original article

Breast arterial calcification on mammography does not predict coronary artery disease by invasive coronary angiography

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BACKGROUND: The relationship between breast arterial calcification (BAC) and angiographic coronary artery disease (CAD) is uncertain. Some studies have shown a positive association between BAC and angiographically proven CAD, while other studies have shown no association.

OBJECTIVE: Examine the association between visually detected BAC on mammography and CAD found on invasive coronary angiography (ICA) in women and compare the frequency of risk factors for CAD between women with normal and abnormal ICA.

DESIGN: Retrospective.

SETTING: Single tertiary care center.

PATIENTS AND METHODS: A review of the radiology databases was performed for female patients who underwent both ICA and mammography within six months of each other. Cases were excluded if there was a history of CAD, such as coronary artery bypass graft or prior percutaneous coronary intervention.

MAIN OUTCOME MEASURES: BAC as a predictor of obstructive CAD on ICA.

SAMPLE SIZE: 203 Saudi women

RESULTS: The association between age at catheterization and ICA was statistically significant (*P*=.01). There was no association between BAC and abnormal ICA (*P*=.108). Women with abnormal ICA were older than women with a normal ICA (*P*=.01). There was a higher frequency of CAD risk factors among the patients with abnormal ICA, except for smoking. In the multiple logistic regression model, ICA was associated with age, a family history of CAD, diabetes mellitus, hypertension and hypercholesterolemia. BAC-positive women were older than BAC-negative women (*P*=.0001). BAC was associated with age, diabetes, hypertension, and chronic kidney disease in the multiple logistic regression model.

CONCLUSIONS: BAC on mammography did not predict angiographically proven CAD. There was a strong association between BAC and age and many other conventional CAD risk factors.

LIMITATIONS: Relatively small sample, single-center retrospective study.

CONFLICT OF INTEREST: None.

Breast arterial calcification (BAC), which can be assessed with mammography, appears to be associated with an increased risk of cardiovascular events. Several studies have shown increased hazards for cardiovascular disease among BAC-positive women, when adjusted for age and conventional risk factors.[1-5] These positive studies outnumber several small studies that have demonstrated no significant association between BAC and coronary artery disease (CAD).[6-8] The relationship between BAC and coronary artery calcification (CAC) has been examined in several small studies; most have shown a positive association between BAC and CAC, while one found no association.[8-12] Overall, most studies have suggested that BAC has a strong association with CAD and that BAC may be associated with an increased risk of CAD in asymptomatic women. Only one study that examined the relationship between BAC and myocardial ischemia on nuclear myocardial perfusion imaging found no relationship between BAC and stress-induced myocardial ischemia.[13] The relationship between BAC and angiographic CAD is uncertain: some studies have shown a positive association,[14-16] and other studies have shown no association between BAC and angiographic CAD.[6-8] Therefore, the main objective of this study was to examine the association between visually detected BAC on diagnostic or screening mammography and obstructive CAD on invasive coronary angiography (ICA) in women and the prevalence of BAC and its association with other conventional CAD risk factors.

PATIENTS AND METHODS

This retrospective study was approved by the local ethical committee and informed consent was waived. A review of the radiology and cardiovascular department databases between January 2017 and April 2019 was performed for cases of female patients who underwent both ICA and either diagnostic or screening mammography within six months of each other. Females with a history of CAD, such as a prior coronary artery bypass graft or prior percutaneous coronary intervention, were excluded.

Mammography

The mammograms were performed using a full-field digital mammography system with acquisition of standard mammographic views (**Figure 1**). BAC was reported by an experienced observer, who was blinded to the ICA results, on a calibrated workstation. BAC scoring was reported as previously described by Mostavi et al.[17] BAC was classified as present or absent and graded into four grades: grade 1: absence of BAC; grade 2: a few punctate calcifications, no tram track or ring calcifications; grade 3: coarse or tram track calcifications affecting fewer than three vessels; grade 4: coarse or tram track calcifications affecting more than three vessels.[17]

Invasive coronary angiography

Conventional ICA was performed within six months of mammography in the cases reviewed for this research. The coronary arteries were divided into segments, according to the American Heart Association system.[18] The angiograms were reported by experienced invasive cardiologists blinded to the mammography results. The stenosis was classified as significant if the lumen reduction was >50%. The ICA results were categorized as follows: 1: no obstructive CAD; 2: single–vessel disease; 3: two-vessel disease; 4: multivessel disease.

Statistical analysis

IBM SPSS version 25 was used for data analysis. Continuous measurements were reported as means and standard deviations, while the categorical variables were reported as numbers and percentages. The chi-square test was used to screen for potential risk factors and/or possible confounders associated with BAC and ICA. Risk factors with a *P* value in the univariate analyses stage >.15 were not included in the multivariate logistic regression models. We set *P* value <.05 for statistical significance.

RESULTS

We identified 203 Saudi women who had ICA performed within 6 months of mammography. **Table 1** includes the demographics and CAD risk factors for the patients with normal and abnormal ICA. Patients with ICA were older than patients with a normal ICA at the time of catheterization (*P*=.01). There was no association between BAC and ICA (*P*=.108). Overall there was a higher frequency of CAD risk factors among the patients with abnormal ICA, except for smoking, hypertension, and chronic kidney disease (CKD). There was a positive statistical association between abnormal ICA and age, a family history of CAD, diabetes mellitus (DM), hypertension, and hypercholesterolemia, but no statistical association between abnormal ICA and BAC, smoking, and CKD.

Multiple logistic regression identified three variables that had a significant association with ICA, including age (*P*=.038, OR 1.046), a family history of CAD (*P*=.046, OR 3.616), and DM (*P*=.044, OR 1.152); there was no significant statistical association between hypertension and hypercholesterolemia (*P*=.709 and .054, respectively) (**Table 2**).

Table 3 shows the demographics and CAD risk factors for the patients with normal and abnormal BAC. BAC patients were older than patients without BAC (*P*=.0001). A higher prevalence of CAD risk factors, except for a family history of CAD, was found among patients with abnormal BAC. There was a positive statistical association between abnormal BAC and age, DM, hypertension, and CKD, but no statistical association between BAC and a family history of CAD.

Multiple logistic regression analysis identified more than one variable that had a significant association with BAC, including age (*P*=.003, OR 1.080), hypertension (*P*=.001, OR 3.717), and CKD (*P*=.016, OR 2.309). There was no association between DM and BAC in the multivariate model (**Table 4**).

DISCUSSION

In this study the presence of BAC among women who underwent mammography and ICA was not associated with angiographically proven CAD on ICA. An examination of other conventional CAD risk factors that may predict obstructive CAD on ICA found that several CAD risk factors associated with CAD in either univariate or both univariate and multivariate analysis. In the univariate analysis, age, a family history of CAD, DM, hypertension, and hypercholesterolemia were associated with CAD shown on ICA, but age, a family history of CAD, DM, and hypercholesterolemia were associated with angiographically proven CAD on ICA. Our study results are consistent with prior studies. For example, Penugonda et al's study of 94 women who underwent both mammography and ICA within a 36-month period found that BAC was not associated with cardiovascular risk factors, documented CAD, or acute cardiovascular events, suggesting that BAC as determined by mammography is not a useful predictor for CAD in intermediate- to high-risk patients.[8] In a similar study, Zgheib et al found that, in women who underwent ICA, the frequency of BAC in women with CAD at ICA was not significantly different from that in women without CAD, even when the CAD severity and location were considered.[6] Henkin et al studied 319 females to investigate the correlation between BAC and angiographically proven CAD and concluded that, despite correlation with some CAD risk factors, the presence of BAC did not differentiate between patients with angiographically proven CAD and those without normal coronary arteries.[7] However, other published studies have demonstrated a positive relationship between BAC and angiographically proven CAD. The largest study to date, by Dale et al, followed 819 women and found an OR of 6.2 (95% CI, 4.3–8.8) for the presence of BAC and angiographically proven CAD, defined as any degree of stenosis.[19] In a similar case-control study by Oliveira et al, consisting of 40 women, the presence of BAC was an independent risk factor for CAD, as were hypertension and a family history of CAD.[20] Similarly, Ferreira et al examined 131 women and found an adjusted OR of 4.6 (95% CI, 1.65–12.83) for any BAC and angiographically proven CAD to at least a mild degree (stenosis < 50% in one or more epicardial coronary vessels).[21]

A difference in the pathophysiology of BAC versus coronary atherosclerosis could potentially explain these conflicting findings. BAC primarily affects the vascular media, while coronary atherosclerosis affects the vascular intima.[22] Functional and microvascular abnormalities in the cardiovascular circulation, rather than luminal stenosis, tend to be a more predominant feature of CAD in women.[17] It is therefore possible that BAC has a role in these microvascular abnormalities, even in the absence of angiographic CAD, and it could have a role in cardiovascular disease risk stratification in women.

In our study, we also examined the prevalence and

Table 1. Demographic and clinical characteristics by normal or abnormal invasive coronary angiography (N=203).

	Normal ICA (n=113, 55.7%)	Abnormal ICA (n=90, 44.3%)	*P* value
Age at catheterization (years)	59.6 (6.5)	62.2 (7.7)	.01
Family history (CAD)			
Yes	4	11	.038
No	108	80	
Smoking			
Yes	12	13	.729
No	99	78	
Diabetes			
Yes	74	74	.009
No	38	16	
Hypertension			
Yes	91	82	.044
No	21	8	
Hypercholesterolemia			
Yes	47	55	.007
No	65	36	
CKD			
Yes	47	37	.836
No	65	54	
BAC			
Yes	62	60	.108
No	51	30	

Data are number (%) or mean (SD). ICA: invasive coronary angiography; BAC: breast arterial calcification; CKD: chronic kidney disease

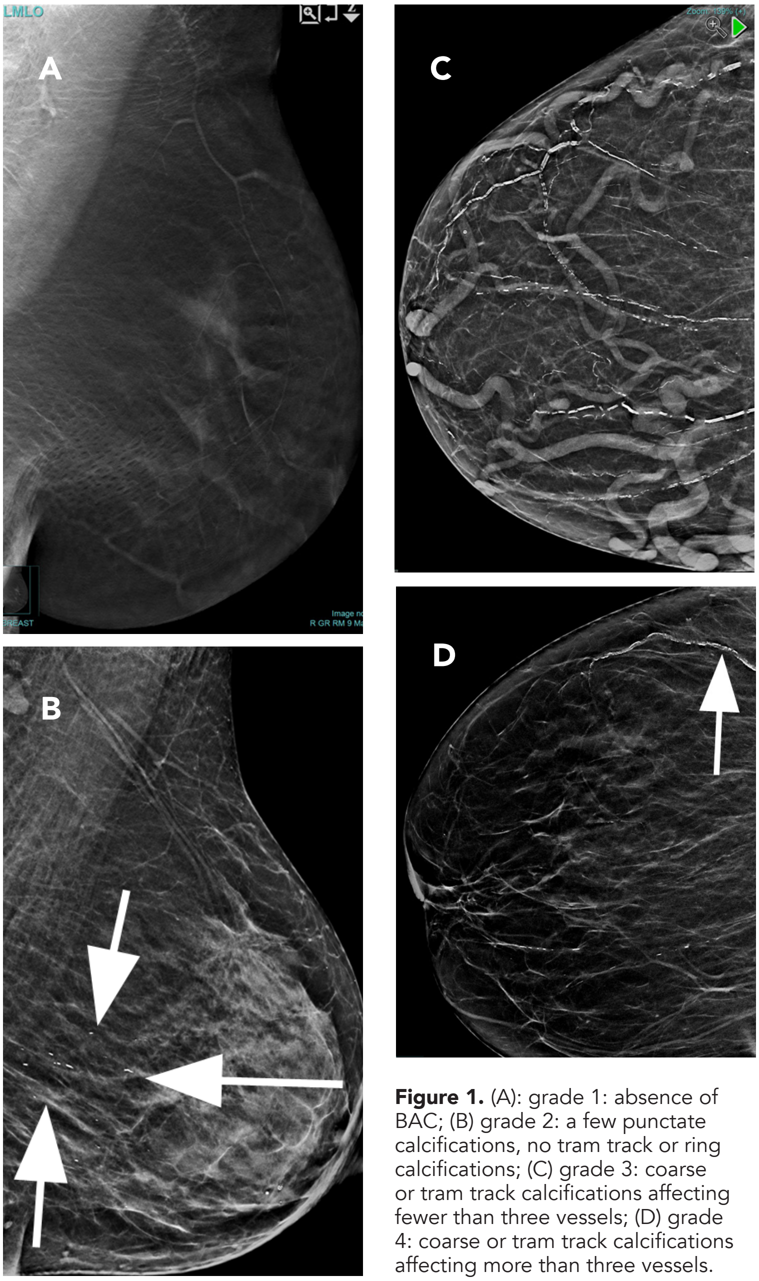

Figure 1. (A): grade 1: absence of BAC; (B) grade 2: a few punctate calcifications, no tram track or ring calcifications; (C) grade 3: coarse or tram track calcifications affecting fewer than three vessels; (D) grade 4: coarse or tram track calcifications affecting more than three vessels.

association of BAC with conventional CAD risk factors. The prevalence of BAC was 60% (120 BAC-positive women out of 203). There was a strong association between BAC and many CAD risk factors, including age, DM, hypertension, hypercholesterolemia, and CKD, in the univariate analysis. In the multivariate analysis, BAC was associated with age, hypertension, and CKD. The prevalence of BAC has been researched in many prior studies, including by our group, and it was 46%.[4] The prevalence of BAC in previous studies varied widely from 81% to only 12%.[9,23] However, the prevalence of BAC in the previously cited studies should be interpreted with caution because of relatively small sample sizes, possible bias selection, and different methods for measuring CAC. Most importantly, some studies were conducted in different geographic areas and among different ethnic groups. The relationship between BAC and CAC risk factors has been examined in prior studies. Margolis et al reported a strong association between BAC and age, hypertension, hypercholesterolemia, DM, smoking, and CKD.[11] Fathala et al reported that BAC positive women were significantly older than BAC negative women and found a strong association between BAC and CAC, DM, hypertension, and CKD.[4] Multiple observational studies have shown an association between BAC and CAC. CAC has emerged as one of the most promising tools to risk stratify patients in the intermediate cardiovascular risk group; one study reported that adding BAC to the 10-year atherosclerotic cardiovascular disease (ASCVD) risk significantly increased the area under the curve and net classification index improvement.[24,25]

Currently, the evidence on the relationship between BAC and angiographically proven CAD is conflicting and inconsistent, with some positive and some negative associations, including the current study. However, the association between BAC and CAC appears to be more consistent, with the vast majority of studies showing a positive association between BAC and CAC in multiple ethnic groups and geographic areas,

Table 2. Multiple logistic regression with invasive coronary angiography as the dependent variable.

Independent variable	Estimate	Standard error	Wald	*P* value	Odds ratio	95% confidence interval
Intercept	-6.746	1.750	14.865	<.001	0.0165	0.00117-0.232
Age	.045	.022	4.138	.042	1.046	1.002-1.092
Family history	1.280	.646	3.928	.047	3.616	1.014-12.751
Diabetes	.895	.390	5.254	.044	2.152	1.138-5.258
Hypertension	.254	.503	.255	.709	1.203	0.481-3.458
Hypercholesterolemia	.645	.311	4.289	.054	1.820	1.035-3.507

Model fit measures: Deviance 253.270, Cox & Snell R-square 0.114, Nagelkerke R-square 0.152

except for a very few studies with small sample sizes. Studies that examined the relationship between BAC and myocardial ischemia on stress perfusion imaging are lacking, except for one study by Fathala et al, which showed no association between BAC and inducible ischemia.[13] The association between BAC and incidence of CVD is apparent from several studies cited in this study. However, the current clinical application of BAC is unknown, due to the lack of prospective/outcomes studies and BAC detection and reporting challenges. Prospective studies to evaluate whether BAC improves risk stratification over standard ASCVD models are needed. The Multiethnic Study of Breast Arterial Calcium Gradation and Cardiovascular Risk (MINERVA), a 5-year prospective multiethnic cohort study, hopes to address some of these challenges and to investigate the value of BAC in predicting CAD, cerebrovascular disease, heart failure, and peripheral vascular disease.[26]

Our study had several limitations. It was a single-center retrospective study of women who had had mammography and ICA for symptomatic women with high-to-intermediate pre-test probability, rather than a prospective evaluation of consecutive patients. Therefore, selection biases cannot be excluded, and caution must be exercised in applying the results to the general population. Our study sample was relatively small and there was no long-term follow-up, which limits our findings with regard to long-term cardiovascular events. Finally, the study was conducted on the local population, i.e., a Mediterranean population with a certain racial, ethnic, and social background, and caution must be taken in applying the results to the worldwide population.

In summary, based on our data, there was no association between BAC and angiographically proven CD, but there was a significant association between BAC and many conventional CAD risk factors. The conflicting relationship between BAC and angiographic CAD may be explained by the differences in the pathophysiology of BAC and CAC. BAC primarily affects the vascular media, while coronary atherosclerosis tends to reside in the vascular intima. The microvascular abnormalities in the cardiovascular circulation rather than luminal stenosis tend to be more predominate in women; therefore, it is possible that BAC provides a good reflection of these microvascular abnormalities, even in the absence of angiographically proven CAD, and BAC may be a useful marker for CAD risk stratification in women. Large prospective studies with cardiovascular outcomes to evaluate whether BAC improves risk stratification over ASCVD models are needed.

Table 3. Demographic and clinical characteristics by presence of breast arterial calcifications (N=202).

	Negative BAC (n=81, 39.9%)	Positive BAC (n=121, 38.6%)	*P* value
Age at catheterization (years)	58.5 (5.9)	62.4 (7.5)	.0001
Family history (CAD)			.183
Yes	8	6	
No	74	115	
Smoking			.401
Yes	12	13	
No	70	108	
Diabetes			.003
Yes	50	97	
No	32	24	
Hypertension			.0001
Yes	61	112	
No	21	9	
Hypercholesterolemia			.089
Yes	46	54	
No	36	67	
CKD			.001
Yes	22	61	
No	60	60	

Data are number (%) or mean (SD). BAC: breast arterial calcification; CKD: chronic kidney disease.

Table 4. Multiple logistic regression with breast arterial calcification as the dependent variable.

Independent variable	Estimate	Standard error	Wald	*P* value	Odds ratio	95% confidence interval
Intercept	-7.635	1.678	20.694	<.001	0.00371	0.0001-0.0685
Age	.076	.025	9.624	.003	1.080	1.029-1.133
Diabetes	.303	.371	.665	.687	1.177	0.654-2.803
Hypertension	.984	.482	4.177	.011	3.717	1.041-6.879
Chronic kidney disease	.751	.336	4.997	.016	2.309	1.097-4.097

Model fit measures: Deviance 241.610, Cox & Snell R-square 0.146, Nagelkerke R-square 0.197

REFERENCES

1. Hendriks EJ, de Jong PA, van der Graaf Y, Mali WP, van der Schouw YT, Beulens JW. Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events. Atherosclerosis. 2015;239(1):11-20.
2. Kemmeren JM, Beijerinck D, van Noord PA, Banga JD, Deurenberg JJ, Pameijer FA, et al. Breast arterial calcifications: association with diabetes mellitus and cardiovascular mortality. Work in progress. Radiology. 1996;201(1):75-8.
3. Iribarren C, Go AS, Tolstykh I, Sidney S, Johnston SC, Spring DB. Breast vascular calcification and risk of coronary heart disease, stroke, and heart failure. Journal of women's health (2002). 2004;13(4):381-9; discussion 90-2.
4. Fathala AL, Alabdulkarim FM, Shoukri M, Alanazi M. Association between breast arterial calcifications found on mammography and coronary artery calcifications in asymptomatic Saudi women. Annals of Saudi medicine. 2018;38(6):433-8.
5. Maas AH, van der Schouw YT, Atsma F, Beijerinck D, Deurenberg JJ, Mali WP, et al. Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different. European journal of radiology. 2007;63(3):396-400.
6. Zgheib MH, Buchbinder SS, Abi Rafeh N, Elya M, Raia C, Ahern K, et al. Breast arterial calcifications on mammograms do not predict coronary heart disease at coronary angiography. Radiology. 2010;254(2):367-73.
7. Henkin Y, Abu-Ful A, Shai I, Crystal P. Lack of association between breast artery calcification seen on mammography and coronary artery disease on angiography. Journal of medical screening. 2003;10(3):139-42.
8. Penugonda N, Billecke SS, Yerkey MW, Rebner M, Marcovitz PA. Usefulness of breast arterial calcium detected on mammography for predicting coronary artery disease or cardiovascular events in women with angina pectoris and/or positive stress tests. The American journal of cardiology. 2010;105(3):359-61.
9. Chadashvili T, Litmanovich D, Hall F, Slanetz PJ. Do breast arterial calcifications on mammography predict elevated risk of coronary artery disease? European journal of radiology. 2016;85(6):1121-4.
10. Matsumura ME, Maksimik C, Martinez MW, Weiss M, Newcomb J, Harris K, et al. Breast artery calcium noted on screening mammography is predictive of high risk coronary calcium in asymptomatic women: a case control study. VASA Zeitschrift fur Gefasskrankheiten. 2013;42(6):429-33.
11. Margolies L, Salvatore M, Hecht HS, Kotkin S, Yip R, Baber U, et al. Digital Mammography and Screening for Coronary Artery Disease. JACC Cardiovascular imaging. 2016;9(4):350-60.
12- Moradi M, Adibi A, Abedi M. Relationship between breast arterial calcification on mammography with CT Calcium scoring and coronary CT angiography results. Advanced biomedical research. 2014;3:79.
13. Fathala A, Salem S, Alanazi F, Abunayyan D, Eldali AM, Alsugair A. Breast Arterial Calcifications on Mammography Do Not Predict Myocardial Ischemia on Myocardial Perfusion Single-Photon Emission Computed Tomography. Cardiol Res. 2017;8(5):220-7.
14. Topal U, Kaderli A, Topal NB, Ozdemir B, Yesilbursa D, Cordan J, et al. Relationship between the arterial calcification detected in mammography and coronary artery disease. European journal of radiology. 2007;63(3):391-5.
15. Abi Rafeh N, Castellanos MR, Khoueiry G, Meghani M, El-Sayegh S, Wetz RV, et al. Association between coronary artery disease diagnosed by coronary angiography and breast arterial calcifications on mammography: meta-analysis of the data. Journal of women's health (2002). 2012;21(10):1053-8.
16. Jiang X, Clark M, Singh RK, Juhn A, Schnatz PF. Association of breast arterial calcification with stroke and angiographically proven coronary artery disease: a meta-analysis. Menopause (New York, NY). 2015;22(2):136-43.
17. Mostafavi L, Marfori W, Arellano C, Tognolini A, Speier W, Adibi A, et al. Prevalence of coronary artery disease evaluated by coronary CT angiography in women with mammographically detected breast arterial calcifications. PLoS One. 2015;10(4):e0122289.
18. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975;51(4 Suppl):5-40.
19. Dale PS, Mascarhenas C, Richards M, Mackie G. Mammography as a screening tool for coronary artery disease. The Journal of surgical research. 2008;148(1):1-6.
20. Oliveira EL, Freitas-Junior R, Afiune-Neto A, Murta EF, Ferro JE, Melo AF. Vascular calcifications seen on mammography: an independent factor indicating coronary artery disease. Clinics (Sao Paulo, Brazil). 2009;64(8):763-7.
21. Fiuza Ferreira EM, Szejnfeld J, Faintuch S. Correlation between intramammary arterial calcifications and CAD. Academic radiology. 2007;14(2):144-50.
22. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. Journal of the American College of Cardiology. 2006;47(3 Suppl):S21-9.
23. Pecchi A, Rossi R, Coppi F, Ligabue G, Modena MG, Romagnoli R. Association of breast arterial calcifications detected by mammography and coronary artery calcifications quantified by multislice CT in a population of post-menopausal women. La Radiologia medica. 2003;106(4):305-12.
24. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1046-e81.
25. Yoon YE, Kim KM, Han JS, Kang SH, Chun EJ, Ahn S, et al. Prediction of Subclinical Coronary Artery Disease With Breast Arterial Calcification and Low Bone Mass in Asymptomatic Women: Registry for the Women Health Cohort for the BBC Study. JACC Cardiovascular imaging. 2019;12(7 Pt 1):1202-11.
26. Iribarren C, Molloi S. Breast Arterial Calcification: a New Marker of Cardiovascular Risk? Curr Cardiovasc Risk Rep. 2013;7(2):126-35.