Original Article

Investigating the Factors Affecting the Mammographic Density of Breast Tissue in Patients Referred to the Breast Cancer Research Center, Iran

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Abstract

Introduction: Of the factors leading to false negative results in mammography is breast tissue density, and by increasing the density of breast tissue in mammography, the mammography sensitivity decreases. On the other hand, increasing the breast tissue density leads to increased risk of breast cancer. Various factors such as inheritance, genetics, hormonal and reproductive factors, and nutritional factors can affect the breast density, but the definitive cause of this issue is unknown. This study investigated the possible factors influencing the increase in breast tissue density in mammography.

Methods: In this cross-sectional study, a total of 428 patients were enrolled; the demographic questionnaire on variables included age, body mass index (BMI), fertility, age of menarche, taking oral contraceptive pills (OCP), menstrual status and breast size, which were completed and evaluated. To determine the relationship between the studied variables and the breast density in mammography, chi-squared test and logistic regression were used.

Results: The results showed significant correlation in age of less than 50 years, small breast cup size, low BMI, and the premenopausal status with dense view in mammography (P < 0.001). No significant relationship was observed in OCP consumption and menarche age with dense view in mammography (P > 0.05).

Conclusions: Higher breast density in premenopausal women with low BMI may lower the sensitivity of mammography. This can underscore the importance and necessity of further controls with short intervals as well as the use of other tools for diagnosing breast cancer in these groups of patients.

INTRODUCTION

Currently, the only method of breast cancer screening which reduces the mortality of this disease is mammography. Reduction of mortality due to breast cancer screening is 22% in women over 50 years and 15% in women with 40-49 years of age [1]. This decrease in mortality is mostly due to the reduced number of diagnosed cancers in the screened population [2]. Various studies have reported the sensitivity for mammography as 65-91% [3, 4]. The factor that leads to false negative results in mammography is the effect of density of the breast tissue; it means that when the breast tissue density increases in mammography (dense breast), the mammographic sensitivity decreases [5]. Dense breast tissue is so common that in one study, 62% of 30-39-year-old, 56% of 40-49-year-old, and 37% of 50-59-year-old women had dense breast tissues [6]. On the other hand, dense breast tissue in mammography (dense breast) causes increased cancer risk.

To express the density of breast tissue in mammography, various categories have been offered such as Wolf and Tabar and absolute category rating (ACR) Breast Imaging Reporting and Data System (BIRADS) categories, and that the last classification is now used by all radiologists [1-3]. The breast tissue is extremely dense

and can lead to unseen lesions in mammography. Breast tissue density is the strongest factor in the increased risk of breast cancer and various studies have indicated that women with a high density of breast tissue are 4-6 times in higher risk of breast cancer than women with low breast tissue density [5, 7-13].

In total, in different studies, various factors such as age, hormones usage, factors associated with parents, body mass index (BMI) and reproductive factors have been considered effective on breast tissue density, but no definitive cause for this issue is known yet [8-14].

Given that the increased density of breast tissue can lead to increased risk of breast cancer, using intervention strategies for reducing its density will be very important. For this reason, knowing the factors that have short-term effects on breast tissue density and the factors that lead to relative changes in breast density will be very important. This study aimed to investigate the possible factors influencing the breast tissue density increase in mammography in women referred to the breast Cancer Research Center of ACECR.

METHODS

In this cross-sectional study, 428 patients who were referred to the radiology ward of the Breast Cancer Research Center of ACECR for mammography in 2012 were enrolled to this study. A checklist was designed based on previous studies in addition to the possible variables affecting breast tissue density in mammography, which were approved by specialists of this field. The checklist was designed based on the study objectives; if the patients had tendency to respond, they would complete the questionnaire.

The check list comprised variables such as age, age of menarche, BMI, use of OCP, and breast size. The men-

tioned variables were considered as independent variables and breast tissue density as the dependent variable. Patients who had been treated for infertility or patients with premature menopause were excluded from the study. In order to unify the report on breast tissue density in mammography, mammographic stereotypes of patients were scanned and evaluated by a radiologist. The checklists information was entered into a computer and the relationships of the studied variables as well as the density of breast tissue in mammography were evaluated. SPSS statistical software, Version 21, was used for data analysis. Mean and dispersion index were used for quantitative variables and frequency and percentage were used for qualitative variables. To evaluate the relationship between variables and the density of breast tissue, chi-squared and logistic regression tests were used.

RESULTS

In this study, a total of 428 patients were enrolled. In the analysis of data, the relationship of demographic and hormonal variables with mammographic breast tissue density was studied and it was found that among the patients, 40.4% had low-density views and 59.6% had high density views (Table 1). The findings of this table shows that among the studied subjects, 46.3% of patients with low tissue density and 77.3% of those with high density were less than 50 years old. Chi-squared test results showed significant correlation between age and dense mammographic view at 5% error level (P < 0.001). In the low tissue density group, most people were 13 years old or more (67%) and in the high density group, 42.7% were more than 13 years old. According to the study findings and the results of chi-squared test, no statistically significant relationship was observed between age of menarche and dense view in mammography (P = 0.19) (Table 1).

Table 1: Comparison of Variations in Tissue Density in Mammography Among the Studied Patients (n = 428)

Variable	Breast Density in Mammography		χ^2, Test Value	P Value
	High Density, (n = 255), No. (%)	Low Density, (n = 173), No. (%)		
Age			47.68	< 0.001
< 50	197 (77.3)	80 (46.3)		
50-54	40 (15.8)	35 (20.3)		
55-59	33 (19.2)	15 (8.7)		
> 60	20 (11.8)	8 (4.7)		
Age of Menarche			4.81	0.19
< 12	26 (10.2)	15 (8.6)		
12	51 (20)	42 (24.4)		
13	69 (27.1)	58 (33.5)		
> 13	109 (42.7)	58 (33.5)		
OCP Use			2.01	0.16
No	159 (62.3)	96 (55.5)		
Yes	96 (37.7)	77 (44.5)		
Breast Cup Size			25.32	< 0.001
A	24 (9.4)	9 (5.2)		
B	80 (31.4)	26 (15.1)		
C	62 (24.3)	39 (22.5)		
D	89 (34.9)	99 (57.2)		

*Significant at the level of 5%.

Among the studied subjects, 255 (59.5%) were not using OCP pills. Most of these individuals (62.3%) were in the high density group. Based on the findings and the chi-squared test results of table 1, no significant relationship was observed between the variable of OCP usage and dense view. One hundred eighty eight cases (43.9%) had a breast cup size of D and among them, 99 subjects were in the low density group. According to the chi-squared test results in Table 1, a statistically significant relationship was observed between breast cup size and mammographic dense view (P < 0.001). According to the findings in Table 2, 191 patients (44.6%) of all the participants had BMIs of 25-29, who were accounted for the highest percentage in the BMI index levels. At this level of BMI, most of the people (121) were in the high density group. According to the result of Fisher's exact test, a significant relationship between BMI index and mammographic dense view was observed at the level of 5% (P < 0.001). Two hundred forty seven cases (57.7%) of all the participants were in the regular

menstruation, which had the highest frequency. Also, in the group with high density tissue in mammography, most subjects had regular menstrual statuses (65.5%). According to results of table 2, the fewest number is assigned for people with hysterectomy.

Logistic regression was used to analyze the data and for this purpose, the variables were defined based on the distribution and biology of the effect of factors on breast tissue density as binary variables. After univariate analysis, the independent variables that had shown statistically significant relationships at 5% alpha error with breast tissue density were entered into multivariate logistic regression model. Results of multivariate logistic regression analysis showed that the odds ratio of dense breast tissue in women with BMIs of less than 25 to 25 and higher is 2.2 with 95% confidence interval (1.253-3.909). Furthermore, the odds ratio of dense breast tissue in A and B cup sizes to C and D sizes and age younger than 50 to 50 years and higher were respectively 1.99 (1.2-3.32) and 3.6 (2.22-5.81) (Table 3).

Table 2: Correlation of Variables of BMI and Menstrual Status With Mammographic Tissue Density

Variable	Breast Density in Mammography		F Test Value, Fishers Exact Test	P Value
	High Density (n = 255), No. (%)	Low Density (n = 173), No. (%)		
BMI			34.93	< 0.001
< 20	7 (2.7)	1 (0.5)		
20-24	75 (29.4)	24 (13.9)		
25-29	121 (47.5)	70 (40.5)		
≥ 30	52 (20.4)	78 (45.1)		
Menstrual Status			26.89	< 0.001
Regular	167 (65.5)	80 (46.3)		
Irregular	44 (17.2)	25 (14.5)		
Menopause	42 (16.5)	67 (38.7)		
Hysterectomy	2 (0.8)	1 (0.5)		

Results of Fisher's exact test show the significant correlation of menstrual status with mammographic tissue density at the level of 5% (P<0.001).

Table 3: Results of Multivariate Logistic Regression Analysis) Factors Affecting the Density of Breast Tissue

Variable	B	SD	OR (%95 CI)	P Value
BMI				
< 25 Compare to ≥ 25	0.794	0.29	(1.253-3.909) 1.999	0.006 *
Breast Cup Size				
A & B Compare to C & D	0.693	0.259	(1.204-3.319) 1.999	0.007 *
Age				
< 50 Compare to ≥50	1.278	0.246	(2.217-5.809) 3.588	< 0.001 *
Menstrual Status				
Regular Compare to Irregular & Menopause & Hysterectomy	0.241	0.239	(0.796-2.033) 1.272	0.313

* Significant at the level of 5%.

DISCUSSION

Radiological appearance of breast tissue in mammography reflects difference in breast tissue composition in different people. In mammography view, fatty tissue is seen as radiolucent or dark, and epithelial and stromal view is seen as just radiodense or bright. Depending on the degree of darkness or lightness of mammographic density of breast tissue view, it is considered from No. I- IV with the ACR scale. Generally, ACR I and II are considered as breast tissues with low density and ACR III-IV as breast tissues with high density. Mammographic tissue density is one of the strongest factors for increased risk of breast cancer. In fact, women with a high mammographic density breast tissue are almost five times at higher risk of developing breast cancer than women with low mammographic density [5, 15-17]. According to studies, breast tissue density is influenced by various factors such as age, menopause, fertility, BMI, and hormonal and nutritional factors [18, 19].

The study of Lundberg et al. on the effect of infertility treatment on mammographic density showed that compared to women with no hormone treatment, infertile women who received hormonal fertility treatment had higher mammographic density [20]. In a study by Nevler et al., 2760 screening mammograms were performed. Results showed that women with denser breast tissues required further screening methods like sonography and more investigations such as tissue biopsy. In these women, the incidence of cancer is likely higher [21].

Since several factors affect the amount of mammographic density and according to conducted surveys until now no research has been conducted in this case in Iran, this study was designed to investigate the factors affecting the density of breast tissue in women referred to the breast clinic of ACECR. Different variables were studied and the relationship between them as well as mammographic density was investigated. In the following, we are going to discuss about them.

Overall, 428 women who underwent mammography in the Radiology Ward of ACECR's breast clinic were enrolled in the study and a questionnaire containing the interest variables was completed for each patient. The relationship between the studied variables and the density of breast tissue in mammography was evaluated in the conducted statistical analysis.

In classification of the breast tissue density by integrating the density, ACR I and ACR II were seen as low density and ACR III and ACR IV as high density; about 40% of patients (173) had low-density breast tissue and 255 (60%) had high-density tissue. The obtained frequency in this study corresponds with international studies [22].

Of the studied variables, age factor can be noted; based on the results of the study, with aging, density of the breast tissue decreases; in this study, age of under 50 years was associated with the highest density of breast tissue and after that age, breast tissue density decreased. This issue is also match up with menopause, meaning that by menopause and increase of its duration, the density of breast tissue reduces. This seems logical because with aging and menopause, by the decreasing levels of ovarian hormone, the hormonal effect of ovary on breast tissue is reduced, which also results in the reduction of epithelial tissue of the breast tissue and its replacement with fatty tissue. Similar results have been reported in other studies [8].

Menarche age is another variable; according to the results, with increasing menarche age dense view also increases. The highest density (25.5%) can be seen in subjects with maturity age of above 13 years. Research findings show an upward trend in age of menarche of subjects in both low-density and high-density groups, but in chi-squared test, no significant relationship was observed between menarche age and mammographic dense view. On the other hand, individuals with regular menstruation have the highest frequency of tissue density (39%). Fisher's exact test showed a significant association between menstruation and dense view. By regular effect of ovarian hormone on breast tissue, hyperplasia of breast epithelial tissue occurs, which leads to an increase in mammographic density; while, the increase of menarche age and irregularity of menstruation leads to lower effect of ovarian hormone on breast tissue and as a result breast tissue density reduces in mammography.

According to the results of this study, no significant relationship was observed between OCP usage and breast density. It is possible that duration and type of OCP usage affect the breast tissue density, which was not investigated in this study. According to the results, a statistically significant relationship was observed between breast cup size and dense view in mammography. This means that by increasing the size of breast, density of breast tissue reduces in mammography; this relationship was also observed for BMI. It was also found that in BMIs of 25-29, most of the cases (121 subjects) (28.3%) were in the high-density group and Fisher's exact test showed a significant association between BMI and dense view in mammography. These results also correspond with the study of Riza [12]. Overall, of the studied variables, age, BMI and breast cup size showed inverse relationships with density of breast tissue in mammography, while menstrual status can have a direct effect on the density of breast tissue in mammography. The results showed that in young and thin women with smaller breast sizes and regular menstruations, breast tissue was denser and consequently the risk of breast cancer will be higher. In these cases, it is necessary that, if needed, doctors and patients pay more attention to performing periodic checkups at shorter intervals and the use of radiology diagnostic methods and more efforts should be made by the health care system in the

field of information and providing the necessary trainings to this group of people.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interests.

ETHICS APPROVAL

The research plan for this study was registered and approved by the Ethics Committee of Breast Cancer Research Center of ACECR.

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