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N. Shah
Northwell Health

V. Chainani
Northwell Health

P. Delafontaine

A. Abdo

J. Lafferty
Northwell Health

See next page for additional authors

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Mammographically Detectable Breast Arterial Calcification and Atherosclerosis

Neeraj Shah, MD[*], **Vinod Chainani, MD**[*], **Patrice Delafontaine, MD**[†], **Abir Abdo, MD**[‡], **James Lafferty, MD**[§], and **Nidal Abi Rafeh, MD**[†]

[*]Department of Medicine, Staten Island University Hospital, Staten Island, NY

[§]Department of Medicine, Division of Cardiology, Staten Island University Hospital, Staten Island, NY

[†]Department of Medicine, Division of Cardiology, Tulane University Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA

[‡]Department of Medicine, Section of Geriatric Medicine, Louisiana State University School of Medicine, New Orleans, LA

Abstract

Breast arterial calcification (BAC), observed as an incidental finding on screening mammograms, represents degenerative calcific changes occurring in the mammary arteries, with increasing age. The aim of this review is to discuss relevant literature examining relation between BAC and atherosclerosis. After a thorough literature search, in OVID and PubMed, 199 studies were identified, of which 25 were relevant to our review. Data were abstracted from each study and statistical analysis was done, including calculation of odds ratios and construction of forest plots. A total of 35,542 patients were enrolled across 25 studies looking at an association between BAC and coronary artery disease, cardiovascular disease, stroke, cerebral artery disease, carotid and peripheral artery diseases, and coronary artery calcification. A majority of the studies showed a statistically significant relation between BAC and presence of coronary artery disease cardiovascular disease and associated mortality. Sensitivity of BAC in predicting cardiovascular events was low, but specificity was high. BAC was predictive of incident and prevalent stroke but not mortality of stroke. Similarly, BAC was predictive of cerebral, carotid, and peripheral artery diseases. The role of BAC as a surrogate marker of coronary and systemic atherosclerosis is currently uncertain. Its role may be further elucidated by more large-scale prospective studies and clinical experience.

Correspondence: Neeraj Shah, MD, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305. neerajshah86@gmail.com.

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Keywords

breast arterial calcification; atherosclerosis; mammography; coronary artery disease; cardiovascular disease; stroke; cerebral artery disease; carotid artery disease; peripheral artery disease; coronary artery calcification

Breast arterial calcification (BAC) is a type of medial calcific or Mönckeberg sclerosis[1] and is defined as nonocclusive calcification of the media of small- to medium-sized mammary arteries. It has a characteristic pattern of linear amorphous calcification bounded by 2 parallel lines giving a tram-track appearance (Fig. 1).[2] BAC involves the entire circumference of the vessel, making it less compliant, and represents arteriosclerosis of peripheral arteries.

The prevalence of BACs on routine screening mammography ranges from 8%[3] to 20%.[4] Calcifications of mammary arteries frequently represent age-related degenerative changes;[5] their incidence increases with age, and they are uncommon in mammograms performed in women less than 50 years of age.

Sickles et al[6] showed that there was a statistically significant correlation between BAC and diabetes mellitus, but concluded that this association was not clinically significant. This spurred several studies looking at an association between BAC and cardiovascular diseases (CVDs) and their risk factors. With the relatively low cost of testing and possible association between BAC, coronary artery disease (CAD), stroke, carotid artery disease, and peripheral arterial disease (PAD), the study of BAC and its relation to these comorbid states may be of clinical benefit for diagnosis and prevention of these conditions. Moreover, mammography is routinely used as a screening test for breast cancer, and its use to detect BAC will not entail any extra cost or radiation exposure. This review article explores the relation between BAC and vascular diseases in an attempt to clearly delineate it as a possible CVD predictor using the current available information in the literature.

METHODS

Two investigators independently searched for all published studies on the relation between BAC and CAD, stroke, PAD, carotid atherosclerosis, carotid intima media thickness (CIMT), and coronary calcification. Literature search was conducted in OVID Medline and PubMed databases using the following keywords or phrases as subject headings or in title or abstract search: “breast arterial calcification,” “breast artery calcification,” “BAC,” “mammary arterial calcification,” “mammary artery calcification,” “intramammary arterial calcification,” “intramammary artery calcification,” “Intramammary Arterial Calcification” (IMAC), “breast vascular calcification,” “vascular calcification and mammography,” “atherosclerosis,” “arteriosclerosis,” “cardiovascular diseases,” “coronary artery disease,” “brain ischemia,” “cerebrovascular disorders,” “cerebral artery disease,” “stroke,” “cerebrovascular accident,” “carotid artery diseases,” “carotid atherosclerosis,” “carotid intima media thickness,” “peripheral vascular diseases,” “peripheral arterial disease,” “peripheral artery disease,” “coronary calcification,” “coronary artery calcification,” and “coronary calcium score.” After screening the studies found in the initial search, the full texts of all articles relevant to our study were retrieved. Subsequently, to identify additional studies, references of all relevant articles were thoroughly reviewed. The demographic characteristics of each study were extracted and tabulated. Information regarding the type of the study, sample size, definition of study endpoint, prevalence of BAC in the study, and statistical significance based on *P* values (with $P < 0.05$ considered significant) were also collected and recorded.

Statistical Analyses

Two-by-two tables delineating any association between BAC and the endpoint (eg, CAD and stroke) were constructed wherever possible for each study using the available data. Using these tables, odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values were calculated for each study. Forest plots of ORs with 95% CIs were then constructed using the crude and adjusted ORs/hazards ratios (HRs) reported in each study. All analyses were performed using Microsoft Excel 2010 and Statistical Analysis Software (SAS) version 9.0.

RESULTS

Our initial search yielded 199 studies. On subsequent screening, 25 studies, with a total of 35,542 patients across 7 countries, were found to be relevant and were included in our review. The study period ranged from 1995 to 2011, and the studies looked at relation between BAC and CVD, cardiovascular (CV) mortality, coronary, cerebral or systemic atherosclerosis, CIMT, and coronary calcium. We found 19 studies[7–25] looking at the association of BAC and CAD and/or CVD, 8 studies between BAC and stroke,[7–9,20,21,23,24,26] 2 studies between BAC and PAD,[27,28] 3 studies between BAC and CIMT,[16,19,29] and 2 studies between BAC and coronary artery calcification (CAC).[30,31] Tables 1 and 2 show detailed information regarding individual studies.

Breast Arterial Calcification, Coronary Artery Disease, Cardiovascular Disease, and Cardiovascular Mortality

We identified 19 studies with a total of 33,583 subjects enrolled across all studies. The mean age of women ranged from 43.4[16] to 66.7[17] years. Most studies included postmenopausal women older than 40 years of age, with only 1 study including premenopausal women.[16] Only 4 of 19 studies did not show an association between BAC and CAD,[10,12,13,16] 13 of 19 (68%) studies showed a clear cut, statistically significant association, and 2 of 19 studies showed significant association only when obstructive CAD (≥50% stenosis) was considered.[11,14] Obstructive CAD was generally defined as ≥50% coronary artery stenosis, except by Sarrafzadegann et al,[16] who used ≥50% stenosis in left main coronary artery and/or ≥75% stenosis in other epicardial arteries as the definition of obstructive CAD. There was 1 prospective cohort study,[7] 2 retrospective cohort studies,[8,9] 9 case-control studies with CAD,[10–18] 1 case-control study with BAC,[19] and 7 cross-sectional (prevalence) studies.[20–25] Table 1 and Figures 2–4 show crude and adjusted ORs calculated from data extracted from each study. Please note that some of the crude ORs and *P* values shown in Table 1 may not be quoted in full text articles of the respective studies, because we calculated these values by a repeat analysis of data based on the information provided in the methods and results sections of each study (see Statistical Analyses under Methods section

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for details). In addition, we were able to access the full-study database of Zgheib et al,[11] because this study was conducted at our institution (Staten Island University Hospital).

All crude and adjusted prevalence and incidence ORs/HRs were statistically significant in cross-sectional and cohort studies. Most case-control studies used angiographically proven CAD as the definition of CAD. For case-control studies, the relation between BAC and obstructive CAD was tenuous, with only 3 of 7 studies involving angiographic obstructive CAD as the endpoint showing a statistically significant relation (Fig. 2; Table 1). One case-control study[17] used angiographically documented CAD (obstructive plus nonobstructive) or history of at least one episode of acute myocardial infarction as the definition of the case, and another study[18] used only angiographically documented CAD (obstructive plus nonobstructive) as the definition of case. Both studies showed a statistically significant relation between BAC and CAD.

Table 3 shows sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of BAC for primary endpoint of each study in this group. For cross-sectional studies, BAC shows high specificity for coexisting CAD/atherosclerotic CVD, ranging from 84.5%[24] to 93%.[22] The sensitivity, PPV, and NPV of BAC to detect coexisting CAD are low, with a maximum sensitivity of 50%.[25] The cohort studies also report high specificity of BAC for incident CAD morbidity and mortality (88%–97%), with low sensitivity, PPV, and NPV. Case-control studies incorporating the gold standard definition of CAD (ie, angiography) showed a higher PPV (35%–70%) and a higher sensitivity (40%–69%). The specificity of BAC to detect angiographic CAD was generally high, except for 2 studies.[10,13]

Breast Arterial Calcification, Stroke, Cerebral Artery Disease, and Stroke Mortality

We found 7 studies which examined the relation between BAC and stroke,[7–9,20,21,23,24] and 1 study[26] between BAC and cerebral artery disease detected on brain magnetic resonance imaging (MRI; Table 2). Not all the studies were primarily designed to evaluate the relation between BAC and stroke. One study was a prospective cohort,[7] 2 studies were retrospective cohorts,[8,9] and 4 studies were cross-sectional.[20,21,23,24] There were a total of 30,673 subjects enrolled across 7 studies, and the mean age of the subjects ranged from 56 to 63 years. Five of 7 studies (71.4%) reported a statistically significant association between BAC and stroke. Table 2 and Figure 5 show the crude and adjusted ORs with 95% CIs.

Breast Arterial Calcification, Peripheral Arterial Disease, Carotid Intima Media Thickness, and Coronary Artery Calcification

There were 2 studies showing the association between BAC and PAD,[27,28] 3 between BAC and CIMT,[16,19,29] and 2 between BAC and CAC.[30,31] Table 2 shows description of the studies along with their ORs and 95% CIs. Both the studies looking at BAC and PAD and BAC and CAC, and 2 of 3 (66%) of the studies looking at BAC and CIMT showed a statistically significant relation.

DISCUSSION

We aimed to analyze whether BAC seen on screening mammograms correlates with the occurrence of coronary and noncoronary atheroscleroses. The relation between BAC and traditional CV risk factors, such as diabetes mellitus and hypertension, has been controversial. Some studies show a significant association between BAC and hypertension,[19,32,33] whereas others show no such association.[4,24,34] Similarly, with diabetes mellitus, some studies show a statistically significant association,[6,19,35,36] whereas others show none.[4,24,37,38]

Breast Arterial Calcification and Cardiovascular Disease

In our review, greater than 3 quarters of the studies, examining an association between BAC and CAD, showed a statistically significant relation. Age was a major confounding factor in the association between BAC and CAD because age is a risk factor for CAD and there is a higher prevalence of BAC with increasing age. We found that 16 of 19 studies had adjusted for age. Although BAC has also been shown to be associated with other confounding CAD risk factors, however, this association has not been consistently observed. Most of the reviewed studies included other CAD risk factors in addition to age in multivariate models where applicable.

There was marked heterogeneity in the definition of CAD across the studies, with some studies defining CAD as angiographically proven coronary artery stenosis and others using self-reported CAD or hospital discharge data. Two studies used atherosclerotic CVD (defined as self-reported angina, history of myocardial infarction or coronary artery bypass graft, or abnormal coronary angiogram or stroke).[20,21] Ferreira et al[22] used CVD, defined as atherosclerotic CVD plus congestive heart failure. Kemmeren et al[9] used CV mortality according to the ICD-9 criteria (defined as death from coronary heart disease, cerebrovascular diseases, heart failure, complications of heart disease, or sudden cardiac death). Oliveira et al[17] used history of myocardial infarction or angiographically documented CAD, and Van Noord et al[23] used only acute myocardial infarction as the endpoint.

Breast Arterial Calcification and Angiographic Coronary Artery Disease (Case Control)

Seven studies looked at the relation between BAC and obstructive CAD diagnosed by the “gold standard” coronary angiography. These studies recruited patients undergoing cardiac catheterization for high-risk chest pain or abnormal stress test. Subsequently, the prevalence of BAC in angiographically proven obstructive CAD (≥50% stenosis, except Sarrafzadegann et al[16]) cases was compared with controls without CAD. Only 3 of 7 studies showed significant *P* values in the association between BAC and obstructive CAD.[11,14,15] In 2[11,14] of these, the association between BAC and obstructive plus nonobstructive CAD was not statistically significant, but became significant ($P < 0.05$) when only obstructive CAD was considered. We reviewed a recently conducted meta-analysis looking at pooled data from 5 of the 7 studies, with a total of 927 subjects, showing an OR of 1.59 (95% CI, 1.21–2.09), thus signifying an overall statistically significant association between BAC and angiographically proven obstructive CAD.[39] The 2 studies not included in the meta-analysis

(Penugonda et al[10] and Sarrafzadegann et al[16]) were not statistically significant, but they were limited due to small sample sizes. The *P* values of Zgheib et al[11] and Topal et al[14] were not adjusted for the confounding effect of age, which precludes any inferences based solely on crude OR. In fact, only 1 study[15] showed a strong relation between BAC and obstructive CAD after adjustment for age and other potential confounders. Moshyedi et al[13] showed that in women younger than 59 years, BAC had a statistically significant association with CAD. Quantification revealed no relation between intensity of BAC and severity of CAD.[14,15] All these studies had high CAD prevalence (33.5%–64.9%) because they consisted of a high-risk population undergoing cardiac catheterization.

Two other case-control studies, Dale et al[18] and Oliveira et al,[17] compared angiographically documented CAD cases to control groups derived from a general population that did not undergo any coronary angiography. Both these studies showed a strong association between BAC and CAD, which remained robust in multivariate analysis, with multivariate ORs of 6.2[18] and 4.7,[17] respectively. Sedighi et al[19] compared self-reported CAD prevalence in BAC-positive women with age-matched BAC-negative controls showing a significant age-matched univariate OR; however, it was nonsignificant in multivariate analysis.

Breast Arterial Calcification and Prevalent Coronary Artery Disease (Cross-Sectional)

Most cross-sectional studies used patient-reported CAD or CVD as the endpoint. Van Noord et al[23] reported an adjusted relative risk of 1.8 (95% CI, 1.1–2.9) between prevalent myocardial infarction and BAC. We were able to calculate a crude OR of 1.76 (1.5–2.1) of prevalent BAC and CVD (defined as history of myocardial infarction, stroke, transient ischemic attack, or the use of CV drugs) from Kemmeren et al.[9] All cross-sectional studies showed significant adjusted cross-sectional ORs (Table 1 and Fig. 3). These studies had large sample sizes, ranging from 30,722 to 12,084.[23] Concomitant existence of BAC and CAD suggests that BAC is a marker of underlying CAD and may represent atherosclerosis elsewhere in the body.

Breast Arterial Calcification and Incident Coronary Artery Disease (Cohort)

Schnatz et al[7] did the lone prospective cohort study looking at the relation between BAC and incident self-reported CAD. The 5-year incidence of CAD in those with BAC was 6.3% compared with 2.3% in those without BAC. Iribarren et al[8] conducted a retrospective study with 12,761 women and ascertained outcomes such as CAD and stroke by hospital discharge and death records, with a median follow-up of 25 years. They showed a 32% increased risk of CAD in a multivariate analysis. Kemmeren et al[9] studied 12,084 patients with CV mortality as the endpoint and a follow-up period of 16–19 years. The age-adjusted HR for mortality from CAD was 1.47 and for overall CV mortality (mortality from CAD, stroke, heart failure, and sudden cardiac arrest) was 1.35. These studies show that women with BAC on screening mammography are at an increased risk of developing or dying from CAD in the subsequent years (Fig. 4).

Sensitivity, Specificity, and Predictive Values—In general, BAC has low sensitivity and predictive values, but high specificity, ranging from 39%[10] to 97%[8] for coexisting or incident CAD endpoints. Case-control studies using angiography showed a higher sensitivity and PPV, possibly because of the higher prevalence of CAD in this population owing to their study design.

Breast Arterial Calcification and Stroke

Stroke was studied as part of the definition of CVD (CAD plus stroke);[20,21,24] other studies looked at stroke as a secondary endpoint.[7,23] Only one study[8] was primarily designed to study the relation between BAC and stroke. The definition of endpoints in different studies was heterogeneous. Kemmeren et al[9] included mortality from stroke (as per ICD-9 coding) as the endpoint, whereas Van Noord et al[23] included transient ischemic attack in addition to stroke as the endpoint. Most studies included patient reporting as the method of detecting stroke, whereas Iribarren et al[8] used hospital discharge data. Again, age was found to be the major confounding factor in this relation, and 5 of 8 studies[8,9,23,24,26] reported multivariate ORs/HRs adjusted for age and/or other confounding variables (Table 2).

The study by Schnatz et al[7] of the relation between BAC and incident CAD also reported stroke as a secondary outcome. This study reported both prevalent stroke and incident stroke at baseline. The OR of prevalent stroke at baseline was 6.3 (95% CI, 2.7–14.7), and the 5-year incidence of stroke was 8.7% vs. 1.4% in the 2 BAC groups with crude incidence OR of 6.9 (95% CI, 3.5–13.6). Iribarren et al[8] reported an age-adjusted multivariate HR of 1.41 (95% CI, 1.1–1.8) for the relation between BAC and ischemic stroke. Kemmeren et al[9] reported no significant association between BAC and mortality from stroke, with adjusted OR of 0.98 (95% CI, 0.56–1.71).

All cross-sectional studies used self-reported stroke as the endpoint. Crystal et al[20] and Rotter et al[21] included stroke as part of atherosclerotic CVD, and crude ORs for stroke were 4.9 and 4.4, respectively (Table 2). Van Noord et al[23] looked at the association between BAC and prevalent strokes and reported an adjusted OR of 1.4 (95% CI, 1.1–1.9). Kataoka et al[24] showed a statistically significant association of BAC with prevalent CAD, but not with prevalent stroke (adjusted OR, 2.02; 95% CI, 0.61–6.69).

Breast Arterial Calcification and Cerebral Artery Disease

The studies discussed earlier used subjective methods such as patient reporting for detecting stroke. A more objective way to demonstrate stroke is an MRI of the brain. Only one study was identified in the literature, which examined the association between BAC and MRI-proven cerebral artery disease,[26] but this study did not use stroke as the endpoint. It used microvascular ischemic changes, demonstrated by either white matter hypodensities (WMHs) or periventricular hypodensities (PVHs), as the endpoint.

The investigators[26] recruited 168 Korean women with age 40–78 years who underwent screening mammograms and brain MRI to study the relation between BAC and T2 hyperintensities on brain MRI (WMH and PVH), which are considered precursors for stroke.[40–42] Cerebral artery disease was defined as grades 2 and 3 WMH or grade 3 PVH. The adjusted OR for WMH was 6.86 (1.83–25.7) and for PVH was 9.04 (1.2–68.3). Thus, BAC may be a marker of higher risk of future stroke in women as demonstrated by its association with precursor WMH in this study.

Breast Arterial Calcification and Systemic Vascular Disease

We found 2 studies looking at the relation between BAC and peripheral vessel atherosclerosis.[27,28] Dale et al[27] looked at women undergoing mammography and identified those with documented PAD using hospital data. They reported a prevalent OR of 3.09, with sensitivity and specificity of BAC being 42% and 80%, respectively. Markopoulos et al[28] divided study subjects into 3 groups as follows: those undergoing mammography, those undergoing vascular surgery, and BAC-negative women undergoing breast surgery. They showed a relation between BAC and systemic vascular disease in carotid or femoral arteries detected by duplex scan.

Breast Arterial Calcification and Carotid Intima Media Thickness

CIMT is itself a marker of atherosclerosis and it has been proposed as a surrogate marker for underlying CAD.[43] There are 3 studies looking at the association between BAC and carotid atherosclerosis detected by CIMT. CIMT greater than 0.8 mm was considered high risk, and ORs were calculated in reference to that value from study data (Table 2). Sedighi et al[19] compared 79 subjects with BAC to 125 age-matched controls and subjected them to carotid ultrasound to measure CIMT. This study showed an association between carotid plaque and BAC, although the association between BAC and IMT was stronger. Yildiz et al[29] conducted a similar study and reported mean CIMT of 0.87 ± 0.17 in BAC-positive women compared with 0.60 ± 0.19 in BAC-negative women with a coefficient of 0.463 ($P < 0.001$). However, Sarrafzadegann et al,[16] who included only premenopausal women referred for coronary angiography, failed to show any statistically significant relation.

Breast Arterial Calcification and Coronary Computerized Tomography

Coronary calcification represents chronic atherosclerotic plaque burden and usually represents more advanced lesions. The use of CAC improves the prediction of risk for future CAD.[44] There is, however, a difference in etiology of the 2 types of calcification, with BAC being predominantly medial compared with CAC which is predominantly intimal calcium deposition.[30] Maas et al[30] randomly selected 499 women undergoing screening mammograms and subjected them to multislice computerized tomography (MSCT) to detect the amount of CAC. Seventy-six percent of the women with BAC had CAC detected on MSCT compared with only 49% of women without BAC, with an adjusted OR of 2. Another study by Pecchi et al,[31] conducted in an Italian population involving only 74 patients, showed a strong correlation between BAC and CAC on MSCT.

Most studies have used patient self-reporting or hospital chart reviews as the method of detecting CAD, which is not very accurate. Other studies have reported coronary angiography, which is the gold standard. However, the drawback of such studies is that they include a high-risk CAD population and inferences from these studies cannot be extended to a low-risk general population. An ideal way to study the relation between BAC and CAD would be to subject all asymptomatic patients undergoing screening mammograms to coronary angiography to detect CAD. However, such large-scale population-based angiographies are neither feasible nor cost effective. Therefore, the best way to accurately document CAD in an asymptomatic population would be to use noninvasive testing such as cardiac computerized tomography for evaluating the coronary circulation.

Breast Arterial Calcification and Smoking

Interestingly, many studies have reported a paradoxical inverse relation between BAC and smoking[8,9,20,23,24] (Table 4). The exact cause of this phenomenon is unclear, especially because smoking has been shown to increase CAC.[45] One explanation may be that smoking-related inflammation plays only a little role in mammary artery calcifications.[5] CV events in smokers are more related to inflammation, thrombosis, and endothelial dysfunction than to vascular calcification.[46,47] Other theories are the selective survival of smokers after the age of 50 and the effect of smoking on weight or estrogen metabolism.[23]

LIMITATIONS

There was a marked heterogeneity in the definition of endpoints (CAD, PAD, or stroke) across all the studies. Adjustment for age was not done in all studies. The population enrolled across different studies was also heterogeneous, with some studies enrolling younger women[16] and others enrolling solely postmenopausal women.[22,24] There was also a potential for an inherent selection bias in all these studies, as the population choosing to undergo screening mammograms may be systematically different from those not choosing to undergo the same. Moreover, publication bias (positive results getting published easily) is a consideration.

CONCLUSIONS

Our analysis of the published data suggests that BAC is associated with CVD, stroke, CIMT, and CAC. BAC's relation with angiographic CAD is uncertain and presently debatable. Future prospective studies and an accumulation of clinical knowledge may further elucidate the place of BAC among the indicators of risk of coronary and systemic atherosclerosis.

RECOMMENDATIONS TO THE RADIOLOGIST

Given the evidence available from the current literature, we recommend that mammograms be carefully scrutinized for the presence of BAC. BAC, if present, should be mentioned in the mammography report and should be flagged for the clinician to correlate clinically with the presence of coronary or systemic atherosclerosis. With the available evidence, we do not recommend any further testing solely based on the presence of BAC at this time.

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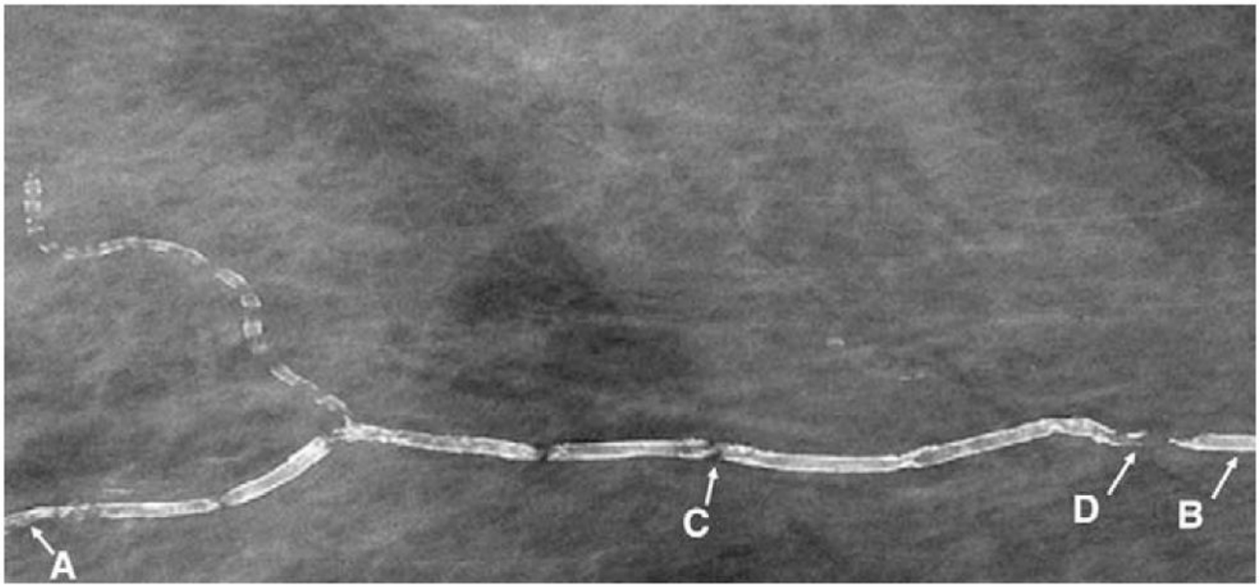

FIGURE 1.
Screening mammogram showing breast arterial calcification. The length of breast arterial calcification is defined as longest continuous calcified segment, which is C to D in the depicted vessel A to B (Reproduced with permission from Zgheib et al[11]).

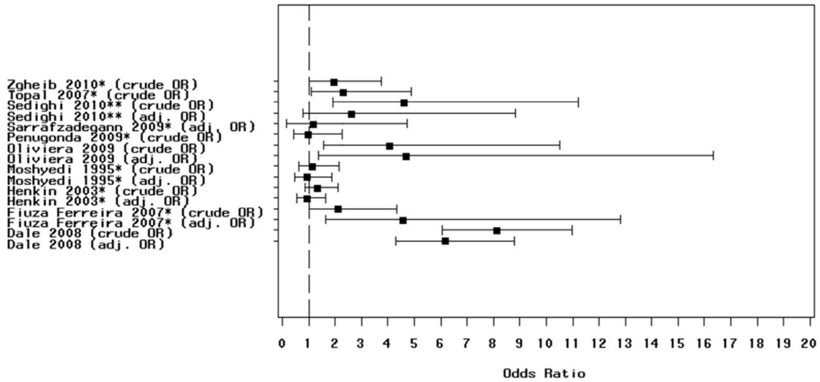

FIGURE 2.

Figure showing crude and adjusted odds ratios (OR) with 95% confidence intervals of case-control studies examining the relation between breast arterial calcification and angiographic coronary artery disease (CAD). *Obstructive CAD (≥50% stenosis) considered as endpoint and ** self-reported CAD used with breast arterial calcification positive considered as case.

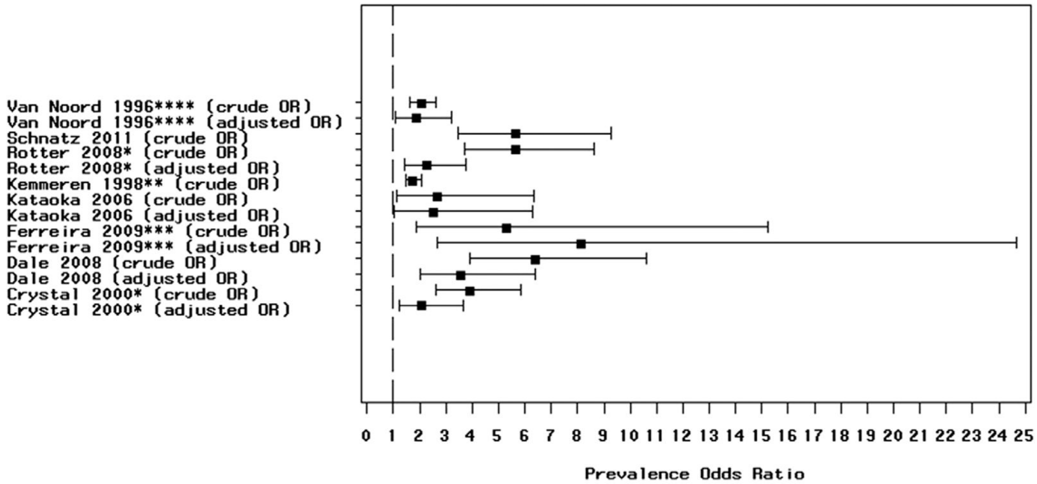

FIGURE 3.

Figure showing crude and adjusted prevalence odds ratios (ORs)/hazards ratios with 95% confidence intervals of cross-sectional studies examining the relation between breast arterial calcification and coronary artery disease, cardiovascular disease (CVD) and cardiovascular mortality. *Atherosclerotic CVD defined as self-reported angina, history of myocardial infarction or coronary artery bypass graft, or abnormal coronary angiogram or stroke; **cardiovascular mortality; ***CVD defined as coronary artery disease or history of myocardial infarction or stroke or congestive heart failure; and ****prevalent myocardial infarction, used as endpoint.

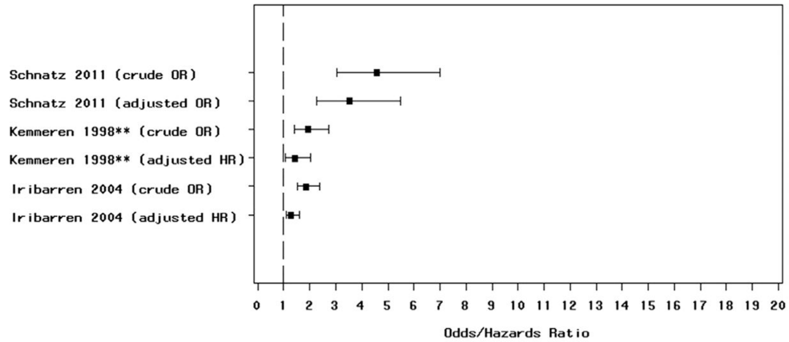

FIGURE 4.

Figure showing crude and adjusted incidence odds ratios (ORs)/hazards ratios with 95% confidence intervals of prospective and retrospective cohort studies examining the relation between breast arterial calcification and coronary artery disease, cardiovascular disease, and cardiovascular mortality. **Cardiovascular mortality used as endpoint.

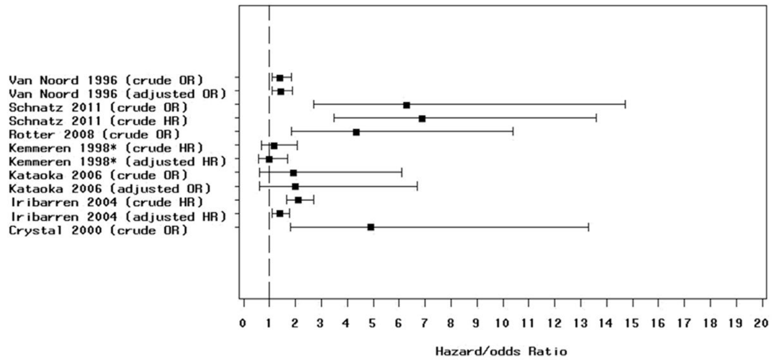

FIGURE 5.

Figure showing crude and adjusted odds ratios (OR)/hazards ratios with 95% confidence intervals of studies examining the relation between breast arterial calcification and stroke and stroke mortality. *Mortality from stroke used as endpoint.

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TABLE 1

Studies Showing Association Between BAC and CAD, CVD, CV Mortality, and CAC

Study	Country	Type of Study	N	Age	BAC Prevalence, %	Endpoint	Method of Detecting Endpoint	Prevalence of Endpoint, %	Result	Crude OR	95% CI	*P*	Adjusted Ratio	95% CI	*P*
Schnatz et al[7]	United States	Prospective	1454	56.3	14.2	CAD	Self-reported	4.9*	S	4.62	3.1–7.0	<0.05	3.54	2.3–5.5	<0.001
Iribarren et al[8]	United States	Retrospective	12,761	56.3	3	CAD	Hospital discharge	17.9	S	1.9	1.5–2.4	<0.001	1.32‡	1.1–1.6	0.007
Kemmeren et al[9]	The Netherlands	Retrospective	12,084	57.7	9.2	CV mortality	ICD-9 coding	10†	S	1.76	1.5–2.1	<0.001	1.47‡	1.1–2.0	<0.05
Penugonda et al[10]	United States	Case control	94	66.7	60.6	CAD§	Coronary angiography	56.4	NS	0.98	0.4–2.3	0.72	—	—	—
Zgheib et al[11]	United States	Case control	172	62.3	33	CAD§	Coronary angiography	54.1	NS/S¶	1.95	1.0–3.8	0.045	—	—	—
Henkin et al[12]	Israel	Case control	319	63	41.1	CAD§	Coronary angiography	58.6	NS	1.32	0.8–2.1	0.23	0.96	0.6–1.6	0.89
Moshyedi et al[13]	United States	Case control	182	64	33.5	CAD§	Coronary angiography	33.5	NS	1.16	0.6–2.2	0.64	0.95	0.5–1.9	0.88
Topal et al[14]	Turkey	Case control	123	56.8	39.8	CAD§	Coronary angiography	39	NS/S¶	2.31	1.1–4.9	0.042	—	—	—
Fiuza Ferreira et al[15]	Brazil	Case control	131	61.1	39.7	CAD§	Coronary angiography	64.9	S	2.12	1.0–4.3	0.007	4.6	1.7–12.8	<0.05
Sarrafzadegann et al[16]	Iran	Case control	84	43.4	7.1	CAD§	Coronary angiography	40.5	NS	—	—	—	1.2	0.1–4.7	0.8
Oliveira et al[17]	Brazil	Case control	80	64.6	42.5	CAD	Coronary angiography or history of MI	50	S	4.06	1.6–10.5	0.003	4.71	1.4–16.3	0.014
Dale et al[18]	United States	Case control	1214	65	23	CAD	Coronary angiography	23	S	8.14	6.0–11	<0.001	6.2	4.3–8.8	<0.05
Sedighi et al[19]	Iran	Case control	204	60.6	14.7	CAD	Self-reported	13.2	S	4.63	1.9–11	<0.001	2.63	0.8–8.8	>0.05
Crystal et al[20]	Israel	Cross-sectional	865	55.9	17.6	ASCVD	Self-reported	16.4	S	3.91	2.6–5.8	<0.001	2.11	1.2–3.7	0.008
Rotter et al[21]	United States	Cross-sectional	1919	56	14	ASCVD	Self-reported	5.1	S	5.65	2.7–8.6	<0.001	2.29	1.4–3.7	<0.001
Ferreira et al[22]	Brazil	Cross-sectional	307	55.2	8.5	CVD	Self-reported and medical records	6.8	S	5.32	1.9–15	<0.001	8.13	2.7–24.7	<0.001
Van Noord et al[23]	The Netherlands	Cross-sectional	12,084	57.7	9.1	MI	Self-reported	4.7	S	2.07	1.6–2.6	<0.001	1.87	1.1–3.2	<0.05
Kataoka et al[24]	United Kingdom	Cross-sectional	1590	63.2	16	CAD	Self-reported	1.5	S	2.68	1.1–6.3	0.019	2.54	1.0–6.3	<0.05
Dale et al[25]	United States	Cross-sectional	1000	57.5	16	CAD	self-reported	7.2	S	6.42	3.9–11	<0.001	3.6	2–6.4	<0.001
Maas et al[30]	The Netherlands	Prospective	499	57.9	12	CAC	MSCT	53	S	3.2	1.7–6.0	<0.001	2.0	1.0–3.9	0.04

*Calculated from prevalent CAD as reported in subjects at the start of the study.

†Calculated from prevalent CVD as reported in subjects at the start of the study.

‡Hazards ratio (adjusted).

§Only obstructive CAD (≥50% stenosis on angiography) considered.

¶Significant only when obstructive CAD (≥50% stenosis) considered as endpoint.

Age indicates median age in years; ASCVD, atherosclerotic cardiovascular disease; BAC, breast arterial calcification; CAC, coronary artery calcification (defined as coronary calcium score >0); CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; ICD-9, International Classification of Diseases, Ninth Revision; MI, myocardial infarction; MSCT, multislice computerized tomography; N, sample size; NS, nonsignificant; OR, odds ratio; S, significant; CI, confidence interval.

TABLE 2

Studies Showing Association Between BAC and Non-CAD Atherosclerotic Vascular Disease (Stroke, Cerebral Artery Disease, Systemic Vascular Disease, and CIMT)

Study	Country	Type	N	Age	BAC Prevalence, %	Endpoint	Method of Detecting Endpoint	Prevalence of Endpoint, %	Result	Crude OR	95% CI	*P*	Adjusted Ratio	95% CI	*P*
Schnatz et al[7]	United States	Prospective	1454	56.3	14.2	Stroke	Self-reported	1.51	S	6.89	3.5–13.6	<0.001	—	—	—
Iribarren et al[8]	United States	Retrospective	12,761	56.3	3	Ischemic stroke	Hospital discharge	10.9	S	2.11	1.6–2.7	<0.001	1.41‡	1.1–1.8	0.004
Kemmeren et al[9]	The Netherlands	Retrospective	12,084	57.7	9.2	Stroke deaths	ICD-9 coding	1.1	NS	1.18	0.7–2.1	0.56	0.98‡	0.6–1.7	>0.05
Crystal et al[20]	Israel	Cross-sectional	865	55.9	17.6	Stroke	Self-reported	1.85	S	4.9	1.8–13.3	0.0006	—	—	—
Rotter et al[21]	United States	Cross-sectional	1919	56	14	Stroke	Self-reported	1.56	S	4.37	1.8–10.4	0.001	—	—	—
Van Noord et al[23]	The Netherlands	Cross-sectional	12,084	57.7	9.1	Stroke/TIA	Self-reported	4.97	S	1.42	1.1–1.8	0.006	1.43	1.1–1.9	<0.05
Kataoka et al[24]	United Kingdom	Cross-sectional	1590	63.2	16	Stroke	Self-reported	0.94	NS	1.93	0.6–6.1	0.26	2.02	0.6–6.7	>0.05
Jin Ahn et al[26]	Korea	Cross-sectional	168	58	17	Cerebral artery disease	Brain MRI	11.9*	S	8.8*	3.2–34*	<0.001	6.86*	1.8–25*	0.004
								3.6†	S	11†	1.9–63†	0.001	9.04†	1.2–68†	0.033
Dale et al[27]	United States	Case control	766	72	19	PAD	Hospital records	15.8	S	3.09	2.1–4.7	<0.001	—	—	—
Markopoulos et al[28]	Greece	Cross-sectional	110	62.2	11	Systemic vascular disease§	Carotid or femoral duplex	62.7	S	3.83	1.7–8.7	0.001	—	—	—
Sedighi et al[19]	Iran	Case control¶	204	60.6	14.7	CIMT >0.8 mm or carotid plaque	Carotid USG	32.4	S	6.55	3.4–12.5	<0.001	4.88[a]	1.5–16[a]	<0.01
													23.4[b]	4.5–120[b]	<0.01
													3.13[c]	1.3–7.6[c]	<0.01
Yildiz et al[29]	Turkey	Case control¶	54	61.1	10.2	CIMT >0.8 mm	Carotid USG	33.3	S	7.95	2.1–29.7	0.001	—	—	—
Sarrafzadegann et al[16]	Iran	Cross-sectional	84	43.4	7.1	CIMT (continuous)	Carotid USG	—	NS	0.05‖	0–33‖	0.51‖	—	—	—
									NS	0.14#	0–13.5#	0.40#	—	—	—

*For WMH.

†For PVH.

‡Hazards ratio (adjusted).

§Defined as >40% stenosis or ≥2.5-mm atheromatous plaque in carotid or femoral arteries.

¶Case control with BAC-positive women as “cases”; a = adjusted OR and 95% CI for medium- vs. low-risk CIMT; b = adjusted OR and 95% CI for high- vs. low-risk CIMT; c = adjusted OR and 95% CI for carotid plaque.

‖Univariate OR, 95% CI, and *P* value for common CIMT (derived from logistic regression with BAC as dependent and CIMT as continuous independent variable).

[#]Univariate OR, 95% CI, and *P* value for internal CIMT (derived from logistic regression with BAC as dependent and CIMT as continuous independent variable).

Age indicates median age in years; BAC, breast arterial calcification; CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima media thickness; ICD-9, International Classification of Diseases, Ninth Revision; MRI, magnetic resonance imaging; N, sample size; NS, nonsignificant; OR, odds ratio; PAD, peripheral arterial disease; PVH, periventricular hypodensities; S, significant; TIA, transient ischemic attack; USG, ultrasound; WMH, white matter hypodensities.

TABLE 3

Studies Showing Sensitivity, Specificity, PPV, and NPV of BAC for CAD, Cardiovascular Disease, and Cardiovascular Mortality

Study	Outcome	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Schnatz et al[7]	CAD	39.1	87.8	20.8	5.4
Iribarren et al[8]	CAD	5	97.3	29.6	18.1
Kemmeren et al[9]	CV death	16.2	91	4.1	2.1
Penugonda et al[10]	CAD*	60.4	39	56.1	56.8
Zgheib et al[11]	CAD*	39.7	74.6	64.9	48.6
Henkin et al[12]	CAD*	43.9	62.9	62.6	55.9
Moshyedi et al[13]	CAD*	57.4	46.3	35	31.7
Topal et al[14]	CAD*	52.1	68	51	31.1
Fiuza Ferreira et al[15]	CAD*	48.5	69.2	61.5	43
Sarrafzadegann et al[16]	CAD*	8.8	94	50	39.7
Oliveira et al[17]	CAD	57.5	75	69.7	36.2
Dale et al[18]	CAD	69.2	78.4	48.9	10.5
Sedighi et al[19]	CAD	70.4	66.1	24.1	6.4
Crystal et al[20]	ASCVD	38	86.4	35.5	12.3
Rotter et al[21]	ASCVD	44.3	87.7	16	3.3
Ferreira et al[22]	CVD	28.5	93	23.1	53.4
Van Noord et al[23]	MI	16.6	91.2	8.5	4.3
Kataoka et al[24]	CAD	33.3	84.3	3.1	1.2
Dale et al[25]	CAD	50	86.5	22.3	4.3

*Obstructive CAD only (≥50% coronary artery stenosis on angiography).

ASCVD indicates atherosclerotic cardiovascular disease; BAC, breast arterial calcification; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

TABLE 4

Studies Showing Relation Between BAC and Smoking

Study	Country	N	OR	95% CI	*P*
Kataoka et al[24]	United Kingdom	1590	0.46	0.23–0.94	<0.05
Iribarren et al[8]	United States	12,761	0.45	0.31–0.63	<0.001
Van Noord et al[23]	The Netherlands	12,084	0.41	0.35–0.49	<0.001
Crystal et al[20]	Israel	865	0.24	0.14–0.43	<0.001
Maas et al[30]	The Netherlands	499	0.6	0.25–1.39	>0.05
Schnatz et al[7]	United States	1454	0.53	0.26–1.06	0.068
Rotter et al[21]	United States	1919	0.41	0.22–0.77	0.004
Penugonda et al[10]	United States	94	0.31	0.12–0.82	0.015
Henkin et al[12]	Israel	319	0.35	0.19–0.65	<0.001
Sedighi et al[19]	Iran	204	0.11	0.01–0.86	0.01

CI indicates confidence interval; BAC, breast arterial calcification; N, sample size; OR, odds ratio.