, et al. Dietary patterns, dietary interventions, and mammographic breast density: a systematic literature review. Nutrients. 2022;14(24):5312. doi: 10.3390/nu14245312.
18. Voon NS, Chelliah KK. Is there an influence of dietary habits on breast density as seen on digital mammograms? Asian Pac J Cancer Prev. 2011;12(8):1969-72.
19. Ohmaru A, Maeda K, Ono H, Kamimura S, Iwasaki K, Mori K, et al. Age-related change in mammographic breast density of women without history of breast cancer over a 10-year retrospective study. PeerJ. 2023;11:e14836. doi: 10.7717/peerj.14836.
20. Tran TX, Moon SG, Kim S, Park B. Association of the interaction between mammographic breast density, body mass index, and menopausal status with breast cancer risk among Korean women. JAMA Netw Open. 2021;4(12):e2139161. doi: 10.1001/jamanetworkopen.2021.39161.
21. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res. 2011;13(6):223. doi: 10.1186/bcr2942.
22. Hack CC, Emons J, Jud SM, Heusinger K, Adler W, Gass P, et al. Association between mammographic density and pregnancies relative to age and BMI: a breast cancer case-only analysis. Breast Cancer Res Treat. 2017;166(3):701-8. doi: 10.1007/s10549-017-4446-7.
23. Boyd NF, Melnichouk O, Martin LJ, Hislop G, Chiarelli AM, Yaffe MJ, et al. Mammographic density, response to hormones, and breast cancer risk. J Clin Oncol. 2011;29(22):2985-92. doi: 10.1200/jco.2010.33.7964.
24. Vabistsevits M, Smith GD, Richardson TG, Richmond RC, Sieh W, Rothstein JH, et al. The mediating role of mammographic density in the protective effect of early-life adiposity on breast cancer risk: a multivariable Mendelian randomization study. medRxiv [Preprint]. September 2, 2023. Available from: https://www.medrxiv.org/content/10.1101/2023.09.01.23294765v1.
25. Douglas JA, Roy-Gagnon MH, Zhou C, Mitchell BD, Shuldiner AR, Chan HP, et al. Mammographic breast density--evidence for genetic correlations with established breast cancer risk factors. Cancer Epidemiol Biomarkers Prev. 2008;17(12):3509-16. doi: 10.1158/1055-9965.epi-08-0480.
26. Yan H, Ren W, Jia M, Xue P, Li Z, Zhang S, et al. Breast cancer risk factors and mammographic density among 12518 average-risk women in rural China. BMC Cancer. 2023;23(1):952. doi: 10.1186/s12885-023-11444-7.
27. Cohn BA, Terry MB. Environmental influences on mammographic breast density in California: a strategy to reduce breast cancer risk. Int J Environ Res Public Health. 2019;16(23):4731. doi: 10.3390/ijerph16234731.
28. Mainiero MB, Lourenco A, Mahoney MC, Newell MS, Bailey L, Barke LD, et al. ACR appropriateness criteria breast cancer screening. J Am Coll Radiol. 2016;13(11 Suppl):R45-9. doi: 10.1016/j.jacr.2016.09.021.
29. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal

patterns and quantitative evaluation of mammographic densities: a case-control study. AJR Am J Roentgenol. 1987;148(6):1087-92. doi: 10.2214/ajr.148.6.1087.
30. Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, Salane M, et al. Mammographic densities and risk of breast cancer. Cancer. 1991;67(11):2833-8. doi: 10.1002/1097-0142(19910601)67:11<2833::aid-cncr2820671121>3.0.co;2-u.
31. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control. 2000;11(7):653-62. doi: 10.1023/a:1008926607428.
32. Nadrljanski MM, Marković BB, Milošević Z. Breast ductal carcinoma in situ: morphologic and kinetic MRI findings. Iran J Radiol. 2013;10(2):99-102. doi: 10.5812/iranjradiol.4876.
33. Azarian A, Mohammadifard M. Analysis of the factors, effective on breast parenchymal density in mammogram. Iran J Obstet Gynecol Infertil. 2008;11(1):9-16. doi: 10.22038/ijogi.2008.5935. [Persian].
34. Kerlikowske K, Ichikawa L, Miglioretti DL, Buist DS, Vacek PM, Smith-Bindman R, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. J Natl Cancer Inst. 2007;99(5):386-95. doi: 10.1093/jnci/djk066.
35. Modugno F, Ngo DL, Allen GO, Kuller LH, Ness RB, Vogel VG, et al. Breast cancer risk factors and mammographic breast density in women over age 70. Breast Cancer Res Treat. 2006;97(2):157-66. doi: 10.1007/s10549-005-9105-8.
36. Moradi M, Ganji K, Teyfouri N, Kolahdoozan F. Performance of double reading mammography in an Iranian population and its effect on patient outcome. Iran J Radiol. 2013;10(2):51-5. doi: 10.5812/iranjradiol.11729.
37. Titus-Ernstoff L, Tosteson AN, Kasales C, Weiss J, Goodrich M, Hatch EE, et al. Breast cancer risk factors in relation to breast density (United States). Cancer Causes Control. 2006;17(10):1281-90. doi: 10.1007/s10552-006-0071-1.
38. Butler LM, Gold EB, Conroy SM, Crandall CJ, Greendale GA, Oestreicher N, et al. Active, but not passive cigarette smoking was inversely associated with mammographic density. Cancer Causes Control. 2010;21(2):301-11. doi: 10.1007/s10552-009-9462-4.
39. Pepłońska B, Kalużny P. Cigarette smoking and mammographic breast density among Polish women. Int J Occup Med Environ Health. 2021;34(6):805-15. doi: 10.13075/ijomeh.1896.01832.
40. Salem C, Atallah D, Safi J, Chahine G, Haddad A, El Kassis N, et al. Breast density and breast cancer incidence in the Lebanese population: results from a retrospective multicenter study. Biomed Res Int. 2017;2017:7594953. doi: 10.1155/2017/7594953.
41. Dorgan JF, Klifa C, Deshmukh S, Egleston BL, Shepherd JA, Kwiterovich PO Jr, et al. Menstrual and reproductive characteristics and breast density in young women. Cancer Causes Control. 2013;24(11):1973-83. doi: 10.1007/s10552-013-0273-2.
42. Ochi T, Tsunoda H, Yamauchi H, Takahashi O. Impact of childbirth history on dense breast in mammographic screening: a cross-sectional study. BMC Womens Health. 2022;22(1):194. doi: 10.1186/s12905-022-01772-4.
43. Zheng Y, Zhang S, Tan Grahn HM, Ye C, Gong Z, Zhang Q. Prophylactic lamivudine to improve the outcome of breast cancer patients with HBsAg positive during chemotherapy: a meta-analysis. Hepat Mon. 2013;13(4):e6496. doi: 10.5812/hepatmon.6496.
44. Jafarizadeh A, Raeisi SA, Ghassab-Abdollahi N, Yarani R, Araj-Khodaei M, Mirghafourvand M. Effect of *Citrullus colocynthis* on glycemic factors and lipid profile in type II diabetic patients: a systematic review and meta-analysis. J Diabetes Metab Disord. 2022;21(2):1785-95. doi: 10.1007/s40200-022-01045-9.
45. Miller B, Chalfant H, Thomas A, Wellberg E, Henson C, McNally MW, et al. Diabetes, obesity, and inflammation: impact on clinical and radiographic features of breast cancer. Int J Mol Sci. 2021;22(5):2757. doi: 10.3390/ijms22052757.
46. Nouri M, Mohsenpour MA, Katsiki N, Ghobadi S, Jafari A, Faghih S, et al. Effect of serum lipid profile on the risk of breast cancer: systematic review and meta-analysis of 1,628,871 women. J Clin Med. 2022;11(15):4503. doi: 10.3390/jcm11154503.