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Association of Reproductive and Menstrual Characteristics with Mammographic Density

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ABSTRACT

Background: Mammographic density has been recognized as a risk factor for breast cancer, but the association between potential effective factors and mammographic density has not been fully studied in Asian women. We conducted a study to investigate the association of mammographic breast density with several menstrual and reproductive characteristics.

Methods: Screening mammography was performed in women above 40 years attending the breast clinic of Arash Women's Hospital, Tehran, Iran, for breast cancer screening. The densities were classified by two expert radiologists according to the parenchymal mammographic classification system of the American College of Radiologists. Those with a history of breast cancer or renal disease, recent hormone replacement therapy, or consumption of vitamin D supplements were excluded.

Results: Overall, 823 patients were assessed. Mammographic density was associated with higher age at first birth ($P < 0.001$), lower parity ($P < 0.001$), BMI ($P < 0.001$), and premenopausal status ($P < 0.001$). However, no associations were observed with age at menarche ($P = 0.057$) and menstrual pattern ($P = 0.973$).

Conclusions: Our study showed an association between mammographic density and age, parity, BMI, and age at first birth, and no association with menstrual pattern in terms of regularity and age at menarche. In addition, mammographic density was significantly higher in premenopausal women.

Introduction

Mammographic density (MD) describes the proportions of dense and lucent components in the mammograms.[1-4] Higher classes of density may compromise the sensitivity of the mammograms; very dense radiographs may have a sensitivity as low as 36% for cancer detection.[5] Most importantly, high mammographic density has been recognized as a risk factor for breast cancer.[4,6-8] The relative risk for breast cancer in the higher categories of density has been reported as 2 to 6 times higher than lower categories.[6,8,9]

Various factors, including physiologic endogenous hormonal alterations, weight and

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genetic factors, reproductive factors, hormone replacement therapy (HRT), age, and type of diet, have been linked to the amount of parenchymal density in imaging.[3,10-14] This study was conducted to investigate the association of mammographic breast density with some of the mentioned risk factors. To our knowledge, studies that determine predictors of mammographic density in middle-eastern women are scarce; thus, the current study was designed and initiated to fulfill this knowledge gap.

Methods

A cross-sectional study was carried out fromNovember 2010 to June 2013 in Arash Women's Hospital, Tehran, Iran. Among women attending the breast clinic merely for breast cancer screening without any breast complaints or any major risk factor for breast cancer, those aged 40 years or more were invited to participate in this research. Exclusion criteria consisted of personal history of breast cancer, recent (preceding year) hormone replacement therapy or consumption of vitamin D supplements, and any types of renal diseases. Besides, data on age, height, and weight, age at menarche, age at first birth, parity, menstrual cycle regularity, and menopausal status were gathered from all participants.

screening bilateral mammgraphy in two standard projections was performed for all of the study subjects. MD can be evaluated by means of several systems, including Breast Imaging Reporting and Data System (BI-RADS) classification of the American College of Radiology (ACR), Wolfe's method, Tabar classification, and computer-assisted planimetry.[1,9,15]

Density of the breast tissues in mammograms was graded by two expert radiologists according to the parenchymal mammographic classification system of the American College of Radiologists (ACR) as follows: 1 = almost entirely fatty (< 25% glandular); 2 = scattered fibroglandular densities (approximately 25-50% glandular), 3 = heterogeneously dense (approximately 51-75% glandular), and 4 = extremely dense.[15]

To facilitate interpretation of categorical variables, they were recoded as dichotomous and compared using chi-square for trend. The association of continuous variables with MD was investigated using analysis of variance (ANOVA). SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA) was used to perform the analyses and P values of less than 0.05 were considered statistically significant.

Results

Overall 823 patients were eligible for the study. Mean age of patients at the time of diagnosis was 48.6 ± 6.3 years. Mean age at menarche and at the first birth were 13.7 ± 1.5 and 20.1 ± 4.1 years, respectively. Distribution of BMI, age at menarche, age at first birth, menopausal status, and parity with respect to different classes of MD are shown in table 1.

There was a significant association between age at the time of diagnosis and MD among the study population ($P < 0.001$). In this regard, women with class 1 MD were the oldest (51.47 ± 6.69 years), followed by participants who were categorized as class 2 (49.89 ± 6.80 years) and class 3 subjects (46.37 ± 4.48 years). The youngest group consisted of class 4 women (44.89 ± 4.03 years) (P for trend < 0.001). Post-hoc analysis using Bonferroni correction by comparing the 4 groups one-by-one showed that the differences between patients' age were not significant when comparing class 1 to class 2 ($P = 0.115$) and class 3 to class 4 ($P = 0.565$). The rest of differences remained statistically significant (1 vs. 3, 1 vs. 4, 2 vs. 3, and 2 vs. 4).

Higher mammographic density was also associated with lower number of pregnancies and lower BMI ($P < 0.001$ for both associations). Additionally, patients with higher age at the time of first birth ($P < 0.001$) and premenopausal women ($P < 0.001$) had higher MD. Age at menarche, and menstrual pattern (regular vs. irregular) were not associated with MD ($P = 0.057$ and $P = 0.973$, respectively). Table 2 demonstrates the frequency of each class of MD in different groups of investigated variables.

Discussion

Previous research has shown that breast density in mammography is a potential risk factor for breast cancer; when more than half of the mammogram appears to be dense, the life-time risk of developing breast cancer might increase as much as 16%.[16]

Among the potential risk factors for high mammographic density are age at first birth and age at menarche. Previous studies have assessed the association of these variables with MD, though considerable controversies still exist. In a crosssectional study carried out by Heng zzz in women aged 45-69 years, more than 24000 screening mammograms were retrospectively reviewed. Results showed that higher age at first birth is associated with higher MD, while such an association was not observed for age at menarche.[17] Riza *et al.* conducted a similar study on nearly 5000 women and detected the same results.[18] Our observation was consistent with the mentioned findings. In contrast, retrospective assessment of more than 140000 screening mammograms in the study of Titus-Ernstoff *et al.* demonstrated that MD is lower in women with higher age at first birth and menarche.[19] Other reports have emphasized the hypothesis that there is no association between MD and age at menarche or first pregnancy.[10,20,21]

Many authors reported that women of higherparities appear to have more dense breasts in

Table 1. Frequency of each category of investigated variables with respect to mammographic density classes

		Mammographic density*			
		Class 1 n (%)	Class 2 n (%)	Class 3 n (%)	Class 4 n (%)
Age at menarche	< 10	(0.0%)	4 (1.1%)	2 (0.9%)	1 (2.0%)
	10-13	37 (44.0%)	169 (46.0%)	106 (46.1%)	32 (65.3%)
	14-17	46 (54.8%)	191 (52.0%)	121 (52.6%)	16 (32.7%)
	> 17	1 (1.2%)	3 (0.8%)	1 (0.4%)	0 (0.0%)
	Total	84 (100%)	367 (100%)	230 (100%)	49 (100%)
BMI**	18.5–25	12 (14.8%)	63 (18.7%)	59 (25.7%)	25 (55.6%)
	25–30	27 (33.3%)	157 (46.6%)	120 (52.2%)	16 (35.6%)
	30–35	32 (39.5%)	95 (28.2%)	43 (18.7%)	4 (8.9%)
	35–40	9 (11.1%)	17 (5.0%)	7 (3.0%)	0 (0.0%)
	> 40	1 (1.2%)	5 (1.5%)	1 (0.4%)	0 (0.0%)
	Total	81 (100%)	337 (100%)	230 (100%)	45 (100%)
Menstrual regularity	Regular	22 (66.7%)	136 (60.4%)	117 (60.0%)	36 (73.5%)
	Irregular	11 (33.3%)	72 (34.6%)	78 (40.0%)	13 (26.5%)
	Total	33 (100%)	208 (100%)	195 (100%)	49 (100%)
Age at 1st birth	⩽19	58 (60.4%)	201 (53.2%)	119 (48.6%)	14 (31.8%)
	20-29	32 (33.3%)	166 (43.9%)	115 (46.9%)	30 (68.2%)
	30-39	6 (6.3%)	11 (2.9%)	11 (4.5%)	0 (0.0%)
	Total	96 (100%)	378 (100%)	245 (100%)	44 (100%)
Parity**	P = 0	0 (0.0%)	2 (0.5%)	4(1.6%)	3 (6.1%)
	1 ⩽ P ⩽ 3	52 (54.7%)	230 (59.3%)	180 (71.7%)	38 (77.6%)
	4 ⩽ P ⩽ 6	37 (38.9%)	141 (36.3%)	62 (24.7%)	8 (16.3%)
	P > 6	6 (6.3%)	15 (3.9%)	5 (2.0%)	0 (0.0%)
	Total	95 (100%)	388 (100%)	251 (100%)	49 (100%)
Menopausal status	Premenopausal	33 (34.0%)	208 (52.9%)	195 (89.1%)	49 (89.1%)
	Postmenopausal	64 (66.0%)	185 (47.1%)	57 (10.9%)	6 (10.9%)
	Total	97 (100%)	393(100%)	252 (100%)	55 (100%)

* *According to the parenchymal mammographic classification system of ACR*
** *Classified according to WHO guidelines*

Table 2. The association of patients' reproductive and menstrual characteristics with mammographic density

		Mammographic density*				P value*
		Class 1	Class 2	Class 3	Class 4	
Age at menarche	< 13	37 (44.0%)	173 (47.1%)	108 (47.0%)	33 (67.3%)	0.057
	⩾ 13	47 (56.0%)	194 (52.9%)	122 (53.0%)	16 (32.7%)	
BMI**	< 30	39 (8.1%)	220 (45.9%)	179 (37.4%)	41 (8.6%)	< 0.001
	⩾ 30	42 (19.6%)	117 (54.7%)	51 (23.8%)	4 (1.9%)	
Menstrual regularity	Regular	22 (66.7%)	136 (65.4%)	117 (60.0%)	36 (73.5%)	0.973
	Irregular	11 (33.3%)	72 (34.6%)	78 (40.0%)	13 (26.5%)	
Age at 1st birth	< 19	46 (14.8%)	167 (53.7%)	88 (28.3%)	10 (3.2%)	< 0.001
	⩾ 19	50 (11.1%)	211 (46.7%)	157 (34.7%)	34 (7.5%)	
Parity**	< 3	24 (8.2%)	126 (42.9%)	117 (39.8%)	27 (9.2%)	< 0.001
	⩾ 3	71 (14.5%)	262 (53.6%)	134 (27.4%)	22 (4.5%)	
Menopausal status	Premenopausal	33 (6.8%)	208 (42.9%)	195 (40.2%)	49 (10.1%)	< 0.001
	Postmenopausal	64 (20.5%)	185 (59.3%)	57 (18.3%)	6 (1.9%)	

* *Calculated using chi-square test for trend*

mammography.[17,18,21] This is while some others failed to detect any statistically significant (1.9%) association between the two.[20]

On the association between menopausal status and MD, multiple studies showed a higher MD in premenopausal women.[19,22,23] In the current study, analysis of the results showed a strong relationship between MD and menopausal status, the most evident physiologic instance of endogenous hormone cessation. This supports the assumption that estrogens enhance the fibrous composition of breast parenchyma and hence radiologic density.[24]

Limited evidence is available regarding the association of menstrual regularity and MD. Similar to the present study, Butler *et al.* inspected the mentioned association and did not find any significant results.[25]

Our study also had some limitations. Data about age at menarche and at first full-term pregnancy were asked from the participants and the latter was not verified by the patients' medical documents. Different types of menstrual cycle irregularities were not classified and all cases of menorrhagia and metrorrhagia were classified as having menstrual irregularities.

In conclusion, our study showed an association between MD and age, parity, BMI, and age at first birth, and no association with menstrual pattern in terms of regularity and age at menarche. Moreover, MD was significantly higher in premenopausal women.

Conflict of interests

The authors have declared no conflicts of interest.

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