Distribution of Coronary Artery Calcium by Race, Gender, and Age
Results from the Multi-Ethnic Study of Atherosclerosis (MESA)

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Background—Coronary artery calcium (CAC) has been demonstrated to be associated with the risk of coronary heart disease. The Multi-Ethnic Study of Atherosclerosis (MESA) provides a unique opportunity to examine the distribution of CAC on the basis of age, gender, and race/ethnicity in a cohort free of clinical cardiovascular disease and treated diabetes.

Methods and Results—MESA is a prospective cohort study designed to investigate subclinical cardiovascular disease in a multiethnic cohort free of clinical cardiovascular disease. The percentiles of the CAC distribution were estimated with nonparametric techniques. Treated diabetics were excluded from analysis. There were 6110 included in the analysis, with 53% female and an average age of 62 years. Men had greater calcium levels than women, and calcium amount and prevalence were steadily higher with increasing age. There were significant differences in calcium by race, and these associations differed across age and gender. For women, whites had the highest percentiles and Hispanics generally had the lowest; in the oldest age group, however, Chinese women had the lowest values. Overall, Chinese and black women were intermediate, with their order dependent on age. For men, whites consistently had the highest percentiles, and Hispanics had the second highest. Blacks were lowest at the younger ages, and Chinese were lowest at the older ages. At the MESA public website (http://www.mesa-nhlbi.org), an interactive form allows one to enter an age, gender, race/ethnicity, and CAC score to obtain a corresponding estimated percentile.

Conclusions—The information provided here can be used to examine whether a patient has a high CAC score relative to others with the same age, gender, and race/ethnicity who do not have clinical cardiovascular disease or treated diabetes. (Circulation. 2006;113:30-37.)

Key Words: arteries ■ calcium ■ epidemiology ■ imaging

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Researchers as to what constitutes high CAC scores in individuals of different gender, ethnicity, and age.

Methods

Study Participants

MESA is designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease in a multiethnic cohort. A detailed description of the study design and methods has been published previously. From 2000 to 2002, 6814 participants 45 to 84 years of age who identified themselves as white, black, Hispanic, or Chinese were recruited from 6 US communities. All participants were free of clinically apparent cardiovascular disease (physician-diagnosed heart attack, angina, stroke, transient ischemic attack, or heart failure; current atrial fibrillation; taking nitrroglycerin; or having undergone angioplasty, coronary artery bypass graft, valve replacement, pacemaker or defibrillator implantation, or any surgery on the heart or arteries). Other exclusions included pregnancy, active treatment for cancer, weight >300

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pounds, cognitive inability as judged by the interviewer, living in a nursing home or on the waiting list for a nursing home, plans to leave the community within 5 years, language barrier (speaks a language other than English, Spanish, Cantonese, or Mandarin), CT scan of the chest within past year, or any serious medical condition that would prevent long-term participation. The communities were Forsyth County, North Carolina; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, Maryland; St Paul, Minn; Chicago, Ill; and Los Angeles County, California. The source population for each field center varies in size and ethnic composition. Each field center developed its sampling frame and recruitment procedures according to the characteristics of its community and available resources, including lists of residents, dwellings, telephone exchanges, Division of Motor Vehicle lists, consumer lists, voter registration lists, and census data. Selection from the sampling frames used simple random samples from the lists and random-digit dialing or proceeded sequentially through predefined neighborhoods. Multiple eligible participants residing in a single household were allowed to participate. Each site recruited an approximately equal number of men and women according to prespecified age and race/ethnicity proportions. All participants gave informed consent. For the present analysis, we excluded subjects with treated diabetes at baseline because this condition is known to be associated with much higher calcium levels. This allows us to estimate CAC percentiles from a cohort that is relatively healthy in terms of their risk factors for CAC.

Measurement of CAC
CAC was measured with either electron-beam computed tomography (EBT) at 3 field centers or multidetector computed tomography (MDCT) at 3 field centers. Each participant was scanned twice consecutively, and these scans were read independently at a centralized reading center. The methodology for acquisition and interpretation of the scans has been documented previously. The results from the 2 scans were averaged to provide a more accurate point estimate of the amount of calcium present. The amount of calcium was quantified with the Agatston scoring method. Calcium scores were adjusted with a standard calcium phantom that was scanned along with the participant. The phantom contained 4 bars of known calcium density. This phantom provides a way of calibrating the degree of brightness between sites and participants. Rescan agreement was found to be high with both EBT and MDCT scanners.

Interobserver agreement and intraobserver agreement were found to be very high (k = 0.93 and 0.90, respectively).

Statistical Analysis
The distribution of baseline CAC in a sample free of clinical cardiovascular disease is heavily skewed, with ~50% of participants having zero calcium. The positive portion of the CAC distribution is fairly symmetric and bell shaped on the log scale. As a first step in obtaining the desired percentiles of the overall distribution, we modeled the mean of the log CAC distribution nonparametrically as a function of age for each gender and race using a local regression smoother with a smoothing span of 0.7. For each observation in the positive log-transformed CAC distribution, we subtract the correlation estimated value. The pooled residuals from this model are then ranked, and we calculate the jth percentile for each of j=1...100 of the residuals. Adding these to the fitted value for a particular age, gender, and race yields an estimated percentile for the log-transformed positive CAC variable (see the article by O’Brien and Dyck for details on this method). The mean of this percentile yields the jth percentile of the positive portion of the CAC distribution. If a certain proportion (p) has zero calcium, then the jth percentile calculated above is the 100×[1−(1−p)j/100] percentile of the overall distribution. We model p as a nonparametric function of age by fitting a local regression smoother within each gender and race. Thus, we estimate the percentiles of the whole distribution as a function of the percentiles of the positive calcium scores, and the process does not involve any parametric assumptions. All calculations were performed with R, version 2.0.1.

A common approach taken in the literature is to categorize age and then calculate the empirical percentiles within each age/gender/race stratum. The nonparametric modeling approach described above has several advantages in that we can consider age as a continuous variable, and by using the pooled residual distribution (after accounting for age, gender, and race), we have substantially more precision to estimate the percentiles. Additionally, we do not use an assumption of a normal distribution in the above calculations, which is important, particularly because the upper percentiles are of primary interest and estimated percentiles derived based on a normal assumption are much better in the central portion of the distribution than in the tails.

As a final analysis, we repeated the percentile estimation on an extremely healthy subset of our MESA cohort. For this purpose, we restricted the analysis to nondiabetics with a 10-year Framingham risk of <10%. For these calculations, the sample sizes were more limited, and we were not able to do race-specific models. Instead, we used a shift model for race (eg, main effect of race only) within each gender. Thus, race effects could be different for men and women but were constant across age.

Results
Table 1 presents the characteristics of our study sample. After exclusion of 704 subjects (680 treated diabetics, 24 with unknown diabetes status), 6110 subjects remained for analysis, with 53% female and an average age of 62 years. The race/ethnicity distribution was balanced across gender by design, with 41% white, 11.8% Chinese-American, 26.4% black, and 20.9% Hispanic. Approximately half the cohort had never smoked, 13% were current smokers, 42.0% had a history of hypertension (defined as diastolic blood pressure >90 mm Hg, systolic blood pressure >140 mm Hg, or use of antihypertensive medications), and 32.4% had dyslipidemia (defined as ratio of total cholesterol to HDL >5.0 or taking a lipid-lowering medication). More than two thirds of subjects were overweight or obese (body mass index >25 kg/m²) according to World Health Organization (WHO) guidelines, 58.7% had a household income below $50 000 per year, and 17% had not completed high school. A greater proportion of women were extremely overweight (5% versus 1.2% for men with body mass index >40 kg/m²).

As previously described, men had higher calcium scores than women, and the amount and prevalence of calcium increased steadily with age. Almost two thirds of women (62%) had calcium scores of zero in this sample, as opposed to 40% of men. Figure 1 displays the probability of a positive CAC score for each gender and race as a function of age. The solid line represents a local regression smoother applied to the raw data. The individual points represent the observed age-specific proportion, with point size reflecting the available sample size at that age (larger points indicate more subjects). Although overall the relationship between the probability of any detectable calcium and age was linear, there were certain gender/race subgroups for which there was discernible nonlinearity. Age relationships for men tended to be concave down (increasing more quickly); for women, they tended to be concave up (increasing more slowly). This was particularly true for white men (who had the highest rate of nonzero calcium) and black or Hispanic women (who had the lowest rate of nonzero calcium). Because neither a linear nor a logistic curve could capture this nonlinearity, a fully nonparametric fit was used. Differences between men and women were greater for whites, particularly in the middle of the age range in which the differences in concavity are most apparent. Hispanic women had the lowest prevalence of nonzero CAC, whereas white women had the highest. Chinese and black women were intermediate, with their order varying, depending
on age. Overall for men, blacks had the lowest prevalence of CAC, although in the highest age group (75 to 84 years), Chinese men had the lowest. Similar to women, white men had the highest prevalence of calcium. White men virtually all had calcium by 80 years of age, whereas 20% of Chinese men were free of calcium at 80 years of age. Hispanic and black men were intermediate, with 10% remaining free of calcium at 80 years of age.

Table 2 displays various estimated percentiles by 10-year age group, gender, and race/ethnicity. For these calculations, the percentile was estimated at the midpoint of the age range. This table underscores the importance of considering race/ethnicity, in addition to age and gender, when interpreting calcium scores.

As Bild et al pointed out, there are significant age-by-ethnicity interactions with respect to calcium score. For women, whites had the highest percentiles and Hispanics generally had the lowest, although again in the oldest age group, the Chinese women had the lowest values. Overall, Chinese and black women were intermediate, with their order dependent on age. For men, whites consistently had the highest percentiles, and Hispanics had the second highest (in contrast to women). Blacks were lowest at the younger ages, and Chinese were lowest at the older ages. For instance, for those 75 to 84 years of age, the estimated percentiles for white men were ~4 times higher than that for Chinese men in the same age range. Further distributional details may be obtained at the MESA public website (http://www.mesa-nhlbi.org), where an interactive form allows
Figures 2 and 3 show the percentile curves for each combination of gender and race/ethnicity as a function of age. Each plot shows the estimated curves for the 50th, 75th, and 90th percentiles of calcium across age. The observed empirical percentiles for each 5-year age interval also appear on the plot for reference. In Figure 4, we provide a set of curves showing a possible upper cut point of calcium distribution. Note that the y axis scales are very different for the 2 genders. With this format, it is easier to compare the races and to determine at a glance what an approximate 90th percentile is for a particular patient. The age interactions are easily visible in this plot. At older ages (above ~70 years of age for men and 75 years of age for women), the Chinese had the lowest values. At younger ages, the lowest values were for Hispanic women and black men. Whites were consistently much higher than the other 3 races.

We explored the question of whether the 2 different types of scanners (EBT and MDCT) result in a similar distribution of CAC scores (data not shown). We found that the estimated percentiles are very similar between EBT and MDCT. Specifically, we looked at quantile-quantile plots within each race, and the results were very linear along $y=x$, indicating that the quantiles for the EBT measurements are very close to the quantiles for MDCT measurements. Additionally, regression models for log calcium as a function of scanner type indicated no large or statistically significant impact of scanner type on average log calcium.

Although we have presented results for phantom-adjusted CAC, these scores are very similar to unadjusted calcium scores and are strongly related to volume scores. In Figure 5, we show a scatter plot of the relationships and accompanying linear regression curve that could be used to approximately calibrate either form of the scale to the phantom-adjusted scale to use our reported percentiles. In virtually all cases, a zero for the CAC volume score or for the unadjusted Agatston score will translate to a zero score after phantom adjustment; hence, these regression lines were estimated only for those with positive scores. For the Agatston score, the observed score could simply be used as though it were a phantom-adjusted CAC score because the line has roughly unit slope with zero intercept. For CAC volume, the observed score should be inflated according to the equation provided.

In Figure 6, we compare our estimated 50th and 90th CAC percentiles with those reported from the recently published Heinz Nixdorf Recall Study, a population-based study con-

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ducted in Germany. These estimates are very comparable for both men and women regardless of age.

Table 3 displays reference values for a very healthy subset of the MESA cohort, specifically nondiabetics with 10-year Framingham risk <10%. This subset consisted of 3586 participants, of whom 1208 (33.7%) had positive CAC scores. Only 917 (26%) of this healthy subset were men. Estimation at the older ages was not possible because of small sample sizes. For women, estimated percentiles were very similar for this healthy subset compared with the general (nondiabetic) MESA population. For men, the percentiles tended to be lower for the healthy subset as expected, although they were actually somewhat higher for Chinese for the 55- to 64-year-old group. Because we were unable to estimate a race-specific model within the healthy subset, information is borrowed from the other races to estimate the age effect.

Figure 2. Estimated percentiles of calcium by age and race/ethnicity for women. Each plot shows the estimated curves for the 50th, 75th, and 90th percentiles of calcium across age. The observed empirical percentiles for each 5-year age interval also appear on the plot (as dots) for reference.

Figure 3. Estimated percentiles of calcium by age and race/ethnicity for men. Each plot shows the estimated curves for the 50th, 75th, and 90th percentiles of calcium across age. The observed empirical percentiles for each 5-year age interval also appear on the plot (as dots) for reference.

Figure 4. Estimated 90th percentile of the CAC distribution by gender, age, and race/ethnicity. Note that the y axis scales for these 2 plots are very different, with the scale for the men >3 times as large as that for the women.

Discussion

MESA provides a unique opportunity to establish age-, gender-, and race/ethnicity-specific percentiles for CAC in a cohort that is free of symptomatic clinical cardiovascular disease and treated diabetes. Unlike most previously published reference studies of CAC, MESA participants are not referred for CAC measurement, and 4 race/ethnic groups are represented. We observed substantial differences among the 4
race/ethnicity groups in terms of CAC distribution, as well as significant interactions of both age and gender with race/ethnicity. These results underscore the importance of factoring race into the estimation of reference ranges for CAC. A previous MESA publication found that overall blacks tended to have the lowest calcium prevalence and levels; however, these analyses were adjusted for a number of other risk factors to understand the independent contributions of race.

The percentiles estimated in MESA for whites are very similar to those recently published from the Heinz Nixdorf Recall Study in Germany. This population-based study excluded subjects with a history of coronary artery bypass surgery, revascularization, or myocardial infarction. They did include 6% diabetics, however, which may have resulted in slightly higher percentiles. Previous studies have presented age- and gender-specific percentiles for asymptomatic subjects using either self-referred or physician-referred patients. Comparing the MESA estimated median and 75th and 90th percentiles with these previous studies (using our estimates for whites) showed that our values were somewhat lower over most of the age range and somewhat higher at the oldest ages (data not shown). Similar findings were reported by Schmermund et al for the Heinz Nixdorf Recall Study; they observed an approximate 5-year shift in CAC values between their population-based study and previously published referral-based studies.

We found no difference in calcium percentiles between EBT and MDCT measurements. In this study, we used phantom-adjusted CAC scores. Each scatter plot has a superimposed linear regression line and corresponding equation. These could be used to approximately calibrate either form of the scale to the phantom-adjusted scale to use our reported percentiles.

Figure 5. Relationship between phantom-adjusted CAC score and (a) unadjusted Agatston CAC score and (b) unadjusted CAC volume score. Each scatter plot has a superimposed linear regression line and corresponding equation. These could be used to approximately calibrate either form of the scale to the phantom-adjusted scale to use our reported percentiles.

Figure 6. Comparability of estimated percentiles from MESA with the Heinz Nixdorf Recall (HNR) Study (MESA estimates are for whites only). The estimated 50th and 90th CAC percentiles obtained for the MESA white subset are compared with those reported from the HNR Study, a comparable population-based study conducted in Germany.
The estimated percentiles obtained on the low-risk subset of MESA (Table 3) can, in some senses, be regarded as target values. For the oldest age groups, there were very few low-risk subjects; hence, percentiles from the whole MESA population are most affected by the survivor bias in the studies, which results in lower-than-expected empirical percentiles. Our approach results in the higher estimated percentiles compared with previous studies at the oldest age range. This approach results in lower-than-expected empirical percentiles. Our smoothing approach provides more realistic estimates for the general population.

The estimated percentiles obtained on the low-risk subset of MESA (Table 3) can, in some senses, be regarded as target values. For the oldest age groups, there were very few low-risk subjects; hence, percentiles from the whole MESA population could be used as the reference values. Even for the lower age groups, the percentiles were quite similar, especially for women, so it may be preferable to simply refer to the whole (non-diabetic) sample estimates (Table 2 and figures) because they are estimated from a larger sample size that permitted race-specific effects. This is not surprising in that traditional cardiovascular risk factors are not strongly predictive of the amount of CAC (given that some calcium is present), despite CAC being a strong predictor of CHD events. In particular, it has been shown that CAC is significantly associated with incident events even after controlling for Framingham Risk Score and hence reflects, to some extent, a different component of the disease process.

Our study has some limitations that should be noted. The MESA sample is not truly a random sample of individuals (subjects were recruited with a variety of methods), and people who agree to participate in research studies generally tend to be healthier overall than the general population. However, the similarity of our estimated percentiles with those from the Heinz Nixdorf Recall study, conducted on a European population, suggests that the results are quite generalizable. Although our ability to estimate the CAC distributions for Chinese participants is unique, only 12% of our cohort was Chinese, so these estimates are more variable than those for the other race/ethnicities. Additionally, there are some differences in scanning methodology between our study and previously published studies. Two scans were obtained and averaged for each participant in MESA, which could increase the prevalence of nonzero calcium compared with obtaining a single scan. The field of view for the MESA scans was 350 mm, which is larger than previous studies, resulting in larger pixels. We also required calcium to be present in 4 adjacent pixels to register as a calcified area, whereas other studies required between 2 and 4 pixels. The combination of these factors implies that the calcium measured following the MESA protocol may tend to be lower than that found in previous studies. Finally, the scanning protocol for MESA was designed for research rather than clinical purposes. Thus, it involved a careful screening out of noise from the images, as well as a high degree of standardization in terms of scanning settings and reading. Scans obtained in a clinical setting may have slightly different properties.

Interpretation of specific calcium scores at this time is a challenging problem. Rumberger et al suggest cut points for CAC based on maximizing sensitivity and specificity for CAC as a predictor of stenosis in a sample of subjects undergoing both angiography and EBCT. Because this is based on patients undergoing angiography, the cut points obtained by such a method will be high and, if used in practice, may miss disease in the low to moderate ranges. Additionally, age, gender, and race were not factored in. Rumberger et al have made additional recommendations for specific cut points for mild, moderate, and severe CAC that have been used frequently in clinical practice. The ACC/AHA Expert Consensus Document states that a zero calcium score makes the presence of atherosclerotic plaque very unlikely and may be consistent with a low risk of a cardiovascular event in the subsequent 2 to 5 years. In contrast, a "high" calcium score indicates greater likelihood of disease and may be consistent with moderate to high risk of a cardiovascular event during that time period.

MESA is an ongoing, prospective cohort study that is systematically obtaining information about cardiovascular events that occur after the baseline examination. Future analyses will determine the predictive power of specific CAC scores and percentiles in the 4 racial/ethnic groups. Raggi et al found that...
age- and gender-specific percentiles were more predictive of incident events than the absolute calcium score. It is currently unknown whether there is also effect modification by race/ethnicity. For example, there is evidence that blacks have higher rates of coronary heart disease events despite having less CAC. If calcium does have a different impact on risk depending on race, then the observed CAC should be evaluated relative to subjects of the same age, gender, and race/ethnicity, as presented here. It is premature to use percentiles from either this study or others to make medical decisions. In other words, at this time, the information presented here cannot necessarily be used to conclude that a patient is “high risk” but can indicate whether they have a high calcium score relative to others with the same age, gender, and race/ethnicity.

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Disclosures

None.

References

11. Acknowledgments

This article provides information that can be used to examine whether a patient has a high CAC score relative to others with the same age, gender, and race/ethnicity.
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