Breast Arterial Calcifications (BAC) Found on Screening Mammography and their Association with Cardiovascular Disease

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Breast Arterial Calcifications (BAC)

1. Diffuse calcifications of breast arterial media.
2. Common but largely unreported findings.
3. Prevalence on screening mammograms: 
   Ranges from 9% - 17.5%.

Arterial Calcifications Subtypes

Two distinct forms of arterial calcifications:

1. Intimal arterial calcifications.
2. Medial arterial calcifications.

A - layer of elastic fibres (tunica adventitia)
B - layer of smooth muscles and elastic fibres (tunica media)
C - endothelium and elastin (tunica intima)
D - blood
E - connective tissue
# Arterial Calcification Subtype

<table>
<thead>
<tr>
<th>Intimal Arterial Calcifications</th>
<th>Medial Arterial Calcifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastic arteries &amp; large muscular arteries(^1).</td>
<td>Small to medium muscular arteries(^1).</td>
</tr>
<tr>
<td>Large, irregular calcium deposits(^2).</td>
<td>Fine grain deposits(^2).</td>
</tr>
<tr>
<td>Predominant component of ASCVD &amp; linked to CAD mortality(^2).</td>
<td>Historically: part of the normal aging process and unknown clinical significance(^2).</td>
</tr>
</tbody>
</table>

Breast Arterial Calcifications (BAC) and Coronary Artery Disease (CAD)

1980: An association was 1st described between BAC & Diabetes (DM):1

- Question of age phenomenon.
- Older quality mammography.

2000: A resurgence of the association between BAC and DM:

- Newer mammography technology (Ca++ < 100 μm)3
- Additional data suggested an association between BAC and DM, HTN, and increased CAD mortality.

Dabate:

- Some data showing no association4.
- Some data showing a positive association5.

Breast Arterial Calcifications: Implications

Annual mammography is highly utilized as a screening tool for breast cancer (Br CA) screening in women over 40.

If BAC has value as marker for CAD disease, then mammograms could be a practical tool for detecting CAD risk in women.

This might contribute to earlier detection of vascular damage, especially important in women at high risk of CAD or with unrecognized heart disease.
Study objectives

To determine whether women with BAC had an increased frequency of:

- CAD risk factors.
- Atherosclerotic Cardiovascular Disease (ASCVD).

To estimate the future risk of ASCVD in patients with BAC.
Study Design


Participation included:

1. Questionnaire.
2. Analysis of each mammogram for presence of BAC.
Questionnaire

A. Demographics.

B. Risk factors for ASCVD:

Major:
1. HTN.
2. Smoking.
3. Diabetes.
4. FHX of ASCVD.
5. Hypercholesterolemia.

Other:
1. Menopause / Age.
2. Exercise.
3. Depression
Questionnaire

C. Hx of ASCVD:
1. Angina.
2. Myocardial infarction (MI).
3. Abnormal coronary angiography.
5. Stroke.

D. Other:
1. Hormonal therapy (HT) use, current and past.
2. Breast cancer (Br CA)
Mammograms

Read independently for BAC by 1 of 21 radiologists, blinded to results of the questionnaire.

**BAC definition**: 

1. “Presence of 2 parallel linear calcium deposits along the periphery of tapered structures (when artery wall imaged longitudinally) or a calcific ring configuration (when artery imaged en face), whose configuration was typical of arteries, distinct from breast ducts.”
2. **BAC+**: if BAC found on 1 of 2 standard views of R, L, or both breasts.

Results

2,082 patients eligible

1,995 enrolled
87 declined

1,919 analyzed
76 excluded
Results: Age

**MEAN:** 56.0 ± 12.7 (range: 25-96)

<table>
<thead>
<tr>
<th>category</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>136 (7%)</td>
</tr>
<tr>
<td>40-49</td>
<td>580 (30%)</td>
</tr>
<tr>
<td>50-59</td>
<td>543 (38%)</td>
</tr>
<tr>
<td>≥60</td>
<td>660 (34%)</td>
</tr>
</tbody>
</table>
Results: Overall prevalence

BAC Positive: 268
BAC Negative: 1651
Total: 1919

Our BAC Prevalence: 14%

Literature BAC Prevalence: 9%-17.5%
Table 1. Prevalence of Main Risk Factors and Cardiovascular Morbidity in BAC-Positive and BAC-Negative Subgroups

<table>
<thead>
<tr>
<th></th>
<th>BAC positive (n = 268)</th>
<th>BAC negative (n = 1651)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs +/- SD)</td>
<td>70 +/- 11</td>
<td>54 +/- 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN</td>
<td>140 (52%)</td>
<td>439 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>125 (47%)</td>
<td>536 (33%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>29 (11%)</td>
<td>69 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (4%)</td>
<td>155 (9%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Family Hx ASCVD</td>
<td>58 (22%)</td>
<td>346 (21%)</td>
<td>0.776</td>
</tr>
<tr>
<td>Menopause</td>
<td>240 (89%)</td>
<td>859 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina</td>
<td>17 (6%)</td>
<td>22 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>11 (4%)</td>
<td>10 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnl Angio</td>
<td>15 (6%)</td>
<td>19 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>11 (4%)</td>
<td>8 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (6%)</td>
<td>15 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT, current</td>
<td>36 (13%)</td>
<td>167 (10%)</td>
<td>0.101</td>
</tr>
<tr>
<td>HT, past</td>
<td>40 (15%)</td>
<td>233 (14%)</td>
<td>0.724</td>
</tr>
<tr>
<td>BR CA</td>
<td>36 (13%)</td>
<td>96 (6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Is there an independent association of the studied variables on ASCVD?

**ASCVD** = any 1 of 5 markers:

1. Angina
2. Myocardial Infarction
3. Abnormal Angiogram
4. CABG
5. Stroke.
Logistic Regression of ASCVD & Coronary Risk Factors for the Presence of BAC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>CI (95%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 ASCVD event</td>
<td>3.49</td>
<td>1.47-8.28</td>
<td>0.005</td>
</tr>
<tr>
<td>1 ASCVD event</td>
<td>2.44</td>
<td>1.42-4.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.91</td>
<td>1.13-3.23</td>
<td>0.015</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>1.11</td>
<td>1.10-1.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (past or current)</td>
<td>0.58</td>
<td>0.42-0.80</td>
<td>0.001</td>
</tr>
</tbody>
</table>
## Logistic Regression of BAC and Coronary Risk Factors for the Presence of ASCVD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>CI (95%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>2.86</td>
<td>1.78-4.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BAC</strong></td>
<td>2.29</td>
<td>1.40-3.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family HX of ASCVD</td>
<td>1.89</td>
<td>1.18-3.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.72</td>
<td>1.08-2.75</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>1.06</td>
<td>1.04-1.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Is the correlation between BAC and ASCVD an age-related phenomenon?
BAC & ASCVD:

Analysis of BAC data with age as a continuous variable

Prevalence of BAC in women with and without ASCVD, within 3 age groups (< 55, 55-64, ≥ 65)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ASCVD-</th>
<th>ASCVD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.008
P = 0.038
P = 0.006
**N=19,007, p<0.0001 [Stroke]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio and 95% CL</th>
<th>OR</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Noord(1996)</td>
<td></td>
<td>1.420</td>
<td>1.110</td>
<td>1.830</td>
</tr>
<tr>
<td>Maas(2006)</td>
<td></td>
<td>1.300</td>
<td>0.380</td>
<td>4.460</td>
</tr>
<tr>
<td>Topal(2007)</td>
<td></td>
<td>1.890</td>
<td>0.880</td>
<td>4.140</td>
</tr>
<tr>
<td>Ritter(2008)</td>
<td></td>
<td>6.090</td>
<td>2.650</td>
<td>10.15</td>
</tr>
<tr>
<td>Eliza FPY(2010)</td>
<td></td>
<td>1.770</td>
<td>1.450</td>
<td>2.160</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.770</td>
<td>1.450</td>
<td>2.160</td>
</tr>
</tbody>
</table>

Favors absence of Stroke: Favor; Favors presence of Stroke: Favor

**N=3,952, p<0.0001 [CAD]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio and 95% CL</th>
<th>OR</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moshiedy(1996)</td>
<td></td>
<td>1.060</td>
<td>1.012</td>
<td>2.380</td>
</tr>
<tr>
<td>Henkin(2003)</td>
<td></td>
<td>1.320</td>
<td>0.840</td>
<td>2.090</td>
</tr>
<tr>
<td>Yerkey(2002)</td>
<td></td>
<td>0.090</td>
<td>0.480</td>
<td>2.150</td>
</tr>
<tr>
<td>Ferreira(2007)</td>
<td></td>
<td>2.950</td>
<td>1.250</td>
<td>7.300</td>
</tr>
<tr>
<td>Topal(2007)</td>
<td></td>
<td>2.310</td>
<td>1.150</td>
<td>4.670</td>
</tr>
<tr>
<td>Ritter(2008)</td>
<td></td>
<td>5.090</td>
<td>2.550</td>
<td>10.15</td>
</tr>
<tr>
<td>Penugonda(2009)</td>
<td></td>
<td>0.980</td>
<td>0.420</td>
<td>2.250</td>
</tr>
<tr>
<td>Zgheib(2010)</td>
<td></td>
<td>1.330</td>
<td>0.650</td>
<td>2.700</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>3.850</td>
<td>3.250</td>
<td>4.690</td>
</tr>
</tbody>
</table>

Favors absence of CAD: Favor; Favors presence of CAD: Favor

Prospective Data Methodology

After the baseline data:

- Same basic study design with surveys being sent annually
- After analyzing the main outcomes, a subpopulation provided an age matched control for BAC - and BAC + patients, & this population was analyzed & compared.
- The main objective was to determine:
  - Whether the presence of BAC’s on routine mammography predicts the development of ASCVD.
The overall prevalence of ASCVD in those women who were BAC+ versus those who were BAC-, throughout the course of the 5 year follow up, was 20.8% versus 5.4% respectively.

5 Year Results Among the women who did not have ASCVD at baseline

Women who were BAC+ had a significantly higher likelihood of developing ASCVD compared to those women who were BAC negative at baseline; 6.3% versus 2.3%, \( P=0.003 \)*

*These results remained significant even when controlling for age

10 Year Results Among the women who did not have ASCVD at baseline*

Women who were BAC+ had a higher likelihood of developing ASCVD and ASCVD risk factors compared to those who were BAC negative at baseline; 9.8% versus 3.3%, P=0.001* and 86.8% versus 76.3%, p=0.01; respectively.

*These results remained significant even when controlling for age

Summary

BAC prevalence among the 1,919 women was 14%.

Five ASCVD risk factors (age, HTN, hypercholesterolemia, DM, & menopause) were significantly more prevalent in the BAC+ patients (p<0.001).

The BAC+ group had a significantly higher occurrence of ASCVD (p<0.001).

Multiple logistic regression analysis found BAC to be strongly associated with ASCVD events (OR=2.29).

The association of BAC with ASCVD was present even after accounting for age.

Therefore: BAC appears to be a risk indicator of the presence of ASCVD.
Summary

More importantly:

In this first prospective analysis of BAC as a risk predictor –

BAC appears to be a risk predictor for the future development of ASCVD
Thank You:

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