SCIENTIFIC LETTER

Arterial calcium on mammograms is not associated with inflammatory markers for heart disease risk

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Calcifications along the wall of the breast arteries are commonly seen on mammograms, but it is still unclear whether they can identify women at risk for coronary heart disease (CHD). In breast cancer screening populations the prevalence of breast arterial calcium (BAC) is 9%, whereas it is present in 23% of women at increased risk for CHD.¹ Although several studies have shown that classic cardiovascular risk factors for atherosclerosis are associated with mammographic arterial calcifications, thus far the correlation with clinical coronary artery disease is controversial.^{2,3} As other factors such as the total number of pregnancies are important in the prevalence of BAC, its multiple causes remain poorly understood.¹

Chronic low grade inflammation is an important aspect of atherosclerosis. Data on inflammatory markers such as fibrinogen and high sensitivity C reactive protein (hs-CRP) in calcification of atherosclerotic arteries are conflicting and not studied in arterial calcifications on mammograms.⁴ To further explore the pathophysiological process of BAC we investigated mammograms and inflammatory markers in women from a breast cancer screening program.

METHODS

We analysed data from 1736 women, aged 49–70 years, scheduled for breast cancer screening as participants in the Prospect-EPIC (European prospective investigation into cancer and nutrition) study. We assessed whether mammographic arterial calcifications were related to serum concentrations of fibrinogen and hs-CRP. Baseline information on cardiovascular risk factors was collected by self administered questionnaire. A medical examination was performed and a 30 ml non-fasting blood sample was donated. All women signed an informed consent and the study was approved by the institutional review board of the University Medical Centre Utrecht.

Hs-CRP was measured in citrated plasma by the Behring BNII nephelometric method (Dade Behring, Deerfield, Illinois, USA). CRP concentrations below the detection limit of 0.2 mg/l ($n = 50$) were set to 0.1 mg/l. Total fibrinogen concentrations were determined in citrated plasma according to the Clauss method by the STA-R automatic coagulation analyser with STA fibrinogen reagent (Diagnostica Stago, Taverny, France).

Baseline mammograms (mediolateral-oblique and cranio-caudal views of both breasts) of 1699 participating women were available for analysis and were scored by two independent radiologists. Breast artery calcium was characterised by calcium deposits along the wall of the breast artery or arteries on mammograms of the right, left, or both breasts.

RESULTS

BAC was present in 194 (11%) of 1699 of participants. Hs-CRP measurements were available for 95% of participants and fibrinogen for 93%. Mean hs-CRP concentrations were not significantly lower (2.37 mg/l) in women with BAC than in women without BAC (mean 2.52 mg/l). No difference was seen in mean fibrinogen concentrations (2.67 g/l). Hs-CRP and fibrinogen divided into quartiles were also not associated

Table 1 Relation of risk markers with breast arterial calcium (BAC)

Quartile	+ BAC	OR*	95% CI
Hs-CRP (mg/l)			
I (0.42)	12.4%	1.0	
II (0.91)	10.6%	0.7	0.5 to 1.1
III (1.86)	9.6%	0.6	0.4 to 0.9
IV (6.8)	11.4%	0.8	0.5 to 1.2
Fibrinogen (g/l)			
I (1.88)	10.3%	1.0	
II (2.39)	9.9%	0.9	0.5 to 1.4
III (2.79)	11.9%	1.1	0.7 to 1.6
IV (3.61)	12.0%	0.9	0.5 to 1.4

*Adjusted for age and number of pregnancies.
CI, confidence interval; OR, odds ratio.

with the prevalence of BAC (table 1). Factors that were significantly associated with BAC were age (odds ratio (OR) 1.1 per year, 95% confidence interval (CI) 1.09 to 1.14), pregnancy ever (OR 5.3, 95% CI 2.2 to 13.2), and lactation after pregnancy (OR 2.2, 95% CI 1.4 to 3.6) (table 2). Smoking was inversely related to BAC (OR 0.6, 95% CI 0.4 to 0.9). The prevalence of diabetes mellitus was too low in this population (2.8%) to estimate its relation with BAC. Hypertension was present in 20% of participants but after multivariate analysis it was not significantly associated with BAC.

DISCUSSION

Our results do not support an association of the CHD risk markers hs-CRP and fibrinogen with mammographic arterial calcifications. We found no significant association with CHD risk factors in this average risk population, although we did find an association of BAC with the total number of CHD risk factors in a previous study in women at high risk.¹ Only aging, a history of pregnancy, and lactation after pregnancy were independently associated with BAC.

Whether hs-CRP and fibrinogen concentrations correlate with the extent of atherosclerosis as measured by coronary artery calcification is controversial, although both markers are clearly related to increased risk of clinical cardiovascular events.⁴ Measurements of calcium deposits and inflammatory markers may reflect different pathophysiological processes in atherogenesis.

From pathology and biochemistry studies it is known that the calcium deposits in breast arteries are located in the media of the vessel wall.⁵ Medial calcification is mostly known from calcifications in the peripheral vessels in diabetic patients. A common pathway in vascular calcification is the activation of vascular smooth muscle cells, present in the media of all arteries, with different embryonic origins in parts of the arterial

Abbreviations: BAC, breast arterial calcium; CHD, coronary heart disease; CI, confidence interval; hs-CRP, high sensitivity C reactive protein; Prospect-EPIC, European prospective investigation into cancer and nutrition; OR, odds ratio

Table 2 Age adjusted multivariate relation between cardiovascular risk factors* and BAC

Variable present	OR	95% CI
Hypertension	0.9	0.6 to 1.3
Hypercholesterolaemia	0.9	0.5 to 1.7
Smoking	0.6	0.4 to 0.9
Pregnancy	5.3	2.2 to 13.2
Lactation	2.2	1.4 to 3.6

*Prevalence of diabetes was too low (2.8%) to estimate its relation with BAC.

system. A variety of stimuli, such as inflammatory cytokines, lipids, glucotoxicity, and hypercalcaemia, are described to induce calcification in vascular smooth muscle cells.⁵ Various causative factors are likely to be involved in the calcification processes in different locations and types of the vascular tree. As pregnancy and breastfeeding are strongly associated with mammographic arterial calcifications, hypercalcaemia during pregnancy and lactation combined with the increased blood flow in the breast arteries may trigger vascular smooth muscle cells to enhance calcification.

We have no explanation, however, for why the prevalence of BAC is higher in women at increased cardiovascular risk than in healthy middle aged women.

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Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort

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Objective: To test the hypothesis that sleep disorders are relevant to the risk of ischaemic stroke and ischaemic heart disease events in older men.

Design: A cohort study.

Setting: The Caerphilly cohort, a representative population sample of older men in South Wales, UK.

Participants: 1986 men aged 55–69 years completed a questionnaire on sleep patterns with help from their partners. This asked about symptoms of disturbed sleep: insomnia, snoring, restless legs, obstructive sleep apnoea, and about daytime sleepiness. During the following 10 years 107 men experienced an ischaemic stroke and 213 had an ischaemic heart disease event.

Main results: Up to one third of the men reported at least one symptom suggestive of sleep disturbance, and one third reported daytime sleepiness. Compared with men who reported no such symptoms, the adjusted relative odds of an ischaemic stroke were significantly increased in men with any sleep disturbance, the strongest association being with sleep apnoea (relative odds 1.97; 1.26 to 3.09). The association with daytime sleepiness was not significant for stroke. Relations with ischaemic heart disease events were all raised in men with symptoms of sleep disturbance, but none was significant, other than daytime sleepiness (relative odds 1.41; 1.04 to 1.92). There were no significant relations with blood pressure.

Conclusion: The risk of an ischaemic stroke is increased in men whose sleep is frequently disturbed, and daytime sleepiness is associated with a significant increase in ischaemic heart disease events.

▲ *Journal of Epidemiology and Community Health* 2006;**60**:69–73.