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Ethnic Differences in the Relationship of Carotid Atherosclerosis to Coronary Calcification: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Ethnic differences in non-invasive measures of atherosclerosis are increasingly being reported, but the relationship of these measures to each other has not been widely explored. Carotid ultrasonographic and computed cardiac tomographic findings were compared in 6,814 participants of White, Black, Hispanic, and Chinese ethnicities free of overt cardiovascular disease. Coronary calcium and carotid atherosclerosis were strongly related to each other in all ethnic groups. Associations of coronary calcium prevalence and common carotid intimal-medial thickness (IMT) differed by ethnicity in women, being weakest among Black women (0.07 mm IMT difference between those with and without coronary calcium) compared to the other three groups (0.10–0.12 mm difference, $p = 0.007$). Estimated percent increments in internal carotid IMT per 10% increment in coronary calcium score were highest in Hispanics (18.5%) and lowest in Blacks (6.1%, $p < 0.01$).

Coronary calcium may be less strongly associated with carotid atherosclerosis in Blacks, particularly Black women, than in other ethnic groups. These differences should be pursued for relationships to coronary events to determine whether coronary calcium carries the same risk information in other ethnic groups as it does in Whites.

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Keywords

atherosclerosis; calcium; carotid arteries; epidemiology

INTRODUCTION

Ethnic differences in prevalence and severity of non-invasive measures of carotid and coronary atherosclerosis are increasingly being reported [1–3], but the relationship of these measures to each other has not been widely explored. Blacks have generally been shown to have thicker common carotid IMT and thinner or equivalent internal carotid IMT compared to Whites [1], but similar or lower coronary calcium prevalence [2,4], despite higher coronary disease morbidity and mortality [5]. Comparisons have generally not been reported in other ethnic groups. If there are indeed ethnic differences in the relationship of coronary calcium to coronary disease events [6], but little ethnic difference in the relationship of carotid atherosclerosis to coronary events [7], the association of coronary calcium to carotid atherosclerosis might also be expected to differ by ethnicity.

Carotid atherosclerosis assessed by ultrasound has been shown to reflect pathologically-defined lesions [8] and to predict subsequent coronary events [9]. Coronary calcium measured by computed tomography also correlates well with pathologically-defined coronary atherosclerosis [10], though its predictive value for coronary events in population-based cohorts, particularly of diverse ethnicity, has been less widely explored [11]. A recent report from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort free of clinical cardiovascular disease at entry, has shown substantially higher prevalences and levels of coronary calcium in Whites compared to Chinese, Hispanics, and Blacks, whose prevalences declined roughly in that order [2]. Distributions of cardiovascular disease risk factors and the relationships of these risk factors to coronary calcium prevalence and scores also differed modestly by ethnicity [2]. Ethnic differences in the relationship of these two non-invasive measures of atherosclerosis, however, and potential factors explaining these differences, have not been widely examined. Given the increasing popularity of coronary calcium screening for risk assessment, ethnic differences in the relationship of coronary calcium to cardiovascular disease risk (as reflected by carotid atherosclerosis) should be considered in interpreting coronary calcium scores, particularly among non-Whites, in whom data are sparse.

In this report we used the baseline carotid ultrasonography and coronary calcium scanning data from MESA to: 1) examine the associations of carotid intimal-medial thicknesses with coronary calcium prevalence and scores; 2) identify ethnic differences in these associations; and 3) determine the degree to which these differences might be explained by ethnicity-related atherosclerosis risk factors and other covariates.

METHODS

MESA is a population-based study of subclinical cardiovascular disease in 6,814 participants of White, Black, Hispanic, and Chinese ethnicities and free of overt cardiovascular disease at entry. MESA participants were initially recruited and examined in 2000–2002 from persons ages 45–84 years in six U.S. communities as previously described [12]. Protocols were approved by the participating Institutional Review Boards and all participants gave written informed consent.

Coronary calcium was measured by multidetector computed tomographic scanning and electron beam computed tomography as previously described [12–14]. Kappa statistics for intra-and inter-reader reproducibility of coronary calcium prevalence were both 0.92. Intra-

class correlation coefficients for intra- and inter-reader reproducibility of coronary calcium scores exceeded 0.99. Carotid ultrasonography was performed and read centrally as previously described [12,15]. Intra-class correlation coefficients for intra-reader reproducibility of common and internal carotid IMT both exceeded 0.98 and for inter-reader reproducibility were 0.87 and 0.94, respectively.

Statistical Analyses

Prevalence of coronary calcium, geometric mean coronary calcium scores, and mean carotid IMT were compared across ethnicities using chi-square and analysis of variance, respectively. Due to the large proportion of persons with coronary calcium scores = 0 (coronary calcium absent) and the resulting strong departures from normality in distribution of these scores [16], bivariate associations with scores as continuous variables are presented only for those with coronary calcium present.

The hypothesis of ethnic differences in the relationship of carotid IMT to coronary calcium was tested in a two-part model, by regressing ln-transformed IMT in mm as the dependent variable on ln-transformed total coronary calcium score (ln [score + 1], including those with 0 calcium) in Agatston units (AU), along with an indicator for presence of coronary calcium, as independent variables. Since neither coronary calcium nor carotid wall thickness is accepted as a “gold standard” of cardiovascular disease risk, testing was repeated by regressing ln coronary calcium score, when >0, on carotid IMT. In addition, presence of coronary calcium was regressed separately on carotid IMT. The probability of a positive calcium score was modeled as an exponential function of the covariates using nonlinear least squares to obtain asymptotically unbiased estimates of the relative risk of a positive CAC score. As results of modeling carotid IMT as a function of coronary calcium, and coronary calcium as a function of carotid IMT, were generally similar, only the former are presented because they allow simultaneous modeling of coronary calcium prevalence and scores in these cross-sectional data.

The primary variable of interest was ethnicity used as a class variable, defined by three indicator variables, with Whites as the comparison group. The interaction of ethnicity with both presence of coronary calcium and ln-transformed calcium score was tested to assess ethnic differences in the relationship of coronary calcium to carotid atherosclerosis. If the 6-degrees of freedom interaction term (3 ethnicity terms × 2 calcium terms) was significant at $p < 0.10$, separate interactions between ethnicity and presence of calcium, and between ethnicity and calcium score, were tested.

Interactions were also tested between age and ethnicity and between age and each of coronary calcium presence, coronary calcium score, and carotid IMT. Significant interactions were found between age and ethnicity and between age and coronary calcium score. Due to the complexity of interaction models, results are presented both unadjusted and after full adjustment accounting for the age interactions. Interactions between sex and each of age and ethnicity, and between sex and coronary calcium, were also tested. When significant interactions with sex were present, models were stratified by sex.

To determine whether any ethnic differences in the relationships of coronary calcium to carotid IMT were explained by differences in prevalence of the risk factor covariates, a final level of adjustment included adding these covariates. Covariates were selected based on prior published risk factor associations with either measure of atherosclerosis and included age, sex, education, body mass index, systolic and diastolic blood pressures, anti-hypertensive medication use, diabetes, LDL- and HDL-cholesterol, cholesterol-lowering medication use, C-reactive protein, IL-6, fibrinogen, current/former smoking, pack-years of smoking, and estrogen use in women.

All analyses were done using SPSS, version 13 (SPSS, Inc. Chicago, IL) or STATA, version 8 (STATA Corp., College Station, TX).

RESULTS

In both women and men, Blacks had the highest common carotid IMT but they were otherwise similar to Whites and Hispanics in internal carotid IMT (Table 1). Chinese participants had the lowest carotid IMT, particularly in the internal carotid, of the four ethnic groups. As has been reported [2], coronary calcium prevalence was highest in Whites and lowest among Hispanics and Blacks, with prevalence in Chinese being intermediate. Coronary calcium scores among those with any calcium, however, were lowest among Chinese but otherwise consistent with ethnic differences in calcium prevalence.

Although carotid IMT and coronary calcium prevalence and scores increased strongly with age, as has been reported [2,17], the age patterns differed modestly by ethnicity (Table 2). These age-ethnicity patterns differed in turn, though minimally so, by sex. In general, Chinese participants, especially men, had the smallest age-related increments in IMT and tied Hispanic men for the lowest increments in ln coronary calcium scores, while Whites had the largest increments in IMT and calcium scores. The association of age with coronary calcium prevalence was greater in Black and Hispanic men than in the other two groups. Though trends were similar in women, ethnic differences were not significant. Subsequent modeling thus included terms for age and ethnicity interactions where appropriate; interaction terms with sex were not significant after these adjustments.

Coronary Calcium and Carotid IMT

Common and internal carotid IMT were greater in women and men who had coronary calcium than in those who did not regardless of ethnicity (all $p < 0.001$, Table 3). In general, Blacks had the thickest carotid IMTs of all four ethnic groups, regardless of presence of coronary calcium. Associations of coronary calcium presence with common carotid thickness differed by ethnicity in women, being smallest among Black women (0.07 mm) compared to the other three groups (0.10–0.12 mm). Common carotid IMT differed little by ethnicity in women with any coronary calcium, but was higher among Black women without coronary calcium (0.86 mm) than in the other three groups (0.76–0.80 mm).

Regression of unadjusted ln common carotid IMT (dependent variable) on ln coronary calcium score (independent variable) did not differ by sex so results for women and men combined, with and without adjustment for sex, are presented (Table 4). Estimated unadjusted percent increments in common carotid IMT per 10% increment in coronary calcium score were largest in Whites (8.6%) and smallest in Hispanics (5.0%, p for ethnicity-coronary calcium interaction = 0.005). After adjustment for age, age-ethnicity interactions, and sex, however, relationships of coronary calcium to carotid IMT did not differ by ethnicity even though ethnic differences in levels of coronary calcium and carotid IMT remained. Further adjustment for risk factor differences reduced the magnitude of these associations but had little impact on their significance.

For the internal carotid artery, ethnic differences in estimated increments in unadjusted IMT per 10% increment in coronary calcium score did not reach nominal significance levels prior to adjustment but did differ after adjustment for age, age-ethnicity interactions, and sex, and after additional adjustment for other risk factors. Adjusted increments in internal carotid IMT per 10% increment in coronary calcium score were highest in Hispanics (18.5%) and lowest in Blacks (6.1%, Table 4, bottom row).

DISCUSSION

Summary of Findings

Coronary calcium prevalence and scores were associated with ultrasound-defined carotid IMT in this multi-ethnic sample of adults free of overt cardiovascular disease. Ethnic differences in relationships of atherosclerosis measures with age, particularly a steep rise in carotid IMT and coronary calcium score with age in White men, complicated the interpretation of ethnic differences in the associations between these measures of atherosclerosis, but two ethnic differences in associations were observed. First, common carotid IMT differed less by presence of coronary calcium in Black women than in the other three groups. Second, unadjusted common carotid IMT increased more per unit increment in coronary calcium score in Whites, and adjusted internal carotid IMT increased less in Blacks, than in other ethnic groups. Further adjustment for risk factor differences had little impact on the observed ethnic differences. Findings were consistent whether coronary calcium score or carotid IMT was the dependent variable, though they were not always significant when modeling coronary calcium score, possibly due to reduced power in the smaller subgroup with prevalent coronary calcium.

Coronary Calcium and Carotid IMT

Although coronary calcium prevalence and scores, and carotid IMT, differed widely across ethnic groups and were strongly associated with each other, these relationships were largely consistent by ethnicity. Moderately strong associations of coronary calcium with measures of carotid atherosclerosis have been reported in young [18] and older subjects [19,20] and in persons with type 2 diabetes [21], but none of these studies has included sizeable numbers of non-White subjects. In the few studies to compare multiple carotid measures, correlations with coronary calcium have been stronger with carotid plaque (focal thickening at any site) than with common carotid IMT [19] and with internal carotid IMT than with common carotid IMT [20]. Ethnic differences in these associations have not to our knowledge been reported.

Relationships of coronary calcium prevalence and scores to carotid IMT were somewhat weaker in Blacks than in the other three groups, particularly for coronary calcium prevalence and common carotid IMT in women (as shown in Table 3), and for coronary calcium scores and internal carotid IMT in women and men (Table 4). That this latter ethnic difference was not significant before adjustment for age and sex, and fell only just below the nominal level of $p < 0.05$ after adjustment, may reduce confidence in its verity. Still, the stronger relationship of coronary calcium to internal carotid IMT observed in Hispanics and weaker relationship in Blacks, which remained after adjustment for other risk factors, raise the possibility that coronary calcium and internal carotid IMT may have different predictive value for subsequent events in these groups. Although these differences are modest in magnitude, the precision afforded by the continuous measure of carotid IMT lends credence to their potential value in examining ethnic differences in atherosclerosis prevalence and severity.

Ethnic Differences in Coronary Calcium and Clinically Manifest Coronary Disease

How do these findings aid in understanding the apparent conflict between lower reported frequency and severity of coronary calcium in Blacks compared to Whites and their known higher CHD incidence and mortality [5]? If coronary calcium has the same relationship to atherosclerosis burden, as measured by carotid IMT (and potentially, to CHD events) in Blacks as in other ethnic groups, one would expect to see similar increments in carotid IMT per increment in coronary calcium. If, in contrast, some ethnic-specific factor were somehow preventing deposition of calcium in coronary arteries in Blacks, irrespective of their overall atherosclerotic burden (or at least until some threshold level were reached), one would expect Blacks to have smaller estimated increments in coronary calcium score per increment in carotid IMT, which was generally the case here.

The pathophysiology of coronary calcification is an active area of investigation but ethnic-specific differences have not been widely explored [22]. Coronary calcification, which involves active osteogenesis within the vascular wall [22], is associated with osteoporosis, as is atherosclerosis itself [23], and osteoporosis prevalence differs strongly by ethnicity with the lowest rates found among Blacks [24]. Both osteoporosis and atherosclerosis are linked to inflammation and lipid deposition [25], and lipid deposition has been demonstrated in bone vasculature [26]. Elevated LDL-cholesterol and lower HDL-cholesterol, which are more common in Whites, have been shown to be related to reduced bone density in women [27], and HDL-cholesterol has been shown *in vitro* to inhibit both calcification of osteoblastic cells and osteogenic activity induced by inflammatory cytokines [28].

Could the lower coronary calcium prevalence among Blacks be related to their typically higher HDL-cholesterol levels? Although HDL-cholesterol levels did differ by ethnicity in the current study, levels in Blacks and Whites were not dissimilar, and HDL-cholesterol was included in risk factor adjustments, so this is not a satisfactory explanation. Still, these findings give support for the existence of factors modifying the relationships between atherosclerotic burden, as measured by carotid IMT, and degree of coronary calcification, and for such factors to be ethnic-specific. This may suggest that the lower rates of coronary calcium in Blacks should not necessarily be interpreted as indicating the same low cardiovascular disease risk as minimal coronary calcium appears to indicate in Whites. One wonders if the greater difference in internal carotid IMT by increment in coronary calcium score in Hispanics may also presage a different relationship of coronary calcium to clinical events in this group. Most importantly, one would prefer to identify the underlying factors contributing to these ethnic differences, as race and ethnicity in and of themselves have little biologic meaning [29]. A recent report on White subjects from Portugal, Brazil, and the US, for example, demonstrated significant differences in coronary calcium levels (highest in US subjects) that paralleled geographic differences in cardiovascular mortality rates, despite the US subjects having the lowest prevalence of CHD risk factors [3]. A more complete understanding of the potential clinical importance of these differences can only be obtained when sufficient events have accrued to allow assessment of differences in risk of overt clinical disease.

Limitations and Strengths

The MESA cohort represents a selected group, in that potential participants with overt cardiovascular disease were excluded at entry, making comparisons with other cohorts that include such persons more difficult. In addition, participation rates were not sufficiently high to avoid the potential for bias, though recruitment methods were similar in all four groups. Selection bias is, however, unlikely to affect results in a study of associations [30], particularly when the outcomes under study are subclinical (that is, largely unassociated with signs and symptoms). The high frequency of zero coronary calcium scores, particularly in women, complicates analysis of these data [16]. The use of multiple comparisons, modeling strategies, and adjustment factors weakens confidence in the nominal significance level of $p < 0.05$ employed here, though findings were largely consistent across approaches. Identification of factors potentially responsible for the ethnic differences observed here, such as dietary and lifestyle differences, is beyond the scope of this paper. Lastly, these are cross-sectional data with the potential for differential survival and birth cohort effects among ethnic groups, particularly because of the exclusion of persons with known cardiovascular disease (and likely higher coronary calcium scores and carotid IMT) at entry. On the other hand, the large size, population-based nature, standardized assessment and quality control procedures, and extensive risk factor and subclinical disease characterization in MESA make it an ideal cohort in which to explore ethnic differences in these associations.

Conclusion

Coronary calcium prevalence and scores were associated with carotid IMT in this population-based sample of four ethnic groups, but associations were somewhat weaker in Blacks than in other ethnic groups. These differences should be pursued for relationships to coronary events and to determine whether coronary calcium carries the same risk information in other ethnic groups as it does in Whites.

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Table 1

Atherosclerosis measures (mean or n, %) by ethnicity.

	White N = 2,619	Black N = 1,898	Hispanic N = 1,494	Chinese N = 803	P-value[1]
Carotid Atherosclerosis					
Common Carotid IMT (mm)	0.87	0.91	0.86	0.83	0.0001
Internal Carotid IMT (mm)	1.13	1.11	1.04	0.87	0.0001
Coronary Calcium					
Present (n, %)	1,494 (57)	824 (43)	676 (45)	404 (50)	0.001
Median (>0) (AU[2])	118	73	72	65	0.0001

[1] P-value for analysis of variance or chi-square across four ethnic groups.

[2] AU = Agatston units.

Table 2

Increment in IMT (μm), coronary calcium presence (relative risk, RR) or ln coronary calcium score (AU) per 1-year increment in age, and significance of differences in increments by ethnicity.

	Sex	White	Black	Hispanic	Chinese	P-value [1]
Common carotid IMT (μm)	Both	9.5 [8.8,10.1]	7.7 [6.9,8.5]	8.2 [7.3,9.0]	6.6 [5.4,7.7]	0.0001
Internal carotid IMT(μm) [2]	Women	21.4 [18.7,24.3]	19.5 [16.2,22.8]	17.2 [13.4,20.9]	12.0 [7.0,17.0]	0.01
Internal carotid IMT(μm)	Men	23.9 [20.7,27.2]	16.8 [12.9,20.8]	22.7 [18.5,26.9]	10.1 [4.4,15.8]	0.0001
Coronary calcium prevalence (RR) [2]	Women	1.048 [1.044,1.053]	1.052 [1.045,1.059]	1.051 [1.043,1.059]	1.043 [1.034,1.052]	0.5
Coronary calcium prevalence (RR)	Men	1.024 [1.021,1.027]	1.033 [1.028,1.039]	1.034 [1.029,1.039]	1.025 [1.017,1.032]	0.002
Ln coronary calcium score (>0) [2]	Women	0.073 [0.059,0.087]	0.061 [0.043,0.079]	0.061 [0.040,0.082]	0.050 [0.023,0.077]	0.5
Ln coronary calcium score (>0)	Men	0.080 [0.068,0.092]	0.068 [0.051,0.084]	0.043 [0.26,0.061]	0.043 [0.020,0.066]	0.002

[1] P-value for ethnic differences in atherosclerosis increments by age.

[2] Ethnic differences in atherosclerosis measures by age differ also by sex, $p < 0.05$.

Table 3

Mean values of carotid wall thickness measures by sex, ethnicity and presence of coronary calcium.

	All	White	Black	Hispanic	Chinese	p-value (ethnicity interaction)
Women **N:**	3,557	1,347	1,032	767	411	
Common carotid wall thickness (mm)						0.007
No coronary calcium (n = 2,135)	0.81	0.79	0.86	0.80	0.76	
Any coronary calcium (n = 1,418)	0.91	0.91	0.93	0.90	0.87	
Internal carotid wall thickness (mm)						0.3
No coronary calcium (n = 2,101)	0.87	0.89	0.93	0.83	0.70	
Any coronary calcium (n = 1,391)	1.23	1.27	1.32	1.18	0.98	
Men **N:**	3,213	1,259	845	719	390	
Common carotid wall thickness (mm)						0.6
No coronary calcium (n = 1,236)	0.83	0.82	0.88	0.81	0.79	
Any coronary calcium (n = 1,937)	0.93	0.92	0.98	0.93	0.88	
Internal carotid wall thickness (mm)						0.3
No coronary calcium (n = 1,225)	0.92	0.94	0.97	0.90	0.78	
Any coronary calcium (n = 1,912)	1.28	1.32	1.31	1.31	1.04	

Table 4

Predicted percent increment [95% CI] in carotid IMT per 10% increment in coronary calcium score

Dependent/Independent	White N = 2,619	Black N = 1,898	Hispanic N = 1,494	Chinese N = 803	P-value[2]	Model R^2
Common Carotid IMT/Coronary Calcium Score						
Unadjusted	8.6 [7.2,10.0]	6.0 [4.1, 7.9]	5.0 [2.9, 7.1]	6.7 [3.6, 9.7]	0.005	0.13
Adjusted for Age, Sex[1]	4.1 [2.8, 5.5]	3.2 [1.4, 5.0]	2.2 [0.3, 4.2]	4.6 [1.8, 7.4]	0.3	0.26
Adjusted for risk factors	2.9 [1.5, 4.2]	1.9 [0.1, 3.7]	2.2 [0.2, 4.1]	4.1 [1.4, 6.9]	0.5	0.31
Internal Carotid IMT/Coronary Calcium Score						
Unadjusted	22.0 [18.6, 25.5]	16.3 [11.8, 20.8]	26.6 [21.1, 32.1]	20.5 [13.2, 27.9]	0.08[3]	0.18
Adjusted for Age, Sex[1]	13.6 [10.2, 17.0]	9.9 [5.5, 14.3]	20.6 [15.3, 25.9]	16.8 [9.6, 23.9]	0.046[4]	0.21
Adjusted for risk factors	10.6 [7.3, 14.0]	6.1 [1.9, 10.4]	18.5 [13.3, 23.8]	14.0 [7.1, 20.9]	0.01[5]	0.25

[1] Includes terms for ethnicity by age, and age by coronary calcium score interactions; effects are estimated at mean age of entire cohort.

[2] Tests whether there is a difference in the association of the carotid IMT with coronary calcium by ethnic group using a 6 degree of freedom test for interactions of race with presence of coronary calcium (intercept) and with ln(1 + Agatston score) [slope].

[3] p = 0.036 for difference in slopes by ethnic group.

[4] p = 0.014 for difference in slopes by ethnic group.

[5] p = 0.003 for difference in slopes by ethnic group