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Calcification of the splenic, iliac, and breast arteries and risk of all-cause and cardiovascular mortality

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ABSTRACT

Background and aims: CVD risks associated with coronary artery calcification (CAC) and aortic calcification (AC) are well known, but less is known about other calcified arteries. We aimed to assess the associations of arterial calcification in the breast, splenic, and internal and external iliac arteries with CVD risk factors and mortality.

Methods: We conducted a case-cohort study nested in a cohort of 5196 individuals who self-referred or were referred by a health care provider for whole body computed tomography (CT), including a random subcohort (n = 395) and total and CVD mortality cases (n = 298 and n = 90), who died during a median follow-up of 9.4 years. Arterial calcification in the breast, splenic, and internal and external iliac arteries on CT was scored using a simple visual score. AC and CAC were previously measured using the Agatston technique. Logistic regression models were made to study associations of CVD risk factors with calcification in the different vascular beds. Prentice-weighted Cox proportional hazards models adjusted for CVD risk factors, and calcification in other vascular beds, were used to study associations with mortality.

Results: In the subcohort, the mean age was 56.6 years (SD 11.1) and 41.3% were female. The prevalence of calcification on CT, was 11.6% in the splenic, 47.9% in the internal iliac and 9.5% in the external iliac arteries, while 3.7% of women had breast artery calcification (BAC). Calcification in the splenic and iliac arteries was associated with calcification in the abdominal aorta but differentially associated with other CVD risk factors in logistic regression models. The prevalence of BAC was too low to fit these multivariable models. Calcification of the external iliac arteries was significantly associated with both all-cause and CVD mortality, but no longer significant when adjusted for CVD risk factors. Breast artery calcification was associated with both all-cause and CVD mortality independent of CVD risk factors and AAC and CAC (all-cause HR 5.67 [95% CI 1.50–21.41]).

Conclusions: Risk factors associated with calcification, and the association of calcification with risk of mortality differ across vascular beds, possibly reflecting different pathophysiology.

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1. Introduction

Most research on arterial calcification has focused on intimal calcification arising within atherosclerotic plaques in the coronary arteries, the aorta, and carotid bifurcation [1–3]. Intimal calcification is closely associated with traditional cardiovascular risk

Abbreviations: MAC, medial arterial calcification; BAC, breast artery calcification; CT, computed tomography; CVD, cardiovascular disease.

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factors, including smoking and hyperlipidemia [1]. However, other patterns of calcification are also recognized and can occur independently, namely calcification occurring in the arterial media and internal elastic lamina [4]. These non-atherosclerotic types of calcification are often lumped together under the heading of "medial arterial calcification" (MAC). MAC seems to share some, but not all, risk factors of intimal calcification [5]. MAC occurs frequently in patients with diabetes and kidney disease and its prevalence increases with older age [6–8] but smoking is associated with a lower prevalence of MAC [9–12] and hyperlipidemia does not associate with MAC [8,11]. This suggests that MAC is a distinct disease process [13].

Classic MAC has a circumferential and continuous "railroad" appearance on radiographs, while intimal calcification is typically spottier, but it remains difficult to distinguish MAC from intimal calcification *in vivo*. MAC is known to occur frequently in female breast arteries, the carotid siphon and leg arteries [6,7,14]. Calcification of the splenic artery is thought to be predominantly medial [15]. Only one previous study related cardiovascular risk factors to the presence of calcium in the splenic artery and found a significant unadjusted correlation of glucose levels with splenic artery calcification, but did not study a comprehensive set of risk factors [16].

There are little data assessing the relationship of MAC with cardiovascular end-points. The few studies that do exist indicate higher risks [7,11,17]. Breast artery calcification (BAC) on mammography has been associated with an increased risk of cardiovascular disease [18]. While prior studies have examined the association of BAC on digital mammography with CT-identified coronary atherosclerosis, to our knowledge, no studies have directly examined BAC on computed tomography (CT) [19]. For the splenic artery, we are not aware of any studies determining associations with clinical outcomes.

Therefore, our first aim was to evaluate the risk factors associated with calcification in a number of small to medium sized arteries, namely the female breast artery, the splenic artery and the internal and external iliac arteries. Our second aim was to determine the associations of arterial calcification in the breast, splenic artery and both internal and external iliac arteries with all-cause and cardiovascular mortality.

2. Patients and methods

2.1. Population

The study population consisted of 5196 community-living individuals that were self-referred or referred by their primary care physician for CT scanning for preventive medicine purposes in San Diego between 2000 and 2003. The study population is described in detail elsewhere [20].

For this study, we designed a nested case-cohort study. This is an efficient design used to evaluate associations between baseline determinants and outcomes by evaluating a random sample of all participants at baseline (the subcohort) and all cases occurring from the entire cohort [21]. This approach made it feasible to validly study calcification in a number of added vascular beds while only measuring them in the subcohort and cases [22]. A sample of 395 (7.5%) participants was drawn randomly from all baseline participants, forming the subcohort. We previously showed that sampling fractions above 5% yield valid estimates of HR and SE, when using Prentice-weighting [22]. Our cases constituted all deceased participants (n = 298), resulting in a total sample size of 670, as some cases were also sampled in the randomly selected subcohort, as expected (Fig. 1).

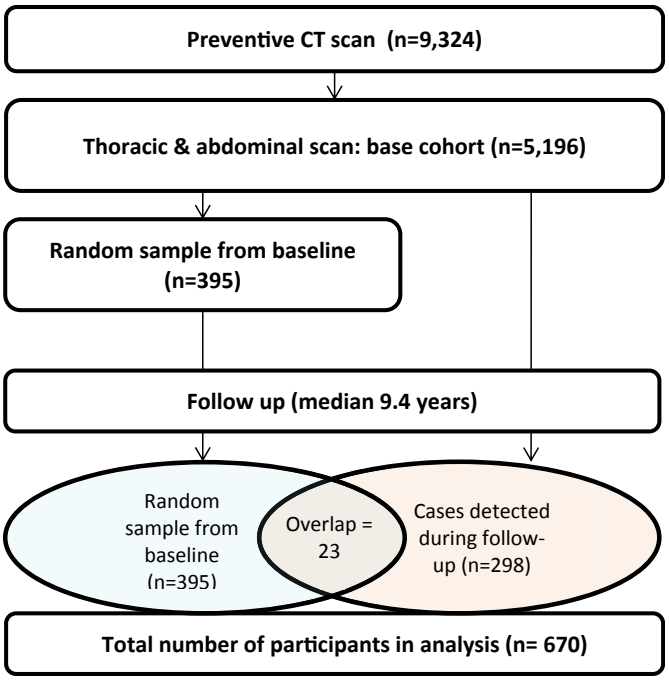

Fig. 1. Participant flowchart.

2.2. Baseline measurement of risk factors

At baseline, all participants provided information on demographics, risk factors and past medical history. Smoking status was self-reported as former, current or never. Height and weight were measured and body mass index (BMI in kg/m^2) was calculated. Trained technicians measured blood pressure after at least 5 min of rest. Random serum lipid and glucose measurements were obtained by finger-stick using the Cholestec LDX system (Hayward, CA, USA). Baseline measurements are described in more detail previously [20]. Diabetes was defined as blood glucose level greater than 200 mg/dl or use of antiglycemic medication. Dyslipidemia was defined as a ratio of total cholesterol to high-density lipoprotein cholesterol greater than 5 or use of a cholesterol-lowering medication. Hypertension was defined as systolic blood pressure greater than 140 mm Hg or diastolic pressure greater than 90 or use of hypertensive medication for this condition.

2.3. Assessment of calcification

All participants underwent "whole body" CT scans i.e. scanning from the base of the skull to the pubic symphysis. Details on scanning procedures are described elsewhere [3]. Within the thoracic aorta, abdominal aorta, carotid, coronary, and iliac arteries (common and external), calcium scores had been calculated previously using the method described by Agatston [23,24]. For this study, we used thoracic and abdominal/pelvic CT scans with a slice thickness of 6 mm to measure breast, splenic, external and internal iliac artery calcification in the subcohort and cases only (Fig. 2).

For all participants in the subcohort, and all death cases, additional scoring of the breast (females), splenic, and internal and external iliac arteries was conducted by a researcher (EJEH) blinded to the patients' clinical data. Calcification in the breast arteries was scored as absent or present. Calcification in the splenic artery and internal and external iliac arteries were scored as absent, mild, moderate, or severe using the following cut-points for artery length

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