Letters

Breast Arterial Calcifications and Their Association With Incident Cardiovascular Disease and Diabetes

The Prospect-EPIC Cohort

Breast arterial calcifications (BACs), which are a type of medial calcification, are prevalent among diabetes patients and are believed to be associated with increased cardiovascular risk. However, longitudinal studies that have examined BACs are scarce. We aimed to investigate the association of BACs with incident cardiovascular disease (CVD) and type 2 diabetes (T2D).

We performed a series of case-cohort studies nested within the larger Prospect-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort study (n = 17,357) [1]. Expert radiologists scored BACs on baseline film mammograms as absent, mild, moderate, or severe. The between-observers Cohen's kappa was 0.48 (95% confidence interval [CI]: 0.37 to 0.59) for BAC presence and/or absence, and the kappa with linear weighting for all 4 categories was 0.53 (95% CI: 0.46 to 0.61) in a sample of 240 mammograms. To obtain vital status, causes of death, and hospital discharge diagnoses, 16,737 women gave consent for database linkage purposes. During a median follow-up of 13.2 years (interquartile range: 12.2 to 14.2 years), incident cases of coronary heart disease (CHD) (n = 1,050), stroke (n = 398), peripheral artery disease (PAD) (n = 257), and T2D (n = 526) were documented. These cases were compared with a 10% random subcohort (n = 1,672) drawn from the baseline. A combined endpoint of CHD, stroke, and PAD (n = 1,551) was also investigated. For the analysis of incident T2D, women with prevalent diabetes were excluded. Hazard ratios (HRs) and 95% CIs were obtained from Cox proportional hazards models adapted to the case-cohort design through Prentice weighting. Multiple imputation techniques were used to handle missing baseline data.

Of the women in the subcohort with available mammograms (n = 1,540), 133 (8.6%) had BACs, which were mild in 75 (4.9%), moderate in 39 (2.5%), or severe in 19 (1.2%) women. Women with BACs tended to be older; they had hypertension more often, smoked less often, had more children, were more often postmenopausal, drank less alcohol, had lower glomerular filtration rates, and used hormone replacement therapy less often.

The presence of BAC was significantly associated with CHD (HR: 1.44; 95% CI: 1.02 to 2.01) and combined CVD (HR: 1.39; 95% CI: 1.00 to 1.93) (Table 1). HRs for stroke and PAD were similar, but were nonsignificant. Larger effect sizes were found for severe BAC, with HRs of 3.37 (95% CI: 1.80 to 6.31) for combined CVD, 3.40 (95% CI: 1.76 to 6.57) for CHD, 2.85 (95% CI: 1.32 to 6.15) for stroke, and 2.93 (95% CI: 1.05 to 8.16) for PAD compared with women without BACs. Part of these effects could be attributable to pulse pressure, especially for stroke and PAD, because of the difference in HRs between models 2 and 3. No associations were found between BAC and T2D.

The strengths of this study included its large sample size and long follow-up, which provided sufficient events for multivariable analysis. A limitation is that we used film mammography from the 1990s, and that BAC scoring is subjective. Current technology and automatic quantification of BACs might possibly show stronger effects. Two limitations inherent to our design were that confounder data were limited to the cross sectionally gathered information at baseline and the potential for residual confounding.

Our results are in line with 2 previous cohort studies that had comparable effect sizes for cardiovascular morbidity and mortality [2,3]. We were the first to examine the risks of BAC in categories of severity. The increased risks were mainly associated with severe BAC, which was only present in 1.2% of the subcohort.

We hypothesized that an association of BAC with increased cardiovascular risk, which was apparently independent of traditional risk factors, might point to a pathophysiological mechanism that differs from the intimal atherosclerotic process. Because BAC could be a marker of a more generalized tendency to

TABLE 1 Associations Between BAC (Presence vs. Absence and Severe vs. Absent) and Incident Cardiovascular Disease and Diabetes

	BAC Presence		BAC Severity Severe	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Composite CVD endpoint				
Model 1	1.16 (0.92-1.48)	0.215	2.25 (1.29-3.94)	0.005
Model 2	1.44 (1.04-1.99)	0.030	3.54 (1.89-6.64)	<0.001
Model 3	1.39 (1.00-1.93)	0.048	3.37 (1.80-6.31)	<0.001
Coronary heart disease				
Model 1	1.22 (0.94-1.58)	0.130	2.40 (1.34-4.29)	0.003
Model 2	1.46 (1.04-2.05)	0.028	3.50 (1.82-6.72)	<0.001
Model 3	1.44 (1.02-2.01)	0.036	3.40 (1.76-6.57)	<0.001
Stroke				
Model 1	1.19 (0.83-1.72)	0.338	2.29 (1.13-4.63)	0.022
Model 2	1.47 (0.98-2.19)	0.059	3.21 (1.51-6.83)	0.003
Model 3	1.39 (0.92-2.08)	0.116	2.85 (1.32-6.15)	0.008
Peripheral artery disease				
Model 1	0.97 (0.61-1.55)	0.912	1.59 (0.62-4.07)	0.335
Model 2	1.43 (0.80-2.58)	0.231	3.24 (1.16-9.00)	0.025
Model 3	1.37 (0.74-2.52)	0.313	2.93 (1.05-8.16)	0.040
Incident diabetes				
Model 1	0.75 (0.51-1.08)	0.125	1.27 (0.58-2.78)	0.555
Model 2*	0.88 (0.58-1.33)	0.542	1.24 (0.48-3.17)	0.658

BAC = breast arterial calcification; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; Model 1 = age-adjusted; Model 2 = multivariable adjusted for age, smoking, high-density lipoprotein (HDL)/total cholesterol ratio, hypertension, physical activity, body mass index, alcohol intake, type 2 diabetes, cardiovascular disease history, parity number, menopausal status; Model 2* = multivariable adjusted for age, body mass index, physical activity, HDL/total cholesterol ratio and smoking; Model 3 = model 2 plus pulse pressure.

develop medial calcification in other vascular beds, this needs further investigation. One study in renal patients showed that BAC was associated with medial calcification in other arterial beds (4). It is hypothesized that medial calcification leads to CVD through increased arterial stiffness (5). This is supported by our data, because we found that adding pulse pressure attenuated the associations. A limited number of studies conducted in specific patient groups reported increased cardiovascular risks associated with medial calcification in other vascular beds, comparable to those we found for severe BAC (5).

The presence of BAC is modestly associated with CVD, with an approximately 3-fold increased risk for severe BAC, independent of traditional risk factors. This indicates a possible contribution of a medial, nonatherosclerotic pathway to CVD.

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Under-Recognition of Aortic and Aortic Valve Disease and the Risk for Sudden Death in Competitive Athletes

Sudden deaths (SDs) in young athletes are unexpected, tragic, and highly visible events. Considerable attention has been focused on pre-participation screening to prevent these events (1). Aortic stenosis (AS) is known as an important cause of SD in the young, whereas aortic dissection/rupture is a catastrophic condition not usually associated with demise early in life (2,3). The role of these diseases in athletic field deaths and their identification by standard routine pre-participation screening (e.g., history and physical examination in the United States) is incompletely understood.

The U.S. National Registry of Sudden Death in Athletes, a forensic and clinical database that collects SDs of competitive athletes under 40 years of age (4),