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Breast Arterial Calcification: a New Marker of Cardiovascular Risk?

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Abstract Mammographically-detected breast arterial calcifications (BAC) are considered to be an incidental finding without clinical importance since they are not associated with increased risk of breast cancer. The goal of this article is to review existing evidence that the presence of BAC on mammography correlates with several (but not all) traditional cardiovascular disease (CVD) risk factors and with prevalent and incident CVD. Thus, BAC detected during routine mammography is a noteworthy finding that could be valuable in identifying asymptomatic women at increased future CVD risk that may be candidates for more aggressive management. In addition, there are notable differences in measures of subclinical atherosclerosis burden in women (ie, coronary artery calcification) by race/ethnic background, and the same appears to be true for BAC, although data are very limited. Another noteworthy limitation of prior research on BAC is the reliance on absence vs presence of BAC; no study to date has determined gradation of BAC. Further research is thus required to elucidate the role of BAC gradation in the prediction of CVD outcomes and to determine whether adding BAC gradation to prediction models based on traditional risk factors improves classification of CVD risk.

Keywords Breast arterial calcification · Cardiovascular disease risk · Cardiovascular risk factors · Risk stratification · Mammography

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Introduction

Although the value of mammographic screening before age 50 and after age 74 has recently been called into question by the US Preventive Services Task Force [1] current clinical practice guidelines recommend annual mammographic screening of all women aged 40 years or older for early detection of breast cancer. However, important information about the presence and severity of subclinical atherosclerosis that is available in mammograms is presently ignored during mammographic assessments. Specifically, this information includes the presence of breast arterial calcification (BAC), which has been shown to be associated with risk of cardiovascular disease (CVD) morbidity, and mortality. Such information may be useful for improvement of CVD risk stratification in a similar manner that coronary artery calcification (CAC) has been shown in numerous prospective studies. Data from CARDIA [2], MESA [3], and other population-based studies indicate that the extent of CAC in women differs importantly by ethnic background, and the same appears to be true for calcification in other vascular beds including the breast, but the data available are very limited.

The leading causes of death among women in the US are heart disease, cancer, and stroke [4]. Even though remarkable advances have been made in the field of CVD prevention, for many asymptomatic individuals the first manifestation of underlying disease is an unexpected acute myocardial infarction or sudden death [5, 6]. Furthermore, prior studies have shown that women with obstructive coronary disease have worse prognosis after acute myocardial infarction compared with men [7–11]. A widespread tool for CVD risk stratification is the Framingham risk score, which classifies patients into low (10–year CVD risk<10 %), intermediate (10–year CVD risk 10 %–20 %) and high (10–year CVD risk>20 %) risk groups based on traditional risk factors [12]. However, published data indicate that up to

20 % of all coronary events occur in the absence of these major risk factors and that 60 % of events are experienced by low-to-intermediate risk patients [13–15]. Therefore, there is great interest in developing new methods, including novel serum biomarkers and noninvasive imaging modalities, to better identify patients who may be appropriate candidates for more aggressive primary prevention [16, 17]. A new algorithm, the Reynolds Risk Score, has been recently developed and (internally) validated in the Women's Health Study [18].

Several non-invasive imaging techniques have been evaluated [19–21]. While ultrasound- and MRI-based techniques rely primarily on images of abnormal vessel anatomy due to atherosclerosis, the CT-based approach is based on estimating vascular calcium deposition. Although all these imaging techniques, particularly CT, appear to predict CVD risk in multiple longitudinal cohort studies [22, 23], critical barriers for widespread use of these imaging modalities are high cost, need for specific types of equipment, and/or specially trained personnel. In addition, concerns have been raised about increased cancer risk following cardiac CT [24], although it should be pointed out that radiation concerns are mainly for higher dosage coronary CT angiography and that radiation from a mammogram vs coronary calcium scan are very similar (0.7–0.9 mSV). BAC detected by widely used mammography in women thus offer a potential new tool for detecting subclinical CVD which may add incremental prognostic value beyond the existing CVD risk classification schemes without additional radiation exposure and cost.

Mammographically-Detected Calcifications

Mammography is a proven tool for early detection of breast cancer that is associated with a decrease in mortality rates [25]. The American Cancer Society presently recommends that "all women age 40 and older should have a screening mammogram every year and should continue to do so for as long as they are in good health". National data indicate that at least 75 % of women age 40 and over have attended a mammographic exam in the last 2 years and 50 % have had a mammogram in the past year [26]. This tallies up to 42 million women over the age of 50. Under managed care, mammography attendance is over 80 % [27]. The attendance to mammographic screening is lower among uninsured, low SES women compared with women in managed care, but mammography is the most common screening test in women, regardless of insurance status. In the 2005 National Health Interview Survey, the self-reported attendance for mammography was 66 % [28]. In the Pennsylvania Centers for Disease Control Behavioral Risk Factor Survey, 64 % of women with less than a high school education self-reported ever having a mammogram [29]. As established in legislation, Medicare and Medicaid provide conditions of coverage for both screening and diagnostic plain film and digital mammography services. Of note, up to 40 % of breast cancers detected by screening are manifested by microcalcifications as the sole mammographic lesion [30]. As a result, the modern mammographic equipment is designed specifically for the detection of microcalcifications [31]. Therefore, this routine screening tool provides a unique opportunity to detect BAC as a possible mammographic sign of atherosclerosis. BAC on the mammogram is identifiable as linear, parallel lines that resemble a railroad track (see Fig. 1).

Vascular Calcification Pathology: Medial vs Intimal

Calcification occurs at 2 anatomic sites within the vascular wall: the intima, where it is invariably associated with atherosclerosis, and the media. These different locations most likely represent 2 pathophysiologically different processes [32–34]. Intimal calcification is an active, regulated process that is similar to bone formation and involves expression of growth factors, matrix proteins, and other bone-related proteins [35], and has been associated with inflammatory cells, lipid deposits, and vascular smooth muscle cells. By contrast, medial arterial or Mönckeberg-type calcification occurs in the absence of macrophages or lipid deposits [36] and has been described in the context of aging, diabetes, end-stage renal disease, neuropathy, and a number of rare genetic syndromes [37–40]. A study of medial calcification among Pima Indians showed it to be significantly associated with type II diabetes and with increased CVD mortality [41]. Additional studies have confirmed that medial calcification is an independent predictor of CVD events in patients with diabetes or end-stage renal disease [42–44].

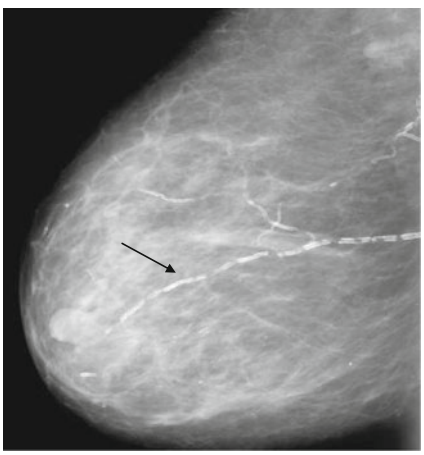

Fig. 1 Detail of a lateral mammogram. The *arrow* shows a linear tubular calcification along the contours of the arterial wall

The proposed putative mechanism by which medial calcification may increase CVD risk is increased arterial stiffness. Consistent with this notion, elastin has been shown to have a strong affinity for calcium and it has been postulated that disruption of the elastic fibers promotes medial calcification [45]. In a pathology study, BAC were localized in the tunica media, but some arteries showed intimal thickening in some cases [46]. With conventional x-ray techniques or with modern digital mammography, it is not possible to differentiate with certainty between intimal and medial calcifications, although the appearance of medial calcifications is more fine and diffused in smaller vessels, compared with the large and discontinuous appearance of intimal calcifications in large and medium size arteries [47, 48]. BAC is mostly (but not entirely) medial, a non-obstructive condition leading to reduced arterial compliance.

Prevalence of BAC on Mammography

The prevalence of BAC in previously published studies varies from 1 % to 49 %. Such large differences may be explained by heterogeneity in the studied populations, variations in sensitivity of mammography equipment and reporting bias. Age is the most powerful factor influencing the prevalence of BAC [49, 50]. Pre-existing coronary artery disease is also related to higher prevalence of BAC [51]. Race/ethnicity is another significant factor in the prevalence of BAC. In a large cohort of women aged 32–92 years who attended routine mammography, Hispanic women had the highest prevalence (34 %), whereas Asian women had the lowest (7 %), vs 24 % in White women, and 25 % in African-American women [52].

Relation of BAC to Cardiovascular Risk Factors and Other Factors

Prior studies have reported associations of BAC presence with older age [49, 52–59], diabetes [55, 58–60], body mass index [61], hypertension [54, 61–63], albuminuria [61], triglycerides [64], homocysteine [64], and hs-CRP [64]. It has been postulated that hyperglycemia may induce medial calcium deposits by upregulating the production of osteogenic proteins such as matrix Gla protein, osteocalcin, and osteoprotegerin [65, 66]. A recent study demonstrated that BAC also correlates with the duration of diabetes [67]. Surprisingly, an inverse association between smoking and BAC has been found by several studies [55, 56, 61, 68]. Another study has also reported an association of BAC with spontaneous or artificial menopause [49]. In the European Prospective Investigation into Cancer and Nutrition Study among women aged 49–70 years, BAC was associated with greater parity and with a history of lactation [68]. The authors speculated that both pregnancy and breast feeding induce transient hypercalcemia to meet requirements for fetal growth and breast milk production [69]. Duration of lactation has been associated with lower prevalence of the metabolic syndrome in midlife, making the BAC-lactation relationship somewhat paradoxical [70]. A significant inverse association has been reported between menopausal hormonal therapy and BAC in 4 studies [55, 71–73]. These data underscore a resemblance between BAC and coronary atherosclerosis, since increased duration of hormonal therapy has been shown to be associated with lower prevalence of CAC [74]. Mild to moderate impairment of renal function has been associated with clinical CAD [75] and with coronary and peripheral atherosclerosis [76]. However, there are no studies that have examined the relationship between renal function and BAC. Although there is a growing recognition of the importance of sleep parameters in subclinical and clinical coronary disease [77–81], no study to date has examined the association of obstructive sleep apnea or sleep duration with BAC.

Recent studies indicate that vitamin D deficiency is associated with increased risk of CVD independently of established risk factors [82–84]. Vascular calcification, along with influences on blood pressure regulation, glycemic control, and inflammation has been proposed as one of the potential mechanisms behind the vitamin D-CVD relationship, yet evidence of an association between vitamin D status and vascular calcification, including BAC, is lacking. Elevated serum calcium (C) levels have been suggested to be a risk factor for atherosclerosis [85] and myocardial infarction [86]. In turn, high serum phosphorus (P), high serum C x P product, and hyperparathyroidism influence the prevalence of vascular calcification, particularly in end-stage renal disease patients [87]. However, the association between these mineral metabolism factors and BAC has never been investigated. Statins have been shown in observational studies to be associated with reduced progression of CAC [88, 89], but clinical trials addressing the question of whether statins retard CAC progression have been disappointing [90, 91]. Emerging evidence indicates that nitrogen-containing bisphosphonates exert beneficial pleiotropic effects in the CVD system including reduction of lipids [92], inflammation [93], and inhibition of vascular calcification [94].

Arterial calcification and osteoporosis commonly accompany one another in postmenopausal women. A recent study has demonstrated that BAC is associated with osteoporotic vertebral fractures in Japanese women [95]. The results suggest that BAC and osteoporotic fractures may share a common metabolic pathway in their pathogenesis. These finding are consistent with prior work demonstrating an association between reduced bone mineral density and BAC [96].

Association of BAC with Clinical and Sub-clinical CVD Outcomes

To date, 17 studies (4 prospective and 13 cross-sectional) have been published relating BAC to clinical or subclinical CVD (Table 1). The 4 cohort studies in Dutch [61, 72] and US populations [55, 97] show consistent associations of moderate strength between BAC presence and incident non-fatal and fatal CVD. Adjusted odds ratios for cross-sectional studies of the relationship between BAC presence and prevalent CHD/CVD or angiographic coronary disease are more heterogeneous, ranging from 1.0 to 8.1 [54, 98–102]. Of note, 1 study found no independent association between BAC and angiographically-defined coronary disease [54]. Recently, Abi Rafeh et al. have published a meta-analysis of previous studies evaluating BAC as a risk marker for coronary artery disease that included 927 patients. There was a 1.59 (95 % confidence interval [CI] 1–21–2.09) increased odds of angiographically defined CAD in patients with BAC seen on mammography [103••]. To date, 1 study has demonstrated significant associations of BAC presence with CAC [57], 2 with carotid intimal-media thickness (C-IMT) [63, 104•], and 1 with positive brain MRI findings [105••]. In the Maas et al. study among 499 women aged 49–70 years, BAC was associated with coronary arterial calcifications after 9 years follow-up (OR 2.1, 95 % CI 1.10–4.23 after adjustment for age at baseline duration of follow-up) [57]. In the Sedighi et al. study, compared with women with C-IMT<0.6 mm, women with 0.6 mm≤C-IMT ≤0.8 mm, and with C-IMT>0.8 mm had multivariate odds ratios (95 % CI) of 4.88 (1.47–16.16) and 23.36 (4.54–120.14) of having any BAC, respectively [63]. The covariates in the model included age, parity, menopausal status, history of CAD, hypertension, diabetes, and smoking. Yildiz et al. reported that BAC on mammography was associated with C-IMT independently of age, parity, postmenopausal duration, diabetes, systolic blood pressure, fasting glucose, and triglyceride levels [104•]. Taken together, these studies highlight the potential of BAC for predicting clinical and sub-clinical CVD.

Multiethnic Study of Breast Arterial Calcium Gradation and Cardiovascular Risk (MINERVA)

Researchers at the Kaiser Permanente Division of Research in Northern California and at the University of California at Irvine have recently launched MINERVA, a new prospective 5-year cohort study funded by the National Heart, Lung, and Blood Institute (RO1HL106-043) that will yield novel insights into ethnic differences in BAC presence and gradation as well as into factors associated with BAC. But more importantly, MINERVA will shed light on the potential value of BAC gradation as a new tool for CVD risk stratification and thus for CVD prevention. Hence, MINERVA's findings will break new ground and could have considerable clinical and public health significance for the millions of women who routinely undergo mammographic screening. MINERVA was designed with 3 specific aims in mind:

(1) To establish a multi-ethnic cohort (n=5400) of women between the ages of 60 and 79 years with equal representation of Caucasian (n=1350; 25 %), African-American (n=1350; 25 %), Asian (n=1350; 25 %), and Hispanic/Latina (n=1350; 25 %) females. All participants will be recruited at the time of their regular mammography screening over a period of 2 years at 3 Kaiser Permanente of Northern California (KPNC) medical centers and will have no history of prior clinical CVD. A new, but rigorously validated densitometry method will be used to estimate BAC mass (in milligrams [mg]) using digital mammograms.
(2) To assess associations of BAC mass with age, race/ethnicity, family history of CVD, traditional and novel CVD risk factors, renal function, reproductive health factors, psychosocial factors, selected mineral metabolism factors, selected medication use (statins and nitrogen-containing bisphosphonates), breast size, and sleep-related factors.
(3) To elucidate the role of BAC mass in the prediction of coronary heart disease (CHD), cerebrovascular disease (transient ischemic attack [TIA], hemorrhagic stroke, and ischemic stroke), heart failure, peripheral vascular disease, and total CVD and to determine whether adding BAC mass to prediction model based on traditional risk factors improves classification of risk for total CVD and its components.

Despite existing evidence suggesting that BAC is a risk factor for subclinical and clinical CVD, it is important to note that all prior studies have relied on conventional (ie, screen film) mammography. Further research is therefore needed to examine the association of BAC with CVD risk factors and CVD events using modern (ie, digital) mammographic techniques that have a much greater sensitivity level. Furthermore, the BAC literature is based on the crude assessment of absence vs presence of BAC and, to date, no study has quantified BAC mass and its relationship with CVD risk factors and events. In addition, there are significant gaps in knowledge including the association of BAC mass with other markers of subclinical CVD (ie, ankle-brachial index), other breast characteristics (ie, breast volume), renal function, preventative medications that may affect calcification (eg, statins or nitrogen-containing bisphosphonate), psychosocial factors, mineral metabolism factors (serum calcium, phosphorus, parathyroid hormone, 25-hydroxy-vitamin D concentrations), and sleep-related

Table 1 Summary of published studies of the association of BAC with CVD

First author, year	Sample size	Outcome[s]	Findings
Cohort Studies			
Van Noord et al. [61]	12,239	TIA/stroke, thrombosis, myocardial infarction	Adjusted RR=1.4 for TIA/stroke, 1.5 for thrombosis, 1.8 for myocardial infarction
Kemmeren et al. [72]	12,239	CVD death, total mortality	Adjusted RR=1.40 for CVD death, 1.30 for total mortality
Iribarren et al. [55]	12,761	Incident fatal or non-fatal CHD, ischemic stroke, heart failure	Adjusted RR=1.32 for CHD, 1.41 for ischemic stroke, 1.52 for heart failure
Schnatz et al. [97]	1454	Incident CHD in 5 years	Age-adjusted OR=2.2
Cross-sectional studies			
Doerger et al. [98]	1803	Angiographic CAD	Adjusted OR=1.4
Fiuza Ferreira et al. [99]	131	Angiographic CAD	Adjusted OR=4.6
Henkin et al. [54]	319	Angiographic CAD	Adjusted OR=1.0
Topal et al. [100]	123	Angiographic CAD	P for contrast of Gensini score=0.05
Kataoka et al. [56]	1590	Prevalent CHD	Adjusted OR=2.5
Maas et al. [57]	499	Coronary artery calcification	Adjusted OR=2.1
Dale et al. [53]	645	Peripheral vascular disease	Sensitivity and specificity of BAC for PVD=42 % and 80 %
Dale et al. [51]	1000	Self-reported history of CAD	Unadjusted OR=3.6
Yildiz et al. [104•]	54	Carotid IMT	Multivariate β for presence of BAC=0.46 [$P<0.001$]
Ferreira et al. [101]	307	Global CVD	Adjusted OR of CVD with BAC=8.1
Oliveira et al. [102]	80	Clinical CAD	Adjusted OR of CAD with BAC=4.7
Sedighi et al. [63]	537	IMT and carotid plaque by ultrasound	OR for carotid plaque=3.1
Ahn et al. [105••]	168	White matter (WMH) and periventricular hyperintensity (PVH) on Brain MRI	Adjusted OR=6.7 for WMH and 9.0 for PVH

factors. Finally, studies like this one are needed to clarify the potential incremental prognostic value of BAC presence and BAC mass for CVD and its components in a contemporary era where widespread preventive efforts are already underway.

The densitometry technique that will be used in the MINERVA study to estimate calcium mass in mammograms is described elsewhere [106••]. In brief, anthropomorphic breast and vessel calcification phantoms were imaged using a full-field digital mammography system. A calcium calibration measurement was performed at each phantom thickness and beam energy. The known (K) and measured (M) calcium mass on phantoms 5 cm and 9 cm thick were tightly related (M=0.964 K−0.288 mg; r=0.997, and M=1.004 K+0.324 mg; r=0.994, respectively). The results indicate that accurate calcium mass measurements can be made without correcting for scatter glare as long as careful calcium calibrations are made for each breast thickness. The uncertainty in magnification is expected to cause up to 5 % and 15 % error in calcium mass for 5 cm and 9 cm breast thicknesses, respectively. These results demonstrate the feasibility and potential utility of our technique for accurate BAC quantification in digital mammograms. In a second study, we have demonstrated adequate reproducibility and inter-reader agreement of the BAC mass measurement [107]. Standard full-field digital mammograms were acquired from medial lateral oblique (MLO) and craniocaudal (CC) projections. Calcium mass was measured in each projection using the technique developed in the previously described phantom study (depicted in Fig. 2). In order to assess the reproducibility of calcium measurement without added radiation exposure, we compared calcium mass from 2 different projections (Fig. 3a). The measured calcium masses in MLO (M_{MLO}) and CC (M_{CC}) projections were highly correlated (r=0.95). A plot of BAC mass measurements (average of MLO and CC projections for right and left breasts) performed by the 2 observers is shown in Fig. 3b. These results indicate excellent inter-reader agreement (intra-class r=0.94) and demonstrate that our densitometry technique for quantifying BAC mass using standard full-view digital mammography is highly reproducible.

In this study, BAC was identified and regions of interest were drawn manually (Fig. 2). To make this methodology more easily adoptable by other groups and implemented in clinical settings, it is desirable to automate this process. In collaboration with 1 of the major manufacturers of mammography systems (Hologic, Inc., Bedford MA), we are in the process of evaluating a fully automated algorithm for BAC detection and extraction from mammograms. There are also other research groups pursuing a similar approach

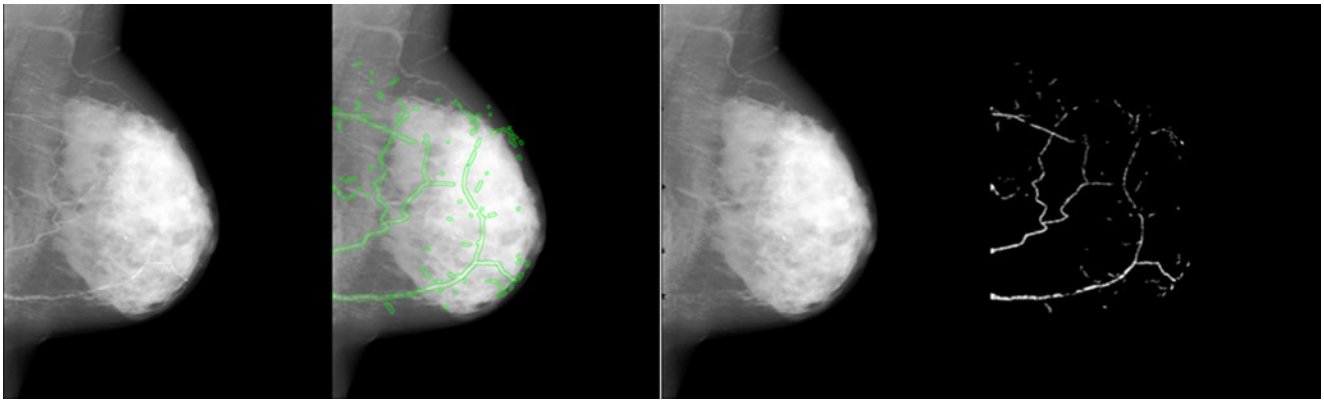

Fig. 2 Densitometry calcium mass measurement in mammograms

[108–110]. The automated technique will completely eliminate the inter-reader variability. It can be combined with our technique to automatically quantify calcium mass from mammograms in a clinical setting. However, the technique will require further optimization and validation before it can be used. The proposed study will provide us the opportunity to compare the results from readers and the fully automatic algorithm.

Potential Public Health and Clinical Contributions

A very large proportion of women undergo screening mammography on a regular basis after the age of 40. There are minimal costs associated with reading and grading BAC. MINERVA will shed light on the epidemiological associations between BAC mass and an extensive array of covariates. More importantly, it will establish (for the first time) the incremental utility of BAC mass for predicting clinical CHD, cerebrovascular disease, heart failure, peripheral vascular disease, and total CVD among women aged 60–79 years. While we recognize that the densitometry method to quantify BAC mass in digital mammograms that we have developed for this proposal is novel and not yet universally available, the transition to digital imaging is a reality in most major university and community hospitals. Our methodology to compute BAC mass can be easily adopted by other groups and medical centers. Furthermore, we are in the process of evaluating a fully automated algorithm for BAC detection from mammograms. The eventual automation of this technique will make its clinical implementation much easier.

What are the clinical implications? First, the discovery of BAC should trigger an investigation of risk factor levels and subsequent treatment as needed to reduce those found to be elevated. Second, a scenario where detecting extensive BAC may be particularly useful in women at moderate cardiovascular risk based on existing clinical risk algorithms. In this instance, BAC may be a useful tool for reclassifying them into the high risk group, where a more aggressive approach may be warranted.

This epidemiological study is a necessary, intermediate step to demonstrate clinical predictive utility of BAC mass. The utility of coronary calcium (which requires a separate CT scan of the heart) to significantly improve net reclassification for CHD has recently been demonstrated in the MESA study [111]. If we are able to demonstrate meaningful added risk assessment performance using BAC mass

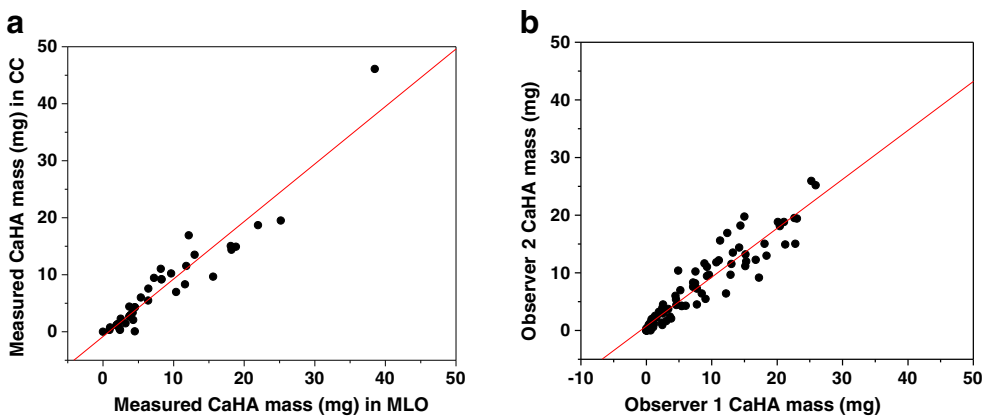

Fig. 3 **a**. Scatter-plot of BAC mass in 2 projections. **b**. Scatter-plot of BAC mass by 2 observers

above and beyond conventional risk factors (ie, at least 10 % improvement in net reclassification with categories) [112], we would then proceed to develop new risk estimation systems for total CVD and for each of its components (CHD, cerebrovascular disease, peripheral vascular disease, and heart failure). First, we would incorporate the BAC mass score to traditional risk factors (the Framingham risk score) and second, we would add the BAC mass score to conventional risk factors plus hs-CRP and family history of CHD (the Reynolds risk score). After, we would seek collaborations to validate these new algorithms in other cohorts. Whether the provision of these new risk-estimation systems will result in benefits to healthcare providers and individual patients, in term of reductions of risk factors and/or clinical outcomes, would require further testing in clinical trials.

Assuming that BAC quantity is associated with an increased risk of CVD events, if a woman is found to have BAC, particularly highly elevated BAC mass, it should trigger an investigation of cardiovascular risk factor profile (diabetes, hypertension, lipid profile, inflammatory status) and this woman should be treated more aggressively if 1 or more of these risk factors are found to be present (in a similar fashion proposed for CAC [113, 114]. We do not advocate the reverse, that is, women presenting with risk factors being referred to mammography. The beauty of mammography is that the indication already exists for the early detection of breast cancer.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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