

Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different

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Abstract

Objective: To study whether calcifications in breast arteries, as seen on mammograms, predict future development of coronary artery calcifications.

Methods: We studied 499 women, aged 49–70 years, participating in a breast cancer screening program and investigated whether arterial calcifications in the breast (BAC) are associated with coronary arterial calcifications (CAC) after 9 years follow-up. Mammograms were reviewed for the presence of BAC. CAC was assessed by multi slice computed tomography (MSCT). With logistic regression analysis the independent effect of various risk factors on BAC and CAC was measured.

Results: BAC was present in 58 of 499 women (12%) and CAC score >0 was present in 262 of 499 women (53%). BAC was strongly associated with CAC (OR 3.2, 95% CI 1.71–6.04) and this remained significant after adjustment for age at baseline and the duration of follow-up (OR 2.1, 95% CI 1.10–4.23). Most CV risk factors were associated with CAC but not with BAC. Only parity was significantly associated with both increased CAC (OR 2.1, 95% CI 1.21–3.60) and increased BAC (OR 5.3, 95% CI 1.23–22.43). Breastfeeding was associated with BAC (OR 3.4, 95% CI 1.40–8.23) but not with CAC (OR 1.3, 95% CI 0.84–1.93).

Conclusion: Breast arterial calcifications are predictive of subsequent development of calcifications in the coronary arteries.

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1. Introduction

Calcium in the coronary vascular wall is a known marker of the presence of atherosclerotic disease in the coronary arteries. The amount of calcium, detected by electron beam computed tomography (EBCT) or multi slice computed tomography scanning (MSCT), is a promising method to measure the risk of coronary heart disease (CHD) events [1,2]. Disadvantages of using these new radiology techniques in risk assessment are the costs and feasibility for its widespread application, the impaired additional diagnostic value in low-risk and high-risk patients and the risks involved in radiation exposure [3–5]. Calcium deposits

are also present in other parts of the vascular tree as a sign of subclinical atherosclerosis. Imaging of calcifications in the thoracic and abdominal aorta on conventional X-rays for example has also been associated with an increased CHD event risk, but its clinical application for screening purposes has not been established [6–8].

Calcifications in the arteries of the breasts can be seen in 3–29% of women undergoing mammography, with the advantage that mammograms are often obtained in already running breast cancer screening programs [9–12]. The simultaneous use of mammograms for screening purposes of breast cancer and CHD could be very cost effective. The clinical significance of breast arterial calcifications however is controversial and thus far has merely been associated with aging, diabetes, parity and lactation [13–16]. It is yet undetermined whether breast arterial calcifications (BAC) and coronary artery calcifications (CAC)

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are related. Furthermore, it is not known whether both types of vascular calcifications share common CHD risk factors. Moreover, to our knowledge it has not been studied whether women with BAC are at greater risk to develop CAC as a sign of atherosclerotic disease. In the current study we investigated the relation between the prevalence of BAC at baseline and CAC scores at 6–11 years follow-up in 499 women participating in a breast-cancer screening program.

2. Methods

2.1. Population

Participating women were recruited from the PROSPECT-EPIC study, one of the Dutch contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC). Characteristics of the population have been described before [17]. In brief, PROSPECT consists of 17,357 healthy women, aged 49–70 years, from a breast cancer screening program in Utrecht and its surroundings, enrolled between 1993 and 1997. The purpose of EPIC is to assess the relation between nutrition and cancer and other chronic diseases. Women were asked to participate along with their invitation for a routine mammography. At baseline women filled in a general questionnaire and a medical examination was performed. All women signed an informed consent prior to study inclusion with permission to use personal data and biologic material in substudies.

The present substudy was performed in a random sample of 573 women from the original total population of 17,357 women. Women were selected from 5844 eligible women from the original cohort, based on the following criteria: no participation in other studies, valid written informed consent, postmenopausal, and currently no use of oral contraceptives (OC) or hormone replacement therapy (HT). A random selection of 1996 women was invited by a personal letter of whom 1000 were willing to participate. Out of this group, a random selection of 573 women were chosen for CAC measurement. In 5 women no calcium scores could be obtained, and for 69 women the baseline mammograms could not be retrieved. Thus, the current study population includes 499 women. The study was approved by the Institutional Review Board of the University Medical Center Utrecht and written informed consent was obtained from all participants. Data collection with regard to calcium scores took place between November 2003 and February 2005.

2.2. Baseline measurements

The baseline questionnaire was obtained at the time of the baseline mammograms and contained information on date of birth, cardiovascular disease history, and established risk factors for cardiovascular disease. Smoking was defined as current, past, or never smoking. Systolic and diastolic blood pressures were measured in duplicate at the left arm with the subjects in sitting position after 10 min of rest with an automated and calibrated oscillomat (Bosch & Son, Jungingen, Germany). Subsequently, the mean systolic and diastolic blood pressures were calculated. Body height was measured to the nearest 0.5 cm

with a wall mounted stadiometer (Lameris, Utrecht, The Netherlands). Body weight was measured in light indoor clothing without shoes to the nearest 0.5 kg with a floor scale (Seca, Atlanta, GA, USA). Body mass index was calculated as weight divided by height squared (kg/m^2). Hypertension was defined as present when women reported that a physician diagnosed this, and/or when they had a measured systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg. Hypercholesterolemia and diabetes mellitus were defined as present when women reported that a physician diagnosed this. Parity was defined as the total number of live born or still born children. Breastfeeding was defined as having breastfed after at least one pregnancy.

2.3. Mammograms

All baseline mammograms (mediolateral-oblique and cranio-caudal views of both breasts) of the 499 eligible women were retrieved from the archives and analysed for the presence of calcium in the breast arteries by 2 experienced radiologists, who were blinded to the clinical data. Breast arterial calcium was defined as present if calcium deposits were seen along the contours of the arterial wall(s) in one or both breasts. If there was disagreement in analysis, occurring in 5% of cases, the mammograms were reviewed by both observers to reach consensus.

2.4. Coronary calcification

The amount of calcium in the coronary arteries was assessed with a MSCT scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Subjects were positioned within the gantry of the MSCT scanner in supine position. A 16-slice scanner with 0.42 s rotation time was used to obtain 1.5 mm thick sections. During a single breath hold, images of the heart, from the level of the tracheal bifurcation to below the base of the heart, were acquired using prospective ECG triggering at 50–80% of the RR-interval, depending on the heart rate. Scan duration was approximately 10 s, depending on heart rate and patient size. From the acquired raw data, 3 mm thick sections were reconstructed. Quantification of CAC was performed on a separate workstation with software for calcium scoring (Heartbeat-CS, EBW, Philips Medical Systems, Best, The Netherlands). All regions with a density over 130 Hounsfield units are identified as potential calcifications. A trained scan reader manually selects only the calcifications within one of the coronary arteries (left main, left anterior descending, left circumflex, right coronary artery, and PDA). To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm^2 . The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. The Agatston calcium score was obtained by multiplying the area by a weighting factor that is dependent on the peak signal anywhere in the lesion [18]. The scores of individual lesions were added to obtain the Agatston calcium score for the entire coronary tree. Reproducibility of the MSCT was assessed by having 199 scans read by two independent observers and by having 58 subjects undergoing a second scan within 3 months. The inter-reader reproducibility

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