JACC: CARDIOVASCULAR IMAGING
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PUBLISHED BY ELSEVIER
VOL. 9, NO. 5, 2016
ISSN 1936-878X/$36.00
http://dx.doi.org/10.1016/j.jcmg.2015.09.020

The Association of Coronary Artery Calcium With Noncardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

OBJECTIVES This study sought to determine if coronary artery calcium (CAC) is associated with incident noncardiovascular disease.

BACKGROUND CAC is considered a measure of vascular aging, associated with increased risk of cardiovascular and all-cause mortality. The relationship with noncardiovascular disease is not well defined.

METHODS A total of 6,814 participants from 6 MESA (Multi-Ethnic Study of Atherosclerosis) field centers were followed for a median of 10.2 years. Modified Cox proportional hazards ratios accounting for the competing risk of fatal coronary heart disease were calculated for new diagnoses of cancer, pneumonia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), deep vein thrombosis/pulmonary embolism, hip fracture, and dementia. Analyses were adjusted for age; sex; race; socioeconomic status; health insurance status; body mass index; physical activity; diet; tobacco use; number of medications used; systolic and diastolic blood pressure; total and high-density lipoprotein cholesterol; antihypertensive, aspirin, and cholesterol medication; and diabetes. The outcome was first incident noncardiovascular disease diagnosis.

RESULTS Compared with those with CAC = 0, those with CAC >400 had an increased hazard of cancer (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.18 to 1.99), CKD (HR: 1.70; 95% CI: 1.21 to 2.39), pneumonia (HR: 1.97; 95% CI: 1.37 to 2.82), COPD (HR: 2.71; 95% CI: 1.60 to 4.57), and hip fracture (HR: 4.29; 95% CI: 1.47 to 12.50). CAC >400 was not associated with dementia or deep vein thrombosis/pulmonary embolism. Those with CAC = 0 had decreased risk of cancer (HR: 0.76; 95% CI: 0.63 to 0.92), CKD (HR: 0.77; 95% CI: 0.60 to 0.98), COPD (HR: 0.61; 95% CI: 0.40 to 0.91), and hip fracture (HR: 0.31; 95% CI: 0.14 to 0.70) compared to those with CAC >0. CAC = 0 was not associated with less pneumonia, dementia, or deep vein thrombosis/pulmonary embolism. The results were attenuated, but remained significant, after removing participants developing interim nonfatal coronary heart disease.

CONCLUSIONS Participants with elevated CAC were at increased risk of cancer, CKD, COPD, and hip fractures. Those with CAC = 0 are less likely to develop common age-related comorbid conditions, and represent a unique population of "healthy agers." (J Am Coll Cardiol Img 2016;9:568–76) © 2016 by the American College of Cardiology Foundation.

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Manuscript received August 4, 2015; revised manuscript received August 31, 2015, accepted September 3, 2015.

Over the last 4 decades, there has been a substantial decline in cardiovascular disease (CVD) mortality, partly from improved identification and modification of risk factors (1). The rate of non-CVD deaths has not declined as rapidly (2), resulting in CVD decreasing to the second leading cause of death in certain populations (3).

Coronary artery calcium (CAC) scoring is a noninvasive, direct measure of coronary atherosclerosis and powerful predictor of incident CVD and all-cause mortality (4). CAC scores increase with chronologic age (5). However, there is considerable heterogeneity within age groups (6) translating into an "equivalent" chronologic age varying up to 30 years (7). This potentially permits CAC scores to reclassify risk independent of age (8). Indeed, CAC retains a strong predictive value for all-cause mortality beyond age (9), raising the idea that CAC scores may provide a superior estimate of "arterial age" (10).

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CAC scores have been associated with the presence of traditional risk factors and likely partially represent the cumulative burden of risk factor exposure. However, even those with no traditional CV risk factors can have elevated CAC scores and increased risk of CVD (11). Higher levels of CAC are also associated with an increased risk of death from non-CVD causes (12). This may be from higher incidences of other age-related diseases, such as cancer, which has been associated with very high CAC scores (13). There have been mixed results when examining the relationship between CAC and other non-CVDs, such as kidney disease (14,15) and decreased bone density (16,17).

To our knowledge, there have been no studies examining the relationship between CAC and other age-related diseases associated with significant morbidity and mortality, such as osteoporotic fractures, pneumonia, dementia, deep vein thrombosis (DVT), or pulmonary embolism (PE). We sought to evaluate whether CAC, as a marker of arterial age, is an independent predictor of non-CVD diagnoses. We hypothesized that having CAC = 0 would be associated with a low risk of disease and having elevated CAC would be associated with a higher burden of non-CVD.

METHODS

STUDY POPULATION. Participants were from MESA (Multi-Ethnic Study of Atherosclerosis) (18). MESA is a prospective, observational cohort of 6,814 people from 6 U.S. cities, between 45 and 84 years old and of diverse backgrounds, who were free of CVD and not under active cancer treatment. Baseline lifestyle characteristics and anthropometric measurements were measured at the initial examination. All participants with CAC scanning at baseline and follow-up data were eligible for inclusion. Institutional Review Board approval was obtained at each site. Each participant gave written informed consent (http://www.mesa-nhlbi.org).

CAC SCORE MEASUREMENTS. Detailed methods for computed tomography scan technique and interpretation were previously described (19). Chicago, Los Angeles, and New York used cardiac-gated electron-beam computed tomography scanning. The other sites used multidetector computed tomography scanning. At the baseline examination, each participant was scanned 2 consecutive times with mean Agatston score used for the analysis. All images were interpreted at a single center, with good intrareader and inter-reader agreement (kappa = 0.92).

FOLLOW-UP. Follow-up occurred every 9 to 12 months for a median of 10.2 years (mean 9.5 years; interquartile range: 9.7 to 10.7 years). New diagnoses were verified by review of hospital records and death certificates. Coronary heart disease (CHD)-related endpoints were adjudicated and classified by 2 physicians from the MESA mortality and morbidity review committee. Non-CVD diagnoses were abstracted from inpatient records by International Classification of Diseases-9 codes. Codes related to the following broader groups were included: chronic kidney disease (CKD) and indicators of end-stage renal failure, any malignant neoplasm, dementia, hip fracture, DVT or PE, pneumonia, and chronic obstructive pulmonary disease (COPD). A full list of codes used is in Online Table 1.

STATISTICAL ANALYSIS. We modeled CAC as a continuous and binary variable (present/absent and zero or >400). In accordance with prior reports, CAC was analyzed as a continuous variable using base-2 logarithm of coronary calcium score plus 1 (log2 [CAC+1]) to determine how the doubling of calcium score affects risk and to include those with CAC = 0 (20). There were no deviations from the linear assumption when modeling continuous CAC.

Baseline characteristics are presented by CAC stratum. Continuous variables are presented as mean ± SD, whereas categorical variables as the number with the attribute (percentage of total). Analysis of variance was used to test means across groups for normally distributed variables and Kruskal-Wallis for not normally distributed variables. Chi-square analysis was used to test differences in distributions for categorical variables.

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CHD = coronary heart disease
CI = confidence interval
CKD = chronic kidney disease
COPD = chronic obstructive pulmonary disease
CVD = cardiovascular disease
DVT = deep vein thrombosis
HR = hazard ratio
PE = pulmonary embolism
SES = socioeconomic status