Breast Arterial Calcifications as A Predictor of Cardiovascular Risk: A Systematic Review


ABSTRACT

Introduction: Breast arterial calcification (BAC) is considered a prediction tool for cardiovascular disease (CVD) screening as it has shown some association. The current systematic review reports the evidence on BAC detected on screening mammography and occurrence risk or likelihood of CVD among women.

Methods: Three databases, including PubMed, Cochrane, and Google Scholar, were searched by three independent reviewers.

Results: A total of 34,887 patients across six studies were assessed in the systematic review. The incidence of BAC on the mammogram was 10.3%. The odds or likelihood of developing CVD was higher among BAC+ women. Hypertension, hypercholesterolemia, and family history of CVD were more prevalent in BAC+ women and menopause.

Conclusion: Further studies are required to develop a semi-quantitative index of BAC for CVD screening to establish BAC as a predictor of CVD further.

Keywords: Age, breast arterial calcification, cardiovascular disease, hypertension, hypercholesterolemia, menopause.

I. INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in women, with a burden of 400,000 deaths yearly [1]-[3]. While there has been a decline in the mortality associated with CVD across both men and women, there is stagnancy in the incidence and mortality rates of CVD among women, especially those younger than 55 years [4]. It is necessary to establish the risk factors in
women to reduce further the incidence and mortality rates associated with CVD [5]. The recognition of risk factors of CVD beyond the traditional ones is necessary for improving outcomes in women [6]. Certain roadblocks for women when identifying their CVD signs and symptoms at presentation have been attributed to biases in the medical sector [7]. For instance, women are more likely to present with atypical chest pain linked with a reduced frequency and diagnosis of CVD [8], [9]. The American Heart Association (AHA) and European Heart Society (ESC) recognize gender gaps in CVD prediction and treatment models such as physiological conditions, e.g. menopause, pregnancy, and psychological factors [10], [11].

Mammography is a common modality used for breast cancer screening among women typically conducted between 50 and 70 years of age [12]. In a recent meta-analysis, the prevalence of breast arterial calcification (BAC) detected on mammography among patients with breast cancer was 12.7% [13]. BAC is an incidental finding in mammography that has shown an association with CVD outcomes [14]. The underlying mechanisms of BAC are separate from that of the calcifications found in CVD and have been associated with medial calcification of small mammary arteries or arterioles [15]. Recent evidence has suggested that there may be a direct association between the incidental findings of BAC and CVD [16]. However, the evidence is currently inconsistent and requires further understanding to understand whether the association of BAC with CVD is dichotomous or increases with the extent of BAC [17]. The following systematic review collates current evidence to evaluate the correlation between BAC and CVD among women.

II. METHODS

A. Search Strategy and Selection

We searched databases including PubMed, Cochrane, and Google Scholar from inception till July 7, 2022. A combination of MESH terms was run through Boolean operators, including "breast arterial calcification," "coronary artery disease," “CAD,” “cardiovascular disease,” and “CVD.” Two investigators screened the studies for inclusion in the study. An umbrella review was also conducted to identify the studies from reference lists of all potential studies. First, the two investigators conducted a screening of the title and abstract. If there were discrepancies between the two investigators, a third investigator solved these with consensus. Second, the full texts were reviewed for eligibility against the selection criteria. There was no restriction on the search, such as time and language. Duplicates were removed using the software Endnote X9.

B. Selection Criteria and Endpoint

Randomized controlled trials (RCTs) and observational cohort studies (OCS) were considered. Only studies that reported patients older than 18 years, patients undergoing mammography screening, and BAC as an outcome measure were considered. We considered studies with a sample size larger than 1,000 participants. The primary endpoint was the prevalence of CVD among participants who were detected to have BAC on a mammogram. The secondary endpoint was the prevalence of traditional CVD risk factors and gender-specific risk factors among participants with and without BAC on a mammogram.

C. Data Management and Analysis

Two investigators extracted data from the finalized studies using Excel’s custom datasheet. The variables were pre-tabulated based on the consensus from three investigators and included total sample size, BAC+ sample size, age, comorbidities, and CVD. All three reviewers utilized the Cochrane Risk of Bias (ROB) tool. A qualitative analysis was conducted to analyze the current evidence regarding the prevalence of CAD among participants who were detected with BAC on screening mammography.

III. RESULTS

A step-by-step approach to the search strategy was reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The overall search process is summarized in Fig. 1. In the first phase, 997 records were identified through different databases. After removing duplicates, 854 records were screened for potential eligibility by titles and abstracts. In the second phase, 829 records were excluded, and 25 records were screened for full-text eligibility. In the final stage, six studies were included in the qualitative analysis.

![Fig. 1. PRISMA flow diagram for this study.](image-url)
The odds of developing CVD among BAC+ participants were 1.32 (95% CI: 1.08-1.60) (22), 2.29 (95% CI: 1.40-3.74) (18), and 2.54 (95% CI: 1.03-6.30) (20) in a prospective longitudinal cohort and two prospective cohorts, respectively. In a prospective longitudinal observational study, the hazard or likelihood ratio of developing CVD was 1.23 (95% CI, 1.00-1.52) (21). In a retrospective longitudinal observational study, the hazard ratio of developing CVD was 1.29 (95% CI: 1.06-1.58) (23). Finally, in a prospective cohort, the likelihood of CVD was 20.8% in BAC+ participants and 5.4% in BAC- participants. BAC+ women were more likely or had higher odds of developing CVD, as summarized in Table I.

The prevalence of hypertension among BAC+ participants with hypertension was 49.6%. Among BAC- participants, the prevalence of hypertension was 31.6%.

Hypercholesterolemia was present in 42.8% of BAC+ participants and 25.0% of BAC- participants. Among BAC+ participants, the prevalence of diabetes mellitus was 10.5%, whereas the prevalence of diabetes mellitus in BAC- participants was 18.3%. The prevalence of smoking among participants with BAC+ was 27.5% and with BAC- was 28.3%. A family history of CVD was prevalent among 37.9% of BAC+ participants with BAC- and 32.5% of BAC+ participants with BAC-.

Table I: Key Characteristics of the Included Studies in This Review

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<tbody>
<tr>
<td>Study type</td>
<td>Retrospective longitudinal observational</td>
<td>Prospective longitudinal observational</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>Prospective longitudinal observational</td>
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<tr>
<td>Sample size (N)</td>
<td>12,104</td>
<td>12,761</td>
<td>1,590</td>
<td>1,919</td>
<td>1,454</td>
<td>5,059</td>
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<tr>
<td>BAC+ sample size (n)</td>
<td>1,107</td>
<td>424</td>
<td>254</td>
<td>268</td>
<td>207</td>
<td>1,338</td>
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<tr>
<td>Prevalence of BAC (%)</td>
<td>9.2%</td>
<td>3.3%</td>
<td>16.0%</td>
<td>14.0%</td>
<td>14.2%</td>
<td>26.4%</td>
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<tr>
<td>Selection criteria</td>
<td>Women being assessed for breast cancer on screening mammography and aged 50-68 years</td>
<td>Women being assessed for breast cancer on screening mammography and aged 40-79 years</td>
<td>Women being assessed for breast cancer on screening mammography, older than 55 years, and not taking hormone replacement therapy</td>
<td>Women being assessed for breast cancer on screening mammography</td>
<td>Women being assessed for breast cancer on screening mammography and aged 60-79 years</td>
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<td>Mean age (years); total or BAC+ and BAC-</td>
<td>60.1 ± 4.0 and 57.5 ± 4.3</td>
<td>66 and 56</td>
<td>63.2 ± 4.6</td>
<td>56.0 ± 12.7</td>
<td>56.3 ± 12.1</td>
<td>67.1 and 65.2</td>
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<tr>
<td>Mean BMI (kg/m²); total or BAC+ and BAC-</td>
<td>NA</td>
<td>25.6 and 25.4</td>
<td>26.2 ± 4.1</td>
<td>28.1 and 27.9</td>
<td>NA</td>
<td>27.8 and 27.7</td>
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<tr>
<td>Cardiovascular risk factors (BAC+ and BAC-)</td>
<td>Diabetes mellitus (71/1,07 and 384/10,977), smoking (157/1,07 and 3,128/10,977)</td>
<td>Hypertension (174/424 and 3,548/12,337), diabetes mellitus (55/424 and 709/12,337), smoking (40/424 and 3,457/12,337)</td>
<td>Hypertension (25/240 and 149/1,279), diabetes mellitus (6/254 and 25/1,336), smoking (253/254 and 529/1322)</td>
<td>Hypertension (52/140 and 27/439), hypercholesterolemia (47/125 and 33/356), diabetes mellitus (11/29 and 4/69), smoking (4/11 and 9/155), family history of CVD (22/58 and 21/346)</td>
<td>Hypertension (110/207 and 342/1,247), hypercholesterolemia (95/207 and 413/1,247), diabetes mellitus (18/207 and 51/1,247), smoking (18/207 and 99/1,247)</td>
<td>Hypertension (804/1,338 and 1,794/3,271), diabetes mellitus (192/1,338 and 1,331/3,271), smoker (455/1,338 and 1,085/3,271)</td>
</tr>
<tr>
<td>Gender-specific risk factors (BAC+ and BAC-)</td>
<td>Current use of hormone therapy (51/1,07 and 911/10,977)</td>
<td>Current use of hormone therapy (58/424 and 3,431/12,337)</td>
<td>NA</td>
<td>Menopause (89/240 and 52/859), current use of hormone therapy (13/36 and 10/167), history of breast cancer (13/36 and 6/96)</td>
<td>Menopause (184/207 and 701/1,247), current use of hormone therapy (28/207 and 136/1247), history of breast cancer (26/207 and 81/1247)</td>
<td>Current use of hormone therapy (128/1,338 and 374/3,271)</td>
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<td>CVD occurrence</td>
<td>Hazard ratio: 1.29 (95% CI: 1.06-1.58)</td>
<td>Odds ratio: 1.32 (95% CI: 1.08-1.60)</td>
<td>Odds ratio: 2.54 (95% CI: 1.03-6.30)</td>
<td>Odds ratio: 2.29 (95% CI: 1.40-3.74)</td>
<td>BAC+: 20.8% likelihood, BAC-: 5.4% likelihood</td>
<td>Hazard ratio: 1.23 (95% CI: 1.00-1.52)</td>
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<td>Comments</td>
<td>Hazard ratio of diabetic women with BAC: 1.74 (95% CI: 1.19-2.56)</td>
<td>Odds ratio of ischemic stroke: 1.41 (95% CI: 1.11-1.78), and odds ratio of heart failure: 1.52 (95% CI: 1.18-1.98)</td>
<td>Sensitivity and specificity of BAC were 32.4% and 85.5%, respectively</td>
<td>Five cardiovascular risk factors (age, hypertension, hypercholesterolemia, diabetes mellitus, and menopause) were significantly more prevalent in the BAC-positive population</td>
<td>BAC+ women had a 6.3% vs. 2.3% of BAC- women to develop CVD</td>
<td>Threshold effect above 95th percentile when BAC + found for CVD</td>
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Menopause was prevalent among 61.1% of women in the BAC+ group and 35.8% of women in the BAC- group. A previous history of breast cancer was prevalent among 12.6% of women in the BAC+ group and 6.5% in the BAC- group. Among gender-specific risk factors, menopause was notably higher among BAC+ women compared to BAC- women, as summarized in Table I.

Overall, the studies comparing participants with BAC+ or BAC- on mammograms reported a higher odds or likelihood of developing CVD events. Associated traditional risk factors of CVD were also strongly predictive of odds or likelihood in the BAC+ group.

IV. DISCUSSION

The objective of our systematic review was to evaluate the association between breast arterial calcification found on mammography and the risk of developing CVD. We reviewed six studies that enrolled women who were attending their screening mammography appointments. We found a 1.2-2.5x odds of developing CVD among BAC+ women compared to those who were BAC- on the screening mammography when the participants were assessed at a single time point or longitudinally. Our findings suggest a higher prevalence of specific cardiovascular and gender-specific risk factors, including hypertension, hypercholesterolemia, family history of CVD, and menopause. We consider these findings pertinent, which require attention as BAC on screening mammograms may be regarded as a gender-specific risk factor for women [24]. However, we do not prove the causality of BAC to cause CVD, merely another prediction model that needs to be considered among women to prevent and treat CVD on time.

The American Heart Association (AHA) and other leading cardiovascular communities have noted gender gaps in CVD diagnosis and management [25]. In our synthesis, we found menopause to be more common among BAC+ women compared to BAC- women, which is already considered a risk factor for CVD [26]. This adds to the gender-gap challenge such that menopausal women aged <55 years may not traditionally be at risk for CVD, but the presence of BAC on mammograms may be predictive [27]; interestingly, screening mammograms begin as early as 40 years of age. Therefore, if a radiologist finds that their patient has a BAC+ finding on her mammogram, they may consider notifying the primary care physician (PCP) of the patient [28]; however, this may only be feasible if a cause-and-effect is clear with BAC and CVD. Regardless, we consider that emerging evidence directs physicians to take a more holistic approach and screen women for CVD, especially those women who are not in the conventional age group for CVD, e.g. 40-65 years of age [29].

We found that hypertension and hypercholesterolemia have a higher frequency among BAC+ women than those who were BAC-. While we do not understand the mechanism, we consider that certain commonalities may exist with these pathological states. For instance, the underlying inflammatory cascade associated with BAC and CVD is similar, and both may lead to the stiffening of arterioles [30], [31]. Similarly, BAC and CVD are known to occur with increasing age [13]. The concurrence of both conditions is potentially tied to co-existent risk factors, including hypertension, hypercholesterolemia, and positive family history found in our synthesis.

Our findings suggest that considering BAC on a mammogram as a potential risk factor for CVD be made. Further studies may build evidence such as grading BAC rather than reporting the presence or absence. Such an approach would mean that further studies consider scoring BAC based on the number, length of vessels, and other characterizing features [32].

Our study has a few limitations. We did not have any data to understand the quantity of BAC and its association with CVD. Albeit, one study in our synthesis reported by [21] noted that there was a threshold effect of BAC above the 95th centile being strongly predictive of CVD, which points further studies in the direction of developing a robust and relevant scoring system for BAC beyond presence or absence on mammography. Second, the association of BAC and CVD could have been merely incidental, with no causality proven in our study. Therefore, we encourage further studies to validate the relationship if there is one. Evidence suggests that BAC may regress, yet this remains disputed for cited reasons, including inter-observer variation. Lastly, while we suggest that mammograms be considered a screening tool for CVD, such findings are only applicable in developed countries as only ~2% of women in developing countries are getting mammogram screening as recommended compared to ~70% in developed countries. We suggest that causes of low mammogram testing be addressed in developing countries, such as misconception, lack of awareness, and socioeconomic challenges.

V. CONCLUSION

The current systematic review reported the evidence on BAC detected on screening mammography and occurrence risk or likelihood of CVD among women. In our findings, we reviewed 34,887, and the incidence of BAC+ on the mammogram was 10.3%. All six studies found that the odds or likelihood of developing CVD were higher among BAC+ women. Further studies are required to develop a semi-quantitative index of BAC for CVD screening to establish BAC as a predictor of CVD further.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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