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The relationship of breast arterial calcification detected in mammographic examinations with cardiovascular diseases, cardiovascular risk factors, parity, and breastfeeding

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Background/aim: We aimed to detect the incidence of breast arterial calcification (BAC) in patients that underwent mammography and to reveal the relationship of BAC with cardiovascular diseases, cardiovascular risk factors, parity, and breastfeeding.

Materials and methods: A total of 1195 female patients were included in this study. Cases that were positive for BAC during mammography were recorded. The relationship of BAC with age, body mass index, parity, breastfeeding, menopause, smoking, alcohol consumption, oral contraceptive use, hormone replacement therapy, and histories of hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), and cerebral vascular diseases were investigated.

Results: Overall, 97 of 1195 cases were positive for BAC. In univariate analysis, age, educational status, parity, breastfeeding, menopause, hyperlipidemia, and DM, HT, and CAD histories were found to be separate risk factors that had an effect on the development of BAC. The effects of age, parity, and breastfeeding history were maintained in the logistic regression analysis ($P = 0.001$, $P = 0.001$, $P = 0.024$, respectively; $P < 0.05$ was significant), while the significance of the other analyzed variables was lost ($P > 0.05$).

Conclusion: We found that BAC is associated with age, parity, and breastfeeding but not with cardiovascular diseases and cardiovascular risk factors.

Key words: Artery, breast, calcification, cardiovascular disease, mammography

1. Introduction

Atherosclerosis is the most important cause of death and disability in developed countries. The fact that the diseases associated with atherosclerosis usually manifest clinical symptoms following a long silent period demonstrates the importance of cardiovascular risk assessment. The disease starts in early childhood and progresses slowly over decades (1). Arterial calcification is a common characteristic of atherosclerosis. Calcium deposits in the arterial wall that can be detected by modern imaging methods may provide information concerning subclinical atherosclerosis (2). The prevalence of breast arterial calcification (BAC) detected during mammography has been reported between 1% and 49% in various studies (3). There are studies in the literature suggesting that BAC is associated with coronary artery disease (CAD) (4–7), diabetes mellitus (DM) (4–6 8), and hypertension (HT) (4,5,9,10), and that BAC can be used as a marker for cardiovascular diseases. However, the clinical importance of mammographically detected calcifications is still unclear.

In this present study, we aimed to detect the incidence of BAC in subjects who underwent mammography for any reason in our clinic and to reveal the relationship of BAC with cardiovascular diseases, cardiovascular risk factors, parity, and breastfeeding.

2. Materials and methods

Overall, 1195 female volunteer subjects whose ages varied from 40 to 79 years (mean age: 51.33 ± 8.82 years) and who underwent mammography in our radiology department between September 2013 and June 2014 were assessed prospectively. The study was approved by the local ethics committee. A questionnaire form that included information about age, weight, height, educational status, parity, breastfeeding, menopause, tobacco and alcohol consumption, oral contraceptive (OCC) use, hormone replacement therapy (HRT), hyperlipidemia, and history of hypertension, diabetes mellitus, coronary artery diseases, and cerebrovascular disease (CVD) was filled out for all volunteers.

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An active smoker was defined as a subject who had smoked half a pack of cigarettes or more for 5 years and longer. Those who had never smoked were considered to be nonsmokers. Those who had breastfed their infants for at least 3 months were considered to have a positive breastfeeding history, and those who had not breastfed were considered to have a negative history. The subjects who had used OCC for 1 year or longer were included in the group of OCC users, and those who had never used OCC were included in the group of nonusers. The subjects who had received HRT for 1 year or longer were included in the group of HRT users, while those who declared that they had never received HRT were included into the group of nonusers. The patients who were using antihypertensive drugs, and those with a diagnosis of HT but not on antihypertensive therapy, were considered to be HT patients. The women who were receiving insulin or oral antidiabetic medications and those who were being followed with a diagnosis of type 2 DM by applying diet regimens were identified as DM patients. Having a total cholesterol level above 200 mg/dL was accepted as hyperlipidemia. Subjects having a history of myocardial infarction (MI), coronary bypass, or angina pectoris and those receiving medications for CAD were considered to be CAD patients. A transient ischemic attack and/or stroke in the medical history was sufficient for the diagnosis of CVD. Cases that did not fulfill the above-mentioned conditions were not included in the study. Additionally, subjects with inadequate anamnesis, those with mastectomy or radiotherapy anamnesis, and those with bad image quality during the examinations in the workstation were excluded from the study.

Body mass indexes (BMIs) were calculated according to the height and weight of the subjects. BMI was calculated using the formula weight (kg) / height $(m)^2$. The cases were divided into 4 groups according to BMI values. The cases with a BMI of <20 were classified as group 1 (slim, n = 20, 1.7%), those with a BMI between 20 and 24.9 were classified as group 2 (normal weight, n = 289; 24.2%), those with a BMI between 25 and 29.9 were classified as group 3 (overweight; n = 459; 38.4%), and those with a BMI of ≥30 were classified as group 4 (obese; n = 427; 35.7%). According to educational status, 4 groups were formed. The illiterate patients were classified as group 1 (n = 126, 10.5%), primary school graduates were classified as group 2 (n = 661, 55.3%), secondary or high school graduates were classified as group 3 (n = 315, 26.4%), and those having an undergraduate, graduate, or postgraduate degree were classified as group 4 (n = 93, 7.8%). Parity was defined as having any pregnancies, including spontaneous abortions. The cases were separated into 4 groups according to the number of parities. The nulliparous subjects were classified as group 1 (n = 91, 7.6%), subjects with 1 to 2 live births were classified as group 2 (n = 442¸ 37.0%), subjects with 3 to 4 live births were classified as group 3 (n = 424, 35.5%), and subjects having >5 live births were classified as group 4 (n = 238, 19.9%). The number of smoking subjects was 207 (17.3%), the number of hypertensive women was 293 (24.5%), the number of diabetics was 176 (14.7%), the number of subjects with hyperlipidemia history was 238 (19.9%), CAD history was seen in 18 (1.5%), CVD history was seen in 18 (1.5%), the number of subjects using OCC was 276 (23.1%), HRT was seen in 73 (6.1%), and the number of menopausal women was 715 (59.8%). None of the women consumed alcohol.

Standard mammography equipment was used (Mammomat, Inspiration Digital Mammography, Siemens 2010) in the examinations, and images acquired in 2 standard mediolateral oblique and craniocaudal projections were examined. The images were transferred to a workstation and reviewed by 2 radiologists, both experienced in mammography. BAC-positive cases were recorded. BAC was defined as the presence of parallel linear calcium deposits along the course of a vessel at least in one mammography image (11). The location of BAC (right or left breast; upper, lower, inner, or outer quadrant of the breast) was recorded. The relationships of BAC with age, BMI, education level, parity, breastfeeding, menopause, smoking status, alcohol consumption, OCC use, and HRT, HT, DM, hyperlipidemia, CAD, and CVD history were investigated.

For statistical analysis, NCSS 2007 and PASS 2008 Statistical Software (Kaysville, UT, USA) were used. Besides descriptive statistical methods (mean, standard deviation, median, frequency, proportion, minimum, and maximum), the Student t-test was used for intergroup comparison of quantitative variables with normal distribution. In the comparison of the qualitative data, the Pearson chi-square test, Fisher exact test, and Yates continuity correction test were used. In the analysis of variables that had an effect on the development of BAC, backward (conditional) logistic regression analysis was used. The significance level was set at $P < 0.01$ and $P < 0.05$.

3. Results

This study was conducted on 1195 volunteer subjects who were referred to our radiology department for a mammography examination during a 10-month period. BAC was detected in the mammographies of 97 of 1195 cases. In univariate analysis, the incidence of BAC was similar in the BMI groups. There was no statistically significant difference in the incidence of BAC in terms of smoking status, HRT, and the presence of CVD history. Since none of the women who participated in the study consumed alcohol, no such comparison could be made.

Age, educational status, parity, breastfeeding, menopause, and history of DM, HT, hyperlipidemia, and CAD, which were found to be the risk factors associated with BAC in univariate analysis, were entered into a logistic regression model. The general coefficient of determination and the sensitivity and specificity of the model were found to be 85.3%, 79.4%, and 85.8%, respectively. The effects of age, parity, and breastfeeding history were maintained in the logistic regression analysis (P = 0.001, P = 0.001, and P = 0.024; P < 0.05 was significant), whereas the significance of the other analyzed variables was lost (P > 0.05). The reference category of age groups was 40 to 45 years, and the hazard ratio was not significant for age groups between 45 and 49 years and between 50 and 54 years. However, the hazard ratio grew according to increasing age in the other age groups. Group 2 was considered to be the reference category in the parity groups. While the hazard ratio was not significant for the cases in Group 3, it was found that the hazard ratio was higher in the cases in Group 1 and Group 4. The hazard ratio of developing BAC was higher in cases with a history of breastfeeding compared to cases without breastfeeding history. The logistic regression model, including age, educational status, parity, breastfeeding history, menopause, and DM, HT, hyperlipidemia, and CAD history, is shown in the Table.

BAC was detected in the right breast in 27 (27.83%), in the left breast in 6 (6.19%), and in both breasts in 64 (65.98%) of 97 cases. BAC was detected in the upper quadrant in 68.4%, in the lower quadrant in 5.7%, in the inner quadrant in 33.3%, in the outer quadrant in 25.9%,

Table. The effects of the age, educational status, parity, breastfeeding, menopause, and history of DM, HT, hyperlipidemia, and CAD, which were risk factors associated with BAC, in univariate evaluations and logistic regression analysis.

	Univariate evaluations				Logistic regression analysis			
	P	Odds	95% CI		P	Odds	95% CI	
			Lower	Upper			Lower	Upper
Age	0.001**				0.001**			
45–49	0.155	3.211	0.643	16.041	0.181	3.016	0.599	15.189
50–54	0.079	4,222	0.844	21.118	0.138	3.414	0.674	17.294
55–59	0.001**	20.000	4.614	86.683	0.001**	14.459	3.284	63.663
60–64	0.001**	24.395	5.396	110.291	0.001**	17.583	3.823	80.871
65–69	0.001**	97.436	22.217	427.326	0.001**	67.438	15.084	301.496
70–74	0.001**	121.600	24.942	592.828	0.001**	98.708	19.705	494.458
≥75	0.001**	282.286	53.319	1494.498	0.001**	152.970	27.866	839.713
Parity•	0.001**				0.001**			
Group 1	0.178	2.083	0.716	6.066	0.006**	24.059	2.540	227.863
Group 3	0.004**	2.728	1.378	5.403	0.078	1.936	0.928	4.039
Group 4	0.001**	9.530	4.961	18.309	0.001**	4.198	2.050	8.599
Breastfeeding (+)	0.024*	3.809	1.188	12.212	0.024*	15.894	1.429	176.843
DM	0.001**	4.038	2.579	6.324	0.248	1.387	0.796	2.415
Menopause	0.001**	14.029	5.659	34.780	0.179	2.171	0.700	6.731
CAD	0.001**	6.905	3.304	14.432	0.169	1.929	0.757	4.913
Hyperlipidemia	0.005**	1.916	1.214	3.024	0.451	1.244	0.705	2.194
HT	0.001**	3.922	2.568	5.988	0.584	1.158	0.685	1.956
Educational status	0.001**				0.678			
Group 4	0.941	1.044	0.332	3.282	0.676	1.317	0.362	4.795
Group 2	0.062	1.819	0.971	3.409	0.752	1.127	0.537	2.363
Group 1	0.001**	7.908	3.987	15.687	0.295	1.586	0.669	3.759

• For parity group 2, for educational status group 3 were referenced.
**: Statistically significant.

and in both upper and lower quadrants in 28.5% of the cases.

4. Discussion

Approximately 250,000 women die annually of acute myocardial infarction in the United States. The fact that more than 60% of females who die of acute CAD have no prior symptoms shows the importance of cardiovascular risk assessment. Imaging methods such as computerized tomography that detect coronary artery calcifications (2), direct radiographies that detect aortic calcifications (12), and mammography that detects BAC (13) may help in determining cardiovascular risk. In the literature, there are conflicting studies about the clinical importance of calcifications detected in mammography. While some authors claim that BAC may be a useful tool in estimating cardiovascular disease risk, others state a contradictory opinion (2,12,14–16).

The prevalence of mammographically detected BAC has been reported in various proportions (3). While Taşkın et al. detected BAC in 7.9% of mammography examinations in their studies (17), Rotter et al. (4) reported the mammographically detected BAC rate as 14% and Akinola et al. (18) reported a rate of 20%. This wide range of differences may stem from the variety of the sensitivity of mammography devices and the heterogeneity of the population studied in different studies (11). In our study, we detected BAC in 8.12% of cases in which mammography was performed.

BAC is a mammographic finding that is not associated with cancer and is usually detected in older women (5). The positive correlation between age and BAC is increasingly emphasized in the literature (2,5,17–19). In accordance with the literature, in the present study, we found that the incidence of BAC increases with advancing age. Maas et al. (2) reported that they found positive correlations between pregnancy and breastfeeding and BAC in their study. The researchers stated that transient hypercalcemia induced by pregnancy and breastfeeding may lead to BAC by causing calcium deposits in breast arteries. We also found a significant relationship between parity and BAC in our study. However, differing from the results of Maas et al., the incidence of BAC that we found was higher in nulliparous subjects than those of women having one or two children (2). We suggest that this may be caused by the higher mean age of the nulliparous subjects participating in the study compared to that of the other 3 groups. Akinola et al. (18) found no relationships between parity and breastfeeding and BAC.

Rotter et al. (4) found a positive correlation between menopause and BAC. In a study conducted by Kim et al. (11), the incidence of BAC was found to be higher in postmenopausal women compared to the results of the other studies conducted on this topic. Akinola et al. (18) detected BAC in 11 patients in a study that included 54 patients. The researchers stated that 34 of 54 patients were in the postmenopausal period and that they detected BAC in 3 of these 34 patients. This result was contradictory to the results obtained by the other researchers. In our study, menopause was found to be one of the risk factors affecting BAC in univariate analysis; however, the significance of menopause was not maintained in regression analysis. Iribarren et al. reported (5) a positive correlation between education level and BAC in their study; however, no significant relationship was found in our study.

Some researchers surprisingly reported that the incidence of BAC was lower in smoking women in comparison to that in nonsmoking women (2,5,20). Iribarren et al. (5) found a significant relationship between BAC and alcohol consumption and HRT, while some researchers reported no such significant relationship (2,18). In this study, we found no significant relationship between BAC and smoking and HRT. Since none of the women who participated in the study consumed alcohol, no such comparison was made.

A strong correlation between OCC use and cardiovascular diseases has been emphasized in several studies (21,22). However, no significant relationship was found between OCC use and BAC in other studies (2,18). In our study, no significant relationship was found between OCC use and BAC.

In the literature, there are conflicting results about the relationship of BAC with DM, HT, BMI, and hyperlipidemia. While some reported a significant relationship between BAC and DM (4–6,8), HT (4,5,9,10), BMI (5), and hyperlipidemia (5), others found no significant relationship between BAC and DM (2,18), HT (2,18), BMI (2,18), or hyperlipidemia (2). In our study, we did not find any relationship between BAC and DM, HT, BMI, or hyperlipidemia.

Rotter et al. (4) declared that there was a positive correlation between mammographically detected BAC and atherosclerotic cardiovascular diseases (history of angina pectoris, MI, stroke, and coronary artery bypass). Dale et al. (6) reported that women with a history of MI had significantly higher rates of BAC in mammographic examination than those without a history of MI. Maas et al. (2) indicated that BAC was predictive of a subsequent development of calcifications in the coronary arteries. They reported that, including previous cardiovascular disease, many cardiovascular risk factors had no association with BAC. According to the results of their study, Ak et al. (23) concluded that it was not appropriate to use BAC as a marker of atherosclerotic cardiovascular diseases. In our study, although CAD was found to be one of the significant risk factors of BAC in univariate analysis, its significance was lost in regression analysis. Neither univariate analysis nor regression analysis revealed any statistically significant effect of CVD history on BAC.

According to the results of the present study, BAC is associated with advancing age, parity, and breastfeeding, but not with cardiovascular disease or cardiovascular disease risk factors. In conclusion, we suggest that BAC cannot be used as a marker for determining the presence of cardiovascular disease and cardiovascular risk.

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