Coronary Calcium, Race, and Genes

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Measurement of coronary calcium has become a useful tool in the investigation of coronary disease and risk, as evidenced by the companion articles in this issue examining the relationship of race and genetic factors to coronary calcium.1,2 Newman et al3 report racial differences in coronary calcium measures in older adults participating in the Cardiovascular Health Study. Among 471 white and 143 black participants with an average age of 80 years, median coronary calcium scores were lower in blacks than in whites, particularly in men, even after adjustment for other black-white differences. Black men were only 20% as likely, and black women 71% as likely, as whites to have increased calcium scores. In the small subgroup of participants with myocardial infarction, who might be expected to be more similar, calcium scores still were lower among blacks than whites.

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This is not the first study to demonstrate racial differences in coronary calcium prevalence; Tang et al4 reported lower calcium prevalence in the 87 black participants of the largely self-referred South Bay Heart Watch. Interestingly, short-term follow-up of that cohort showed blacks to have higher risk of clinical coronary events despite their lower scores,4 raising the question of whether the relationship of calcium to subsequent events differs by race. Another small study of young adults did not identify but did not exclude the possibility of racial differences in coronary calcium.5

These findings may cause us to question the premise that coronary calcium and clinically overt coronary disease have common antecedents, but other explanations should first be considered. More limited access to medical care and less aggressive risk factor management in blacks might be expected to produce more, rather than less, coronary disease in blacks, and in fact, blacks recruited into the Cardiovascular Health Study generally had worse health indicators at entry than their white counterparts.6 Of the many biases that may be expected to produce more, rather than less, coronary disease in blacks, and in fact, blacks recruited into the Cardiovascular Health Study generally had worse health indicators at entry than their white counterparts.6 Of the many biases that may be operative and that are cited by the authors, only decreased survival of blacks with significant coronary disease might be expected to produce lower scores in elderly blacks studied cross-sectionally. Given the lower survival of blacks with coronary disease7 and the higher prevalence of atherosclerosis in blacks in autopsy studies of young adults,8 as well as the cross-sectional nature, small size, and advanced age of this cohort, survival bias cannot be excluded as an explanation for the findings of Newman et al.1

But what of the possibility that coronary calcium has a different pathologic or prognostic significance in blacks, or perhaps more precisely, that the antecedents and promoters of coronary calcium differ from those for clinically overt coronary disease? Calcium is used investigatively as a window on the coronary vascular wall and is used clinically as a measure of risk of subsequent clinical disease. In both these applications, it is an imperfect indicator, because our understanding of the relationship of the calcium we can image to the atherosclerosis and thrombosis we cannot is at present so incomplete. Newman et al1 suggest some intriguing possibilities, including the process of calcification differing by race (or the concomitants of race) or plaque rupture and erosion being related to lower calcium content of vulnerable plaque. They note that their study is too small to compare the associations of risk factors with coronary calcium and coronary events across race-gender groups.

Such comparisons are critical if racial differences in subclinical disease are to be appropriately understood and applied in research and clinical practice. Newman et al1 raise some important questions about the relationship of cardiovascular risk factors to coronary calcium, although in their study, these questions are framed by the overall issue of racial differences. Race, especially black race in the United States, is confounded by so many factors related to disease risk and outcome, including higher levels of many risk factors, poorer access to care, and lower socioeconomic status, that perhaps race should be one of the last things we consider in studying coronary disease pathogenesis and risk rather than one of the first. Having looked for racial differences and (not unexpectedly) found them, it is critical not to stop here lest we fall into a similar trap as those who concluded decades ago that coronary disease was uncommon in blacks, not recognizing that the disease manifested itself, and was more often fatal, at much younger ages than in whites. If certain coronary risk factors that are more common in blacks are somehow associated with increased severity of atherosclerosis and thrombosis but decreased severity of calcification, lower calcium scores in blacks might not adequately reflect their subsequent coronary risk, despite attempts to adjust statistically for these factors. More importantly, if other as yet undetermined factors are more common in blacks and modify the relationship between coronary calcium and overt disease, identifying these factors may help elucidate the pathogenesis of clinical coronary disease in all persons, regardless of race. The real issue may then not be to explain black-white differences in calcium but to explain interindividual differences in calcium-overt disease relationships so that calcium measures may be more effectively used to guide therapy. While one could argue strenuously against the concept of

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taiored therapeutic approaches based on race, which in itself has little biologic meaning, one could strongly support the concept of tailored approaches based on differences in risk factors and subclinical disease indicators. Much needed research to develop these approaches, unfortunately, remains to be done.

The article by Lange et al\textsuperscript{2} reports a genome-wide linkage scan in 105 Caucasian sibships drawn from the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Coronary calcium was assessed by using similar methods as the previous study but was dichotomized above and below the 70th percentile value rather than analyzed as a continuous, or quantitative, trait. Regions on chromosomes 6 and 10 were shared more often among siblings similar for calcium presence than among siblings dissimilar for this trait. Linkage was stronger for the chromosome 10 region, which contains genes related to collagen and bone formation. No excess sharing was seen in regions linked to a number of previously reported candidate genes.

Lange et al\textsuperscript{2} note that their sample had a high prevalence (77\%) of hypertension and that this may have influenced their ability to detect linkages in regions not previously identified by other investigators and vice versa. That genetic variants may have different associations with outcome in the presence of different risk factors has been demonstrated repeatedly, for example, for the apolipoprotein E4 allele and coronary risk factors such as smoking and elevated cholesterol.\textsuperscript{9,10} Common apolipoprotein E genotypes have even been shown to modify the relationship of common risk factors and coronary calcium prevalence.\textsuperscript{11} It is conceivable, and perhaps rather likely, that the impact of genetic polymorphisms on disease risk differs in the presence of other risk factors such as hypertension. If this is true, it could be quite relevant to the understanding of racial/ethnic differences in clinical coronary disease and coronary calcification, particularly for those who would interpret racial differences as evidence of genetic or biologic differences by race. Although there clearly are racial differences in allele frequencies at many loci, there is much more genetic variation within racial/ethnic subgroups than between them.\textsuperscript{12} The combination of (1) differing frequencies of genetic variants related to calcification and (2) different prevalences and severities of risk factors for calcification among racial/ethnic groups may indeed be expected to manifest as racial differences in the presence and prognostic significance of coronary calcium. The search is on for genes related to coronary calcification and, perhaps more importantly, the genetic variants that affect the relationship of calcium to development of overt disease. These variants must not be studied in isolation, without consideration of the other risk factors with which they undoubtedly interact, just as black-white differences must not be interpreted without consideration of the many social, medical, and physiological concomitants of race.

What are the clinical implications of these findings? They would appear limited at present, as the clinical implications of coronary calcium itself have yet to be fully elucidated. It is probably reasonable to conclude that low calcium scores in blacks should not deter the practicing physician from optimal risk factor management, just as they should not in whites. The significance of absent calcium, which is taken by many researchers to indicate a very low likelihood of subsequent coronary events, may be less clear in blacks, but this remains to be determined in long-term studies including adequate and population-based samples of blacks. In the interim, calcium imaging can potentially be utilized as a motivational tool for encouraging coronary risk reduction, regardless of race, when calcium is present. The implications of its absence in designing preventive strategies for coronary disease, particularly among blacks, remain to be determined.

References


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