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ORIGINAL ARTICLE

Breast artery calcification as an opportunistic predictor of cardiovascular disease

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Abstract

Background Atherosclerotic cardiovascular disease is still the leading cause of mortality for women. Breast cancer screening with mammography is recommended in all women aged over 40 years.
Aims Whether breast artery calcification (BAC) is associated with cardiovascular disease is not clear. We aimed to evaluate the association between BAC and the presence of coronary atherosclerosis determined by CT.
Methods All patients who underwent both mammography and coronary CT angiography between January 2010 and December 2016 were screened, and patients with a duration of less than 12 months between CT and mammography were included.
Results A total of 320 women were included and BAC was detected in 47 (14.6%) patients. BAC was correlated with age and CT coronary calcium score. Both the frequency of critical coronary artery stenosis (34% vs 10.6%; $p = 0.001$) and CT coronary calcium score (5.5 vs 0; $p = 0.001$) was significantly higher in patients with BAC. The absence of BAC was a strong predictor of the absence of significant coronary artery disease ($p = 0.001$). BAC was independently associated with all-cause mortality after excluding patients with breast cancer (HR: 5.32; $p = 0.013$).
Conclusion Breast artery calcification is associated with coronary calcium score and significant coronary stenosis. A high BAC score is related to increased mortality.

Keywords Breast artery calcification · Cardiovascular risk · Coronary calcium score

Introduction

The recent European Cardiovascular Disease Statistics have shown that cardiovascular diseases are the leading cause of mortality in women, especially in middle-income countries. Breast cancer is the most common cancer in females and a significant cause of mortality. Guidelines recommend breast cancer screening in all women aged over 40 years old by mammography. However, imaging is not routinely used for cardiovascular disease screening, according to recent prevention guidelines [1, 2]. Cardiovascular risk predicting scores such as SCORE and Pooled Cohort Equation estimate the probability of the occurrence of future cardiovascular events [3]. However, existing risk scores may underestimate the long-term risk in primary prevention, especially in younger women [4, 5].

The presence of coronary artery calcification detected by computed tomography (CT) in asymptomatic patients is a well-defined risk predictor for cardiovascular disease [6]. Calcium scoring is recommended as a risk modifier in the ESC guidelines and is used for discrimination, reclassification, and statin treatment allocation in intermediate-risk subjects in the ACC/AHA Guidelines. CT angiography is associated with a higher radiation dose and risk of contrast injection and is therefore not routinely used for screening but is increasingly used to rule out CAD [4, 5].

Mammography is a widely used screening test in women and 40% of breast cancer diagnoses are made by the detection

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of microcalcification in the mammography images. In addition, mammography also gives the opportunity for the identification of breast artery calcification (BAC). BAC usually develops as a result of calcification of the medial layer of the artery [7]. It is not well known if there is a relationship between breast artery calcification and coronary artery disease (CAD) since there are publications claiming diverse results [8, 9].

If breast artery calcification, which can be detected easily by mammography, is an indicator of future cardiovascular events, it can be used as a cardiovascular risk predicting factor in women undergoing breast cancer screening. In this study, we aimed to evaluate the relationship between BAC and CAD and all-cause mortality.

Methods

Study population

All the patients who underwent both mammography and coronary CT angiography in Hacettepe University Hospital between January 2010 and December 2016 were screened. Patients with a duration of more than 12 months between CT and mammography were excluded. Demographic and clinical features of the patients were collected from the electronic database of the hospital and the mortality status of the patients was assessed from the government electronic death declaration system. The ethical approval of the study was confirmed by Hacettepe University Local Ethics Committee.

Assessment of mammography

Standard craniocaudal and mediolateral oblique mammograms were obtained using Senographe Essential Digital Mammography System (General Electric, USA). A second radiologist with more than 20 years of experience in mammography, blinded to the CAC results, reviewed the mammograms of the 320 women. All mammograms were reviewed on standard 5-megapixel mammography monitors. All cases were evaluated for BAC. The grade of calcification ranged from 0 to 3. No calcification is graded "0," few scattered punctate or short linear calcifications are graded "1," more abundant punctate or short linear calcifications are graded "2," continuous circumferential calcifications are graded "3" [10]. The grading of BAC is illustrated with examples in Fig. 1.

Assessment of cardiac CT angiography

CT angiography was performed in patients with chest pain having low-intermediate cardiovascular risk. Coronary artery

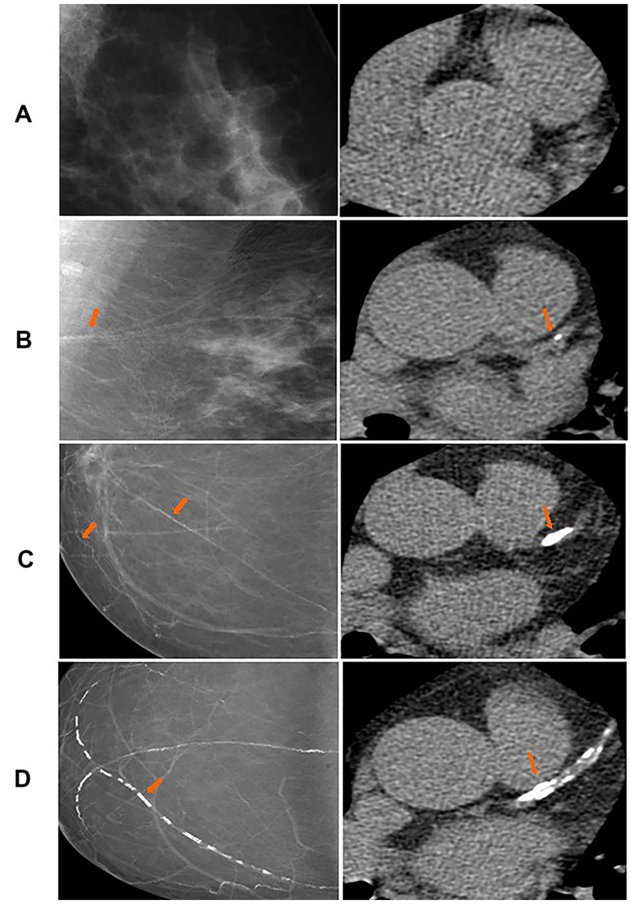

Fig. 1 **A** A 49-year-old woman with normal mammogram with BAC grade = 0 (left) and normal CT scan with Agatston score = 0 and CAD-RADS = 0 (right). **B** A 65-year-old woman with mammogram with BAC grade = 1 (left), CT scan with Agatston score = 14, and CAD-RADS = 1 (right). **C** A 82-year-old woman with mammogram with BAC grade = 2 (left), CT scan with Agatston score = 163, and CAD-RADS = 2 (right). **D** A 83-year-old woman with mammogram with BAC grade = 3 (left), CT scan with Agatston score = 550, and CAD-RADS = 3/N (right). Arrows show to arterial calcification. BAC, breast arterial calcium; CAC, coronary artery calcium; CT, computed tomography

calcium (CAC) scores were assessed by a non-contrast study before the coronary computed tomography (CT) angiography. Retrospective electrocardiographic gating was utilized on a 64-slice dual-source CT system (SOMATOM Definition, Siemens Healthcare, Forchheim, Germany). Image acquisition occurred within 70% of the electrocardiographic R-R interval. Images were reconstructed with a standard calcium scoring kernel (B35f) and a slice thickness of 3.0 mm. Images were transferred to an image processing workstation (Leonardo, Siemens AG, Healthcare Sector, Forchheim, Germany). Then CAC scores were calculated semi-automatically according to Agatston's method by the cardiac radiologist.

Patients were categorized into 3 groups according to the degree of coronary stenosis. Coronary artery lesions causing stenosis equal to or more than 50% were defined as critical stenosis. Lesions causing lower than 50% stenosis were defined as noncritical stenosis, and patients without any atherosclerotic plaque formation were classified as patients with normal coronary arteries.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 20; SpSS Inc., Chicago, IL, USA). Continuous variables were expressed as a mean with standard deviation (SD). Categorical datas were expressed as counts (%) and compared with Pearson's chi-square test. All tests for significance were two-sided and used a threshold of $P < 0.05$. The student's t-test was used while comparing independent groups with continuous variables, and the Mann–Whitney U test was used when comparing independent groups with numeric discrete data. Chi-square and Fischer's exact test were used in the analysis of categorical variables. The Cox proportional hazards model was performed to identify mortality predictive factors. Spearman correlation test was used to assess the correlation between BAC and CAD. Predictors of all-cause mortality with $p < 0.05$ in univariate analyses were accepted as statistically significant, and parameters with $p < 0.2$ were further included in the multivariate model as covariates. Survival analysis was performed using Kaplan–Meier curves and log-rank tests.

Results

A total of 320 women fulfilling the criteria were included in the study. BAC was detected in 47 (14.6%) patients. The mean age was 57.9 ± 8.4 years. Baseline characteristics, risk factors, and medications of the patients are presented in Table 1.

BAC was correlated with age ($r = 0.338$; $p < 0.001$) and CT coronary calcium score ($r = 0.306$; $p < 0.001$) in all of the patients. The correlation persisted after patients with diabetes and coronary artery disease were excluded for age ($r = 0.304$; $p < 0.001$) and CT coronary calcium score ($r = 0.289$; $p = 0.005$ (Table 2)).

Breast artery calcification and CT coronary angiography findings

Median CT calcium score was significantly higher in patients with BAC than in counterparts (5.5 vs 0; $p = 0.001$). In the BAC (+) group, the ratio of patients with moderate (21.3% vs 13.9%; $p < 0.001$), moderate to high (19.1%

Table 1 Baseline characteristics

Variables	Total population $n = 320$	BAC Yes $n = 47$	BAC No $n = 273$	p
Age, years	57.9 ± 8.4	64.7 ± 7.8	56.7 ± 7.9	< 0.001*
Smoking, n (%)	66 (20.6)	13 (27.7)	53 (19.4)	0.240
Hypertension, n (%)	197 (61.6)	35 (74.5)	162 (59.3)	0.053
Diabetes, n (%)	77 (24.1)	15 (31.9)	62 (22.7)	0.196
AF, n (%)	40 (12.5)	6 (12.8)	34 (12.5)	0.999
CAD, n (%)	29 (9.1)	9 (19.1)	20 (7.3)	0.020*
HL, n (%)	107 (33.4)	12 (25.5)	95 (34.8)	0.244
CKD, n (%)	1 (0.3)	-	1 (0.4)	0.999
Malignancy, n (%)	23 (7.2)	6 (12.8)	17 (6.2)	0.194
BB, n (%)	76 (23.8)	16 (34.0)	60 (22.0)	0.107
CCB, n (%)	51 (15.9)	10 (21.3)	41 (15.0)	0.284
RAS blocker, n (%)	121 (37.8)	25 (53.2)	96 (35.2)	0.023*
Statin, n (%)	91 (28.4)	14 (29.8)	77 (28.2)	0.862
Creatinine, mg/dL	0.7 (0.4–1.1)	0.7 (0.5–1.1)	0.7 (0.4–1.1)	0.275
Vitamin D, mg/mL	21.5 (3–68)	22.6 (5–61)	21 (3–68)	0.771
Total cholesterol, mg/dL	215.4 ± 59.1	208.6 ± 41.7	216.7 ± 61.8	0.412
LDL, mg/dL	139.8 ± 39.8	134.3 ± 33.8	140.8 ± 40.8	0.303

AF atrial fibrillation, *CAD* coronary artery disease, *HL* hyperlipidemia, *CKD* chronic kidney disease, *BB* beta blockers, *CCB* calcium channel blockers, *RAS* renin–angiotensin–aldosterone system, *LDL* low density lipoprotein

*$p < 0.05$ statistically significant results

Table 2 Correlation analysis between BAC and other parameters

Variables	All study population		Population without diabetes and CAD	
	r	*p*	*r*	*p*
Age	0.338	< 0.001*	0.304	< 0.001*
CT calcium score	0.296	< 0.001*	0.289	0.005*
CAD RADS	0.022	0.701	−0.005	0.938
Creatinine	0.065	0.247	0.023	0.733
Vitamin D	−0.023	0.735	0.015	0.862

BAC breast artery calcification, *CAD* coronary artery disease, *CAD RADS* coronary artery disease reporting and data system, *CAD* coronary artery disease

*$p < 0.05$ statistically significant results

vs 3.7%; $p < 0.001$) and high (8.5% vs 2.9%; $p < 0.001$) CT coronary calcium scores were higher than BAC (−) group (Table 3). Critical coronary artery stenosis was detected in 45 (12.2%) patients and it was significantly more frequent in patients with BAC than without BAC (34% vs 10.6%; $p = 0.001$) while normal coronary arteries were more frequent in patients without BAC (23.4% vs 42.5%; $p = 0.001$).

The positive predictive value of BAC for detecting coronary artery calcification was 55.3%, while the negative predictive value was 62.3%. The power of the negative predictivity was higher in patients with higher coronary calcium score levels. In patients with zero BAC, it was possible to rule out significant coronary calcium where the negative predictive value of BAC reached 97.6% in patients with coronary calcium score > 400 Agatston score.

After the patients with diabetes or coronary artery disease were excluded, analyses were repeated. Frequency of the patients with critical coronary artery stenosis (29.6% vs 4.5%; $p = 0.001$) and median CT coronary calcium score (4 vs 0; $p = 0.006$) were significantly higher in BAC (+) patients. Ratio of the patients with moderate (21.3% vs 13.9%; $p < 0.001$), moderate to high (11.1% vs 4%; $p = 0.008$)

Table 3 Association between CT coronary angiography datas and BAC

Variables	Total population (all study population) $n = 320$	BAC		*p*-value
		Yes $n = 47$	No $n = 273$	
CT findings, *n* (%)				
*Normal coronary arteries	127 (39,7)	11 (23.4)	116 (42.5)	0.001*
*Non-critic lesion	148 (46.3)	20 (42.6)	128 (46.9)	
*Critic lesion	45 (12.2)	16 (27.7)	29 (9.5)	
CT coronary calcium score, Agatston score, median (min–max)	0 (0–8401)	5.5 (0–1081)	0 (0–8401)	0.001*
Very low, *n* (%)	192 (60.0)	21 (44.7)	171 (62.6)	
Low, *n* (%)	49 (15.3)	3 (6.4)	46 (16.8)	
Moderate, *n* (%)	48 (15.0)	10 (21.3)	38 (13.9)	0.001*
Moderate to high, *n* (%)	19 (5.9)	9 (19.1)	10 (3.7)	
High, *n* (%)	12 (3.8)	4 (8.5)	8 (2.9)	
Variables	**Total population (CAD and diabetes excluded) $n = 225$**	**BAC**		***p*-value**
		Yes $n = 27$	**No $n = 198$**	
CT findings, *n* (%);				
*Normal coronary arteries	101 (44.9)	7 (25.9)	94 (47.5)	0.001*
*Non-critic lesion	105 (46.7)	12 (44.4)	93 (47.0)	
*Critic lesion	19 (8.4)	8 (29.6)	9 (4.5)	
CT coronary calcium score, Agatston score, median (min–max)	0 (0–1427)	4 (0–1081)	0 (0–1427)	0.006*
Very low, *n* (%)	149 (66.2)	13 (48.1)	136 (68.7)	
Low, *n* (%)	29 (12.9)	2 (7.4)	27 (13.6)	0.008*
Moderate, *n* (%)	30 (13.3)	6 (22.2)	24 (12.1)	
Moderate to high, *n* (%)	11 (4.9)	3 (11.1)	8 (4.0)	
High, *n* (%)	6 (2.7)	3 (11.1)	3 (1.5)	

BAC breast artery calcification, *CAD* coronary artery disease, *CAD* coronary artery disease

*$p < 0.05$ statistically significant results

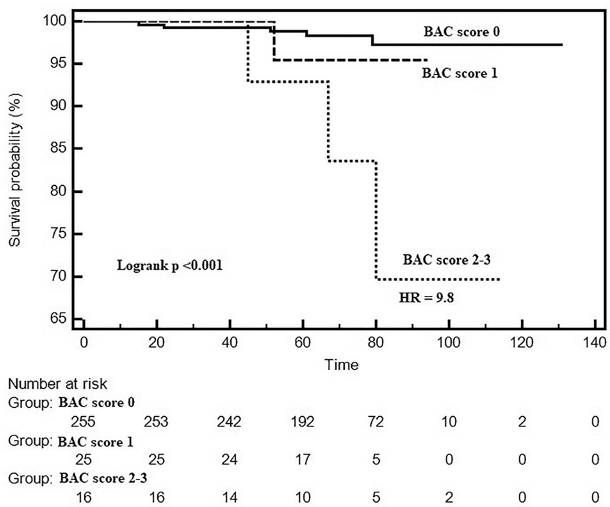

Fig. 2 Mortality risk classified by BAC score

and high (11.1% vs 1.5%; $p = 0.008$) CT coronary calcium score were distinctly lower in BAC (−) group (Table 3).

Association of BAC and CT coronary angiography findings with mortality

Patients with breast cancer were excluded from the mortality analysis. The all-cause mortality rate was significantly higher in patients with BAC than without BAC (HR: 5.32; $p = 0.013$). Kaplan–Meier survival analysis of patients according to BAC score is demonstrated in Fig. 2. Mortality risk was 9.81-fold increased in patients with BAC scores 2 and 3 compared with patients without BAC (Table 4).

Discussion

We aimed to evaluate the value of breast artery calcification as a cardiovascular risk predictor, which can be easily detected by mammography performed due to breast cancer screening in this study. Findings of this study demonstrated that the absence of breast artery calcification had a high negative predictive value for significant coronary artery disease and coronary artery calcium score was higher in cases with breast artery calcification than in counterparts. BAC was also found to be a predictor of all-cause mortality. These findings support that breast artery calcification may be used as an opportunistic cardiovascular risk factor.

The 10-year follow-up of the MESA study has shown that calcium score is an important predictor of cardiovascular outcomes [11]. This has led to the incorporation of calcium scoring in the guidelines for risk prediction, especially in low or intermediate-risk subjects. Vascular calcifications other than coronary arteries are also associated with increased cardiovascular event rates. Vascular calcification may develop in the tunica intima and tunica media of the arteries with different pathophysiologic pathways [12]. Intimal calcification is characterized by increased expression of growth factors, matrix proteins, and deposition of the smooth muscle cells, lipid deposits and inflammatory cells and is associated with atherosclerosis. On the other hand, lipid deposits and macrophages do not play a role in medial calcification (Mönckeberg type). Medial calcification has been related to diabetes, aging, end-stage renal disease, neuropathy, and some genetic syndromes [13, 14]. It is reported that medial arterial calcification is an independent predictor of cardiovascular events in patients with diabetes and end-stage renal disease [15, 16].

Table 4 Mortality risk according to BAC scores in nonmalignant patients

Variables	Nonmalignant population $n=297$	Survival: Alive $n=288$	Survival: Died $n=9$	HR	95% CI Lower–upper	p
BAC						
Absent	256 (86.2)	251 (87.2)	5 (55.6)	Ref		
Present	41 (13.8)	37 (12.8)	4 (44.4)	5.32	1.43–19.82	0.013*
BAC score						
0	256 (86.2)	251 (87.2)	5 (55.6)	Ref		
1	25 (8.4)	24 (8.3)	1 (11.1)	2.24	0.26–19.24	0.461
2	9 (3.0)	7 (2.4)	2 (22.2)	13.44	2.60–69.45	0.002*
3	7 (2.4)	6 (2.1)	1 (11.1)	6.35	0.74–54.77	0.093
BAC score						
0	256 (86.2)	251 (87.2)	5 (55.6)	Ref		
1	25 (8.4)	24 (8.3)	1 (11.1)	2.24	0.26–19.18	0.463
2–3	16 (5.4)	13 (4.5)	3 (33.3)	9.81	2.34–41.11	0.002*

Univariable Cox regression analysis was performed

HR hazard ratio, *CI* confidence intervals

*$p < 0.05$ statistically significant results

Breast artery calcification usually develops in tunica media and the prevalence has been reported as between 1 and 49% in the literature. The hypervariability of the prevalence rates between the studies is explained by the difference in the sensitivity of used mammography devices, study populations, and the discrepancy between the assessment of mammography images by radiologists. It is shown that age is the strongest predictor of BAC [17]. Breast artery calcification increases with aging and the prevalence of BAC is high in the elder population [9]. BAC prevalence was 14.7% in the present study, and the presence and the severity increased with age.

Can breast artery calcification predict future cardiovascular events? BAC is associated with hypertension, diabetes, dyslipidemia, and renal dysfunction, all of which are cardiovascular risk factors [18]. Previous studies looking at the association between BAC and CV events have shown controversial results. A meta-analysis including 19 trials concluded that although there are some studies that deny the relationship between BAC and cardiovascular events; BAC comes out as a cardiovascular risk factor in most of the studies [19, 20]. In the present study, we demonstrated that BAC is correlated with CT calcium score and the severity of coronary artery stenosis, especially in patients with higher BAC scores (2 and 3). We found that the absence of BAC was a negative predictor of significant coronary artery disease that may be useful in routine clinical practice.

Correlation between CT coronary calcium score and BAC has been demonstrated in previous studies where CT coronary calcium score was significantly higher in patients with BAC. The absence of BAC predicted the absence of severe coronary artery disease with high specificity [21, 22]. In our study, BAC was associated with both coronary artery calcification score and the severity of coronary artery stenosis in CT angiogram.

The link between the BAC and mortality has been assessed in previous trials. BAC has been associated with all-cause mortality only in diabetic patients [23]. We found that BAC was related to all-cause mortality in patients without breast cancer, and patients with higher BAC score (BAC scores 2 and 3) had higher mortality rates. The relationship between BAC and all-cause mortality persisted after patients with diabetes and coronary artery disease were excluded.

Limitations

Although this study represents new insights into the literature, it has some limitations. First of all, this study is a retrospective single-center study. Age was higher in the BAC group and may have been a confounding factor for increased mortality. Despite increased experience in evaluating CT images, the positive predictive value of coronary CT angiography is still limited. Therefore, another limitation of the study is that, coronary artery lesions determined by CT angiography were not confirmed with the gold standard invasive coronary angiography. Finally, despite patients with a duration between mammography and cardiac CT of more than 12 months were excluded, heterogenicity of the interval duration between CT and mammography may have influenced the results.

Conclusion

Breast artery calcification is associated with cardiovascular risk factors, CT coronary calcium score, and increased mortality. Mammography is frequently performed in women for breast cancer screening, and BAC can be detected easily by mammography. The absence of BAC practically excludes severe coronary artery disease. In light of this study, the presence and severity of BAC detected in routine mammography can alert to increased cardiovascular risk without any additional imaging and radiation exposure.

Author contribution M.O. collected data and wrote the manuscript. Y.Z.Ş. visualized, wrote, and reviewed the manuscript. Y.S. and S.A. collected data and performed analysis. A.Y. helped writing the manuscript, conceptualization, and collecting data. M.G.A helped with data curation and analysis. U.C. helped collecting data and analysis. T.H. took a role in visualization and supervision. N.Ö. reviewed and supervised the manuscript. S.L.T. took a role in methodology, supervision, and conceptualization.

Declarations

Conflict of interest The authors declare no competing interests.

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