JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2018

PUBLISHED BY ELSEVIER

Coronary Artery Calcium Scores and Atherosclerotic Cardiovascular Disease Risk Stratification in Smokers

MESA

Adam Leigh, MD,[a] John W. McEvoy, MBBCH, MHS,[b] Parveen Garg, MD,[c] J. Jeffrey Carr, MD, MSC,[d] Veit Sandfort, MD,[e] Elizabeth C. Oelsner, MD, MPH,[f] Matthew Budoff, MD,[g] David Herrington, MD, MHS,[a] Joseph Yeboah, MD, MS[a]

ABSTRACT

OBJECTIVES This study assessed the utility of the pooled cohort equation (PCE) and/or coronary artery calcium (CAC) for atherosclerotic cardiovascular disease (ASCVD) risk assessment in smokers, especially those who were lung cancer screening eligible (LCSE).

BACKGROUND The U.S. Preventive Services Task Force recommended and the Centers for Medicare & Medicaid Services currently pays for annual screening for lung cancer with low-dose computed tomography scans in a specified group of cigarette smokers. CAC can be obtained from these low-dose scans. The incremental utility of CAC for ASCVD risk stratification remains unclear in this high-risk group.

METHODS Of 6,814 MESA (Multi-Ethnic Study of Atherosclerosis) participants, 3,356 (49.2% of total cohort) were smokers (2,476 former and 880 current), and 14.3% were LCSE. Kaplan-Meier, Cox proportional hazards, area under the curve, and net reclassification improvement (NRI) analyses were used to assess the association between PCE and/or CAC and incident ASCVD. Incident ASCVD was defined as coronary death, nonfatal myocardial infarction, or fatal or nonfatal stroke.

RESULTS Smokers had a mean age of 62.1 years, 43.5% were female, and all had a mean of 23.0 pack-years of smoking. The LCSE sample had a mean age of 65.3 years, 39.1% were female, and all had a mean of 56.7 pack-years of smoking. After a mean of 11.1 years of follow-up 13.4% of all smokers and 20.8% of LCSE smokers had ASCVD events; 6.7% of all smokers and 14.2% of LCSE smokers with CAC = 0 had an ASCVD event during the follow-up. One SD increase in the PCE 10-year risk was associated with a 68% increase risk for ASCVD events in all smokers (hazard ratio: 1.68; 95% confidence interval: 1.57 to 1.80) and a 22% increase in risk for ASCVD events in the LCSE smokers (hazard ratio: 1.22; 95% confidence interval: 1.00 to 1.47). CAC was associated with increased ASCVD risk in all smokers and in LCSE smokers in all the Cox models. The C-statistic of the PCE for ASCVD was higher in all smokers compared with LCSE smokers (0.693 vs. 0.545). CAC significantly improved the C-statistics of the PCE in all smokers but not in LCSE smokers. The event and nonevent net reclassification improvements for all smokers and LCSE smokers were 0.018 and −0.126 versus 0.16 and −0.196, respectively.

CONCLUSIONS In this well-characterized, multiethnic U.S. cohort, CAC was predictive of ASCVD in all smokers and in LCSE smokers but modestly improved discrimination over and beyond the PCE. However, 6.7% of all smokers and 14.2% of LCSE smokers with CAC = 0 had an ASCVD event during follow-up. (J Am Coll Cardiol Img 2018;■:■–■)

From the [a]Heart and Vascular Center of Excellence, Wake Forest University School of Medicine, Winston Salem, North Carolina; [b]Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland; [c]Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; [d]Departments of Cardiology and Radiology, Vanderbilt University School of Medicine, Nashville, Tennessee; [e]Clinical Center, National Institutes of Health, Bethesda, Maryland; [f]Departments of Medicine and Epidemiology, Columbia University, New York, New York; and the [g]Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles, Torrance California. This research was supported by grant T32HL076132 and contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from the National

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2017.12.017

ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology and American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CVD = cardiovascular disease

CT = computed tomography

LCSE = lung cancer screening eligible

LDL = low-density lipoprotein

NRI = net reclassification improvement

PCE = pooled cohort equation

USPSTF = U.S. Preventive Services Task Force

In 2015, the Centers for Medicare & Medicaid Services published a decision memorandum to pay for annual low-dose computed tomography (CT) of the chest for lung cancer screening in a specified subgroup of cigarette smokers (1). This was followed in 2016 by the U.S. Preventive Services Task Force (USPSTF) recommendations for low-dose CT in smokers who met the Centers for Medicare & Medicaid Services criteria but with an expanded age range (grade B) (2). To be eligible for lung cancer screening according to the Centers for Medicare & Medicaid Services (1), a person must be between the ages of 55 and77 years, have no signs or symptoms of lung cancer, be a current smoker or former smoker who has quit within the last 15 years, and have a tobacco smoking history of at least 30 pack-years. The lung cancer screening recommendation was formulated largely on the basis of results from the NLST (National Lung Screening Trial), which showed a significant reduction in mortality in the low-dose CT arm compared with the chest radiography arm (3,4). The NLST also showed that atherosclerotic cardiovascular disease (ASCVD) was the most common cause of death in the trial, similar to findings in the general population (5,6), and highlighted the need to reduce cardiovascular risk in this subgroup of smokers.

At present, most radiologists provide data on coronary artery calcium (CAC), a marker of subclinical atherosclerosis associated with a heightened risk of ASCVD events (7), qualitatively or quantitatively on the report of this lung cancer screening test. These data often present a dilemma to clinicians in terms of ASCVD risk assessment because the value of CAC in this unique population is understudied. The gold standard for the assessment of CAC is cardiac-gated CT scanning; however, assessments can also be made from nongated CT scans with a high degree of agreement (8–10).

In 2013, the American College of Cardiology and American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol recommended statins for ASCVD risk reduction in 4 main statin benefit groups: patients with prior ASCVD; those with low-density lipoprotein (LDL) cholesterol ≥190 mg/dl; those with diabetes mellitus; and those with a 10-year ASCVD risk calculated using the pooled cohort equation (PCE) ≥7.5% (11). The PCE includes cigarette smoking status as a variable. The ACC/AHA cholesterol guidelines emphasized a patient-clinician dialogue to guide the initiation of statins and also recommended the use of additional markers to improve ASCVD risk assessment and medical decision making, especially when the decision to initiate statins is unclear. The additional markers mentioned included other genetic hyperlipidemias, family history of premature ASCVD, high-sensitivity C-reactive protein levels, lifetime ASCVD risk, ankle-brachial index, and CAC score (11).

The discriminative ability of the PCE in smokers remains unclear, especially in those eligible for lung cancer screening (LCSE), a subgroup of smokers who were shown in the NLST (3,4) trial to have a significantly high cardiovascular risk. It also remains unclear whether CAC (qualitative or quantitative) is as informative for ASCVD risk assessment in smokers, especially LCSE smokers, as has been demonstrated in the general population for primary prevention.

In this study we assessed the discriminative ability of the PCE and the improvement in discrimination afforded by the addition of CAC to the PCE for ASCVD events in smokers and also in the LCSE subgroup of participants who are part of the ongoing MESA (Multi-Ethnic Study of Atherosclerosis) study.

METHODS

STUDY POPULATION AND DATA COLLECTION. A detailed description of the study design for MESA has been published (12). In brief, MESA is a cohort study that began in July 2000 to investigate the prevalence, correlates, and progression of subclinical ASCVD. At baseline, the cohort included 6,814 women and men 45 to 84 years of age who were recruited from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). MESA participants were recruited from 4 specific racial and ethnic groups. In the final sample, 38% were white, 28% were African American, 22% were Hispanic, and 12% were Chinese. Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack or who had undergone an invasive procedure for ASCVD (coronary artery bypass graft,

Center for Research Resources. Dr. Herrington is the principal investigator for grant T32HL076132 from the National Heart, Lung, and Blood Institute. Dr. Budoff has received grant support from the National Institutes of Health and GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 8, 2017; revised manuscript received December 21, 2017, accepted December 23, 2017.

angioplasty, valve replacement, pacemaker placement, or other vascular surgery) were excluded.

Demographics, medical history, and anthropometric and laboratory data for these analyses were obtained at the first MESA examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the past 30 days. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl or use of hypoglycemic medications. Use of antihypertensive and other medications was determined by review of prescribed medication containers. Resting blood pressure was measured 3 times with the participant in a seated position, and the average of the second and third readings was used. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg) / height^2 (m^2). Total cholesterol and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast. LDL cholesterol was estimated by the Friedewald equation. The MESA study was approved by the Institutional Review Boards of each study site, and written informed consent was obtained from all participants.

CIGARETTE SMOKING STATUS. Cigarette smoking status in MESA was collected through a questionnaire administered during the baseline examination. Smoking status and pack-years were assessed by standard American Thoracic Society questionnaire items: "Have you smoked at least 100 cigarettes in your lifetime?"; "How old were you when you first started smoking cigarettes?"; "Have you smoked during the last 30 days?"; "How old were you when you quit smoking cigarettes?"; "On average, about how many cigarettes a day do/did you smoke?". Participants who reported smoking fewer than 100 cigarettes in their lifetime were classified as "never" smokers. Among participants who reported smoking more than 100 cigarettes in their lifetime, those who reported smoking during the last 30 days were classified as "current" smokers and those who did not were classified as "former" smokers. Pack-years of cigarette smoking were calculated from age of starting to quitting (or current age among smokers) times (cigarettes per day / 20). For the purpose of this analysis, participants were excluded if they lacked baseline data on smoking status or the necessary information to use the PCE. We also defined a subsample of smokers as LCSE using the USPSTF criteria, namely: age of 55 to 80 years, no signs or symptoms of lung cancer, current smoker or former smoker who has quit within the last 15 years, and a tobacco smoking history of at least 30 pack-years.

MEASUREMENT OF CORONARY ARTERY CALCIUM SCORE. Details of the MESA CT scanning and interpretation methods have been reported previously (13). Scanning centers assessed CAC by noncontrast cardiac CT with either an electron-beam CT scanner (Chicago, Illinois; Los Angeles, California; and New York, New York field centers) or a multidetector CT system (Baltimore, Maryland; Forsyth County, North Carolina; and St. Paul, Minnesota field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles, Torrance, California). We used the mean Agatston score for the 2 scans in all analyses. Intraobserver and interobserver agreements were $\kappa = 0.93$ and 0.90, respectively.

CAC was used as a continuous variable after log-transformation, ln (CAC + 1). Categorical CAC variables used included the presence or absence of calcium and a 3-level variable (CAC of 0, 1 to 300, and >300). The 3-level variable was determined on the basis of the ACC/AHA recommendations for using CAC >300 as a nontraditional risk factor for upward revision of risk assessment (14).

ASCERTAINMENT OF OUTCOMES IN MESA. The primary outcome was incident ASCVD, which was composed of fatal and nonfatal myocardial infarction, other fatal and nonfatal coronary heart disease, and fatal and nonfatal cerebrovascular disease. Only the first ASCVD event was considered for this analysis. Participants were followed from baseline through December 31, 2012. Follow-up time was defined as the time between the baseline risk score assessment until a diagnosis of ASCVD, loss to follow-up, or end of follow-up. Every 9 to 12 months, participants were contacted by telephone to inquire about interim hospital admissions, cardiovascular diagnoses, procedures, and deaths. Additionally, MESA identified medical encounters through cohort clinic visits, participant call-ins, medical record abstractions, and obituaries.

STATISTICAL ANALYSIS. Demographic, clinical, and CVD risk factor characteristics were reported for MESA participants who were current or former smokers during the baseline examination as well as for the subsample of patients who were deemed to have met eligibility criteria for lung cancer screening. Mean and standard deviations or percentages were reported for continuous and categorical variables, respectively.

Kaplan-Meier analysis was used to assess the association between CAC strata and ASCVD event-free survival and the curves were compared using the

TABLE 1 Demographic and Cardiovascular Risk Factor Distribution of All Smokers LCSE Smokers per the USPSTF

	Total MESA Cohort (N = 6,814)	All Smokers (N = 3,356)	LCSE Smokers (N = 481)	p Value (All Smokers vs. LCSE)
Age, yrs	62.2 ± 10.2	62.1 ± 9.9	65.3 ± 6.9	<0.001*
Female	47.2	43.5	39.1	0.07†
Race or ethnicity				
White	38.4	43.2	49.3	<0.001†
Chinese	11.8	5.9	5.0	
Black	27.8	30.4	32.6	
Hispanics	22.0	20.5	13.1	
BMI, kg/m^2	28.3 ± 5.5	28.5 ± 5.4	28.4± 5.1	0.70*
Cholesterol, mg/dl				
Total	194.2 ± 35.7	192.5 ± 36.1	193.1 ± 38.7	0.74*
LDL	117.2 ± 31.5	116.3 ± 31.5	117.7 ± 34.8	0.37*
HDL	51.0 ± 14.8	50.2 ± 14.9	48.8 ± 14.2	0.053*
Triglycerides	131.6 ± 88.8	132.4 ± 92.4	134.8 ± 74.0	0.59*
Blood pressure, mm Hg				
Systolic	126.6 ± 21.5	126.2 ± 21.1	128.1 ± 20.6	0.06*
Diastolic	71.9 ± 10.3	72.3 ± 10.4	72.3 ± 10.6	0.99*
Cigarette smoking status				
Former	36.6	26.2	45.7	<0.001†
Current	13.1	73.8	54.3	
Pack-years	11.3 ± 20.9	23.0 ± 24.9	56.7 ± 28.1	<0.0001*
Diabetes mellitus	11.3	11.5	15.0	0.03†
Statin use	14.9	15.2	19.3	0.02†
Antihypertensive use	37.2	36.7	40.3	0.13†
ASCVD risk, %	13.5 ± 13.1	14.4 ± 12.8	17.6 ± 11.9	<0.0001*
≥7.5 10-yr risk	56.7	62.1	81.5	<0.0001†
5.0–7.5		12.0	10.4	
≤5.0		26.9	8.1	
CAC				
Agatston score	146.1 ± 417.2	177.1 ± 459.8	282.6 ± 576.0	<0.0001*
CAC = 0	50.1	44.3	27.9	<0.0001†
CAC >0	49.9	55.7	72.1	
CAC 1–300	37.5	40.6	47.6	
CAC >300	12.4	15.1	24.5	

Values are mean ± SD or %. *Student *t* test. †Chi-square test.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; HDL = high-density lipoprotein; LCSE = lung cancer screening eligible; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; USPSTF = U.S. Preventive Services Task Force.

log-rank test. Cox proportional hazards regression analysis was used to assess the association between CAC and incident ASCVD in multivariable models adjusting for the confounders such as age, sex, race or ethnicity, systolic blood pressure, diastolic blood pressure, LDL and high-density lipoprotein cholesterol, body mass index, diabetes mellitus, statin use, antihypertensive medication use, and smoking status. Receiver-operating characteristic curve analysis was used to assess the improvement in discrimination afforded by the addition of CAC to the PCE for ASCVD events in all smokers and LCSE smokers (15). Net reclassification improvement (NRI) analysis (16) was also used to assess the potential for CAC to improve discrimination over and beyond the PCE in individuals classified into low (≤5%), intermediate (5.0% to 7.5%), and high (≥7.5%) ASCVD risk categories on the basis of the clinically determined ASCVD risk cutoffs (11). We additionally eliminated participants who were taking statins (15.2%) at the baseline MESA examination and repeated the foregoing analysis as a sensitivity analyses. A p value of <0.05 was considered significant for all calculations. All statistical analyses were performed using SAS version 9.4 or JMP Pro version 12.0 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 3,356 of 6,814 (49.2%) MESA participants were smokers (2,476 former smokers, 880 current smokers), had complete data, and therefore were included in these analyses. In addition, 481 of 3,356

(14.3%) were LCSE according to the USPSTF criteria for lung cancer screening. After a mean of 11.1 ± 2.9 years of follow-up, 445 of 3,356 (13.4%) of all smokers and 100 of 481 (20.8%) of the LCSE MESA participants had an adjudicated ASCVD event. Only 117 of 3,356 (3.5%) and 20 of 481 (4.2%) of the adjudicated events in all smokers and LCSE smokers were strokes. Thus most of the events that occurred in this cohort were fatal and nonfatal coronary heart disease events.

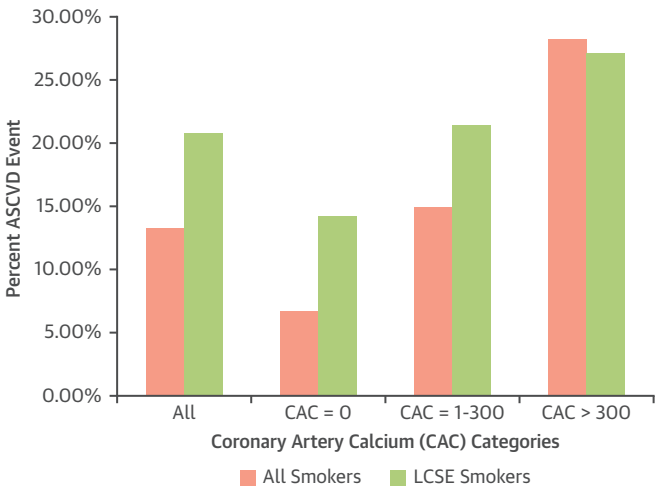
Table 1 shows the demographic, clinical, and CVD risk factors in the total MESA cohort, all smokers, and the LCSE MESA participants. Compared with all smokers, the LCSE participants were older and were more likely to be taking statins, have diabetes mellitus, be current smokers, have higher mean 10-year ASCVD risk score, and have high CAC.

Figure 1 shows the percentage of participants who had an adjudicated ASCVD event by strata of CAC scores during the follow-up period. It should be noted that even though participants in higher CAC categories had a higher percentage of ASCVD events, 6.7% of CAC = 0 participants in all smokers and 14.2% of LCSE CAC = 0 participants had an event during follow-up. **Figure 2** is a display of tertiles of pack-year of cigarette smoking by CAC categories and percentage of ASCVD in smokers in this cohort. Within the strata of CAC = 0 and CAC 1 to 300, higher pack-years of smoking correlated with higher ASCVD events, but in the strata of CAC >300, higher pack-years correlated with fewer events.

On the basis of the statin eligibility criteria of the 2013 ACC/AHA cholesterol guidelines for primary prevention (diabetes mellitus, ASCVD risk ≥7.5%, and LDL ≥190 mg/dl), 397 of 481 (82.5%) of the LCSE participants in our study were eligible. A total of 99 of 397 (24.9%) of the statin-eligible LCSE participants had CAC = 0, and 14 of 99 (20.6%) of the statin-eligible LCSE participants according to the 2013 ACC/AHA cholesterol guidelines who had CAC = 0 had an adjudicated ASCVD event during the follow-up. A total of 89 of 481 (18.5%) of the LCSE participants had a calculated 10-year ASCVD risk (PCE) of 7.5% to 15.0%, so-called intermediate risk. A total of 37 of 89 (41.6%) of the LCSE participants with a PCE of 7.5% to 15.0% had CAC = 0.

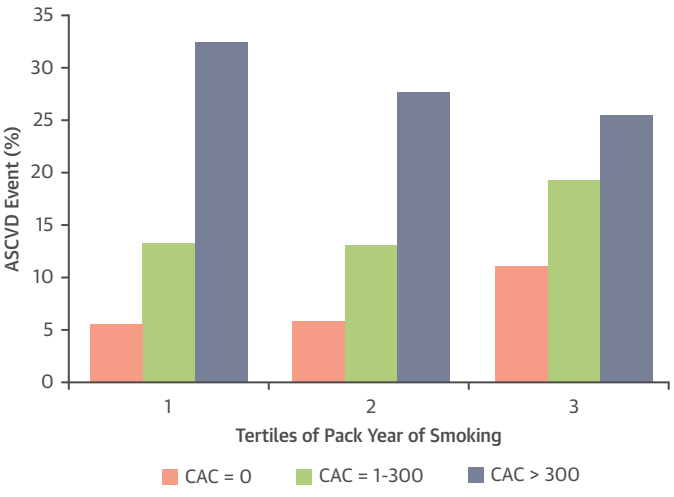
Figures 3A and 3B show the ASCVD event-free survival of all smokers (**Figure 3A**) and the LCSE smokers (**Figure 3B**) over the follow-up period by CAC categories. Compared with smokers with absent CAC, smokers with the presence of CAC, CAC 1 to 300, or CAC >300 had lower ASCVD event-free survival (log-rank $p < 0.01$ for all comparisons). An increase of 1 standard deviation (12.8% for all smokers and 11.9% for LCSE) in the ASCVD score was associated with a 68% increase risk for ASCVD events in all smokers (hazard ratio: 1.68; 95% confidence interval: 1.57 to 1.80) and a 22% increase in risk for ASCVD event in the LCSE smokers (hazard ratio: 1.22; 95% confidence interval: 1.00 to 1.47). CAC was significantly associated with future ASCVD events in all smokers and in LCSE smokers in both univariate and multivariable

FIGURE 1 CAC Categories by ASCVD Events in Smokers



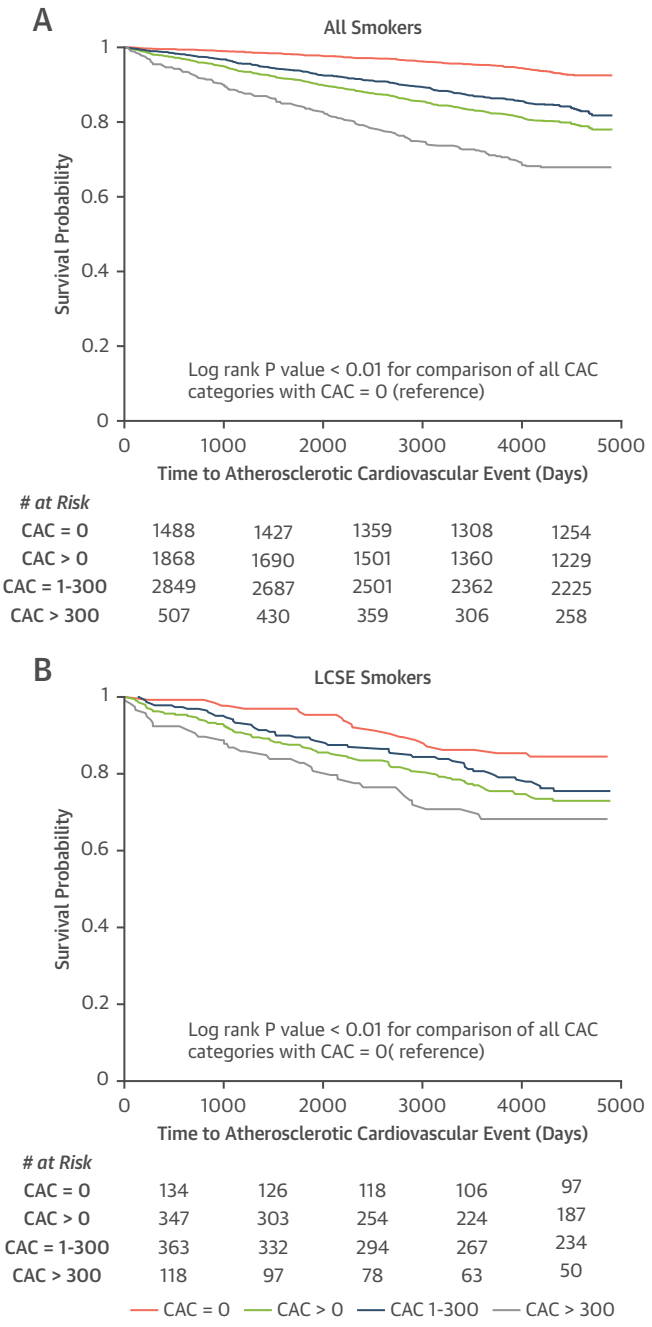
Percentage of all smokers and lung cancer screening eligible (LCSE) smokers within coronary calcium score (CAC) categories with an atherosclerotic cardiovascular disease (ASCVD) event after a mean of 11.1 years of follow-up.

FIGURE 2 Degree of Smoking by CAC Categories and ASCVD Events



Display of tertiles of pack-years of cigarette smoking by coronary artery calcium (CAC) scores categories and atherosclerotic cardiovascular disease (ASCVD) events in MESA (Multi-Ethnic Study of Atherosclerosis).

FIGURE 3 Survival of Smokers by CAC Categories



(A) Survival curves showing the atherosclerotic cardiovascular disease event-free survival of all cigarette smokers with coronary artery calcium (CAC) scores or coronary artery calcium categories and those with coronary artery calcium absent at baseline MESA (Multi-Ethnic Study of Atherosclerosis) examination. **(B)** Survival curves showing the atherosclerotic cardiovascular disease event-free survival of lung cancer screening eligible (LCSE) smokers with coronary artery calcium scores or coronary artery calcium categories and those with coronary artery calcium absent at baseline MESA examination.

Cox models (Table 2). Table 3 is a frequency table of clinically relevant categories of the PCE risk categories and CAC categories in all smokers and those who were LCSE according to the USPSTF guidelines.

The PCE had a significantly higher discriminative ability in all smokers compared with smokers who were LCSE (C-statistics of 0.693 vs. 0.545; p = 0.002, respectively). The addition of ln (CAC + 1) or CAC categories improved the discriminative ability of the PCE for future ASCVD events in all smokers (C-statistics 0.693 vs. 0.717; p = 0.009) but marginally for the subset who were LCSE (C-statistics 0.545 vs. 0.596; p = 0.07) (Online Figures 1 and 2). The Harrell's C-statistic of the PCE and PCE plus ln (CAC + 1) for ASCVD events in all smokers were 0.700 and 0.726, respectively. The Harrell's C-statistic of the PCE and PCE plus ln (CAC + 1) for ASCVD events in the LCSE were 0.557 and 0.619, respectively.

As shown in Table 4 and using the clinically established PCE categories of 0% to 5%, 5% to 7.5%, and ≥7.5%, the event NRIs when ln (CAC + 1) was added to the PCE for all smokers and LCSE smokers were 0.018 and 0.160, respectively. The nonevent NRIs when ln (CAC + 1) was added to the PCE for all smokers and LCSE smokers were −0.126 and −0.196, respectively. Thus CAC improved reclassification in those participants who had events but not in those who did not have events during the follow-up period. Overall, CAC did not improve the net reclassification in all smokers or in those who were LCSE (−0.108 vs. −0.036, respectively).

Our sensitivity analyses eliminating the ~15% of participants who were taking statins during the MESA baseline examination (all smokers N = 2,846; LCSE smokers N = 389) yielded similar point estimates and conclusions, albeit slightly wider confidence intervals (data not shown). For example, of the 389 LCSE smokers not taking statins at baseline, 19.3% had an adjudicated ASCVD event during follow-up, 29.6% had CAC = 0, and 21% of those participants with CAC = 0 had an adjudicated ASCVD event during follow-up.

DISCUSSION

The goal of this study was to examine the discriminative ability of the PCE for ASCVD events and the improvement afforded by the addition of CAC in smokers, particularly those eligible for lung cancer screening according to the USPSTF guidelines. Our study showed that the PCE had good discriminative ability assessed using area under the curve in all

TABLE 2 HRs and 95% CIs of the Association Between CAC Variables and Incident ASCVD Events

	All Smokers		LCSE Smokers	
	Univariate HR (95% CI)	Multivariable* HR (95% CI)	Univariate HR (95% CI)	Multivariable* HR (95% CI)
Ln (CAC + 1)	1.30 (1.25–1.35)	1.19 (1.14–1.24)	1.15 (1.06–1.26)	1.15 (1.06–1.26)
CAC = 0	Reference	Reference	Reference	Reference
CAC >0	3.21 (2.58–4.03)	1.93 (1.51–2.47)	1.91 (1.18–3.23)	1.81 (1.08–3.17)
CAC 1–300	2.47 (1.95–3.15)	1.66 (0.99–2.88)	1.69 (1.31–2.19)	1.65 (0.96–2.94)
CAC >300	5.62 (4.35–7.28)	2.93 (2.18–3.95)	2.48 (1.42–4.45)	2.39 (1.26–4.61)

*Multivariable models were adjusted for age, sex, race or ethnicity, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body mass index, diabetes mellitus, cigarette smoking status, statin use, and blood pressure medication use.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

smokers but modest or poor discriminative ability in the subsample of participants who were LCSE. The addition of CAC significantly improved the discrimination of the PCE in all smokers but marginally (nonsignificant) in the LCSE subsample. In the NRI analysis, CAC improved the discriminative ability of the PCE in smokers or LCSE smokers who had events but not in those who did not have events during the follow-up period.

The USPSTF recommends screening for those who meet the Medicare criteria but are 55 to 80 years of age (grade B) (2). These recommendations were formulated largely on the basis of results from the NLST, a randomized, double-blind study that compared survival of smokers who were screened for lung cancer with either annual chest radiography or low-dose CT (3,4). The primary result of the NLST study showed a 20% reduction in lung cancer mortality in the low-dose CT arm compared with study subjects who underwent chest radiography. However, it was observed that for the entire study, ASCVD was the most common cause of death (24.8%). Thus a significant need exists to assess ASCVD risk in this population more accurately and to target lifestyle changes and therapeutics more effectively to reduce this heightened risk in this subgroup of smokers.

Limited data exist on the value of CAC assessed using nongated low-dose CT scans for ASCVD risk assessment (17–23). Jacobs et al. (19) used data from a Dutch-Belgian randomized lung cancer screening trial (NELSON) to show that Agatston scores of CAC measured from low-dose CT scans performed for lung cancer screening were predictive of all-cause mortality and ASCVD events (17,19,22,23). Using the NLST data, Chiles et al. (18) used a case-cohort design to examine the relationships among multiple CAC scoring methods, coronary heart disease mortality, and all-cause mortality. These investigators showed that overall subjective assessment of CAC, coronary artery segment CAC totals, and Agatston score-based strata of CAC were all associated with coronary heart disease death and all-cause mortality (18). Sverzellati et al. (21) used data from the MILD (Multicentric Italian Lung Detection) trial to show that modified CAC from low-dose CT scans is a better predictor of cardiovascular events and all-cause mortality than forced expiratory volume in 1 s and emphysema extent and may contribute to the identification of high-risk individuals in a lung cancer screening setting.

TABLE 3 Frequency Table of PCE Risk Categories and CAC Categories in All Smokers and LCSE Smokers per the USPSTF Guidelines

PCE Risk Category: All Smokers, %	CAC = 0 (n = 1,488)	CAC >0 (n = 1,868)	CAC 1-300 (n = 1,363)	CAC >300 (n = 505)
0–5.0 (n = 872)	641 (73.5)	231 (26.5)	211 (24.2)	20 (5.7)
5.0–7.5 (n = 402)	195 (48.5)	207 (51.5)	183 (45.5)	24 (6.0)
>7.5 (n = 2,082)	652 (31.3)	1,430 (68.7)	969 (46.5)	461 (22.1)
PCE Risk Category: LCSE Smokers, %	**CAC = 0 (n = 134)**	**CAC >0 (n = 347)**	**CAC 1-300 (n = 229)**	**CAC >300 (n = 118)**
0–5.0 (n = 39)	17 (43.6)	22 (56.4)	21 (53.8)	1 (2.6)
5.0–7.5 (n = 50)	20 (40.0)	30 (60.0)	25 (50)	5 (10.0)
>7.5 (n = 392)	97 (24.7)	295 (75.3)	183 (46.7)	112 (28.6)

Values are n (%).

PCE = pooled cohort equation; other abbreviations as in Table 1.

TABLE 4 Net Reclassification Improvement Afforded by the Addition CAC Scores to the PCE for All Smokers and LCSE Smokers

	Risk Category			Reclassified (%)		Net Correct Reclassified (%)	NRI
	Low	Intermediate	High	Down	Up		
All smokers							
Events				10.6	12.4	1.8	−0.108
PCE alone	31	32	382	–	–	–	
PCE + [ln CAC + 1]	8	58	379	–	–	–	
No Events				19.7	32.3	−12.6	
PCE alone	841	370	1,700	–	–	–	
PCE + [ln CAC + 1]	301	938	1,672	–	–	–	
LCSE smokers							
Events				0	16.0	16.0	−0.036
PCE alone	5	11	84	–	–	–	
PCE + [ln CAC + 1]	0	0	100	–	–	–	
No Events				0	19.2	−19.6	
PCE alone	34	39	308	–	–	–	
PCE + [ln CAC + 1]	0	0	318	–	–	–	

Values are n, %, and NRI.

NRI = net reclassification improvement; other abbreviations as in Tables 1 and 3.

Shemesh et al. (20) used CAC quantified from low-dose CT scans from 8,782 men and women at high risk for lung cancer in New York State to show that ordinal CAC scoring is predictive of death from cardiovascular disease (CVD). These studies (17-23) were, however, limited by the paucity of CVD risk factor profile and nonfatal ASCVD event information collected. In addition, the limited reporting of CVD risk factor profile in these studies or clinical trials made it impossible for the investigators to assess the clinical utility of CAC over and above current risk scores as recommended by current guidelines (11).

The present study used a well-characterized but relatively small cohort of population-based adults to show that LCSE status identifies a high-risk subset of smokers whose PCE may have significant limitations for ASCVD risk assessment. Even though CAC showed a trend toward improving the C-statistics of the LCSE subgroup in this analysis, the overall C-statistics of PCE plus CAC were still modest or poor. Our study needs replication in larger cohorts but will support treating the current LCSE smokers according to the USPSTF recommendation as high risk and therefore statin eligible, possibly to reduce the high observed risk found in the NLST study.

Current data (24-27) suggest that individuals with CAC = 0 have a low risk for future ASCVD, and therefore some investigators have suggested the use of CAC = 0 as a tool for reducing the overestimation of risk and the high statin eligibility associated with the 2013 ACC/AHA cholesterol guidelines (11). In the present analysis, 6.7% of all smokers and 14.2% of LCSE smokers with CAC = 0 at baseline had an adjudicated ASCVD event during the follow-up period. A total of 25% of the LCSE smokers who were statin eligible according to the 2013 ACC/AHA cholesterol guidelines for primary prevention and 41.6% of the LCSE smokers with a calculated 10-year ASCVD risk of 7.5% to 15.0% (intermediate risk) had CAC = 0. Moreover, 21% of the LCSE participants who were eligible for statin therapy according to the 2013 ACC/AHA cholesterol guidelines and CAC = 0 had an adjudicated ASCVD event during follow-up. Thus the notion that CAC = 0 implies minimal ASCVD risk may not be applicable in all populations for primary ASCVD risk assessment and should be tempered in smokers (28), especially in those who are LCSE according to the USPSTF recommendations.

Our findings, if confirmed in larger cohorts, will have significant implications for the estimated 9 million Americans who are LCSE annually according to the USPSTF recommendations (2,3). Larger studies on the observed ASCVD risk in smokers, especially in those smokers who are LCSE according to the USPSTF recommendations, are needed.

STUDY LIMITATIONS. First, in the MESA study, all CT scans used in this analysis were performed using electrocardiographic gating. Although this is the preferred method for a detailed assessment of CAC, nongated protocols are used in the low-dose CT scans performed for lung cancer screening. Even though the difference in protocol is significant, there is a wealth of evidence showing a high degree of concordance between gated and nongated scans (8-10). In addition, we also assessed categories of CAC that may mirror the qualitative reporting of CAC and found

similar results. The sample size of our LCSE subgroup was relatively small (n = 481) and may have affected the results and conclusions. However, this small subgroup is the best characterized sample so far used to answer this important question. Approximately 15% of our cohort was taking statins at baseline, and it is plausible that even more patients may have been prescribed statins during the follow-up period. Our sensitivity analyses suggest similar findings and conclusions when those patients taking statins at baseline are eliminated, but these analyses do not account for those patients who were not taking statins at baseline but may have been prescribed statins during follow-up. Nonetheless, statin use reduces ASCVD events, and hence the significantly high ASCVD event rate observed in the LCSE subsample (or all smokers) is likely an underestimation. This likely underestimation of the observed ASCVD events in our study coupled with the high ASCVD event rate in those participants with CAC = 0 supports the notion that LCSE status should be considered a statin eligibility criterion. More studies using larger, well-characterized LCSE cohorts are needed. This is an observational study, and so our results may reflect residual confounding.

CONCLUSIONS

CAC is a predictor of future ASCVD events in all smokers and in LCSE smokers in this multiethnic study. The USPSTF-recommended lung cancer screening eligibility criteria identify a subgroup of smokers with high ASCVD risk who may warrant statin eligibility. The discriminative ability of the PCE was good in all smokers but poor in LCSE smokers. The addition of CAC to the PCE modestly or poorly improved the discriminative ability for future ASCVD events in our cohort. Additional, larger studies are needed to assess the observed ASCVD risk and the utility of the PCE and the PCE combined with the CAC in individuals who are LCSE according to the USPSTF lung cancer screening guidelines.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

ADDRESS FOR CORRESPONDENCE: Dr. Joseph Yeboah, Heart and Vascular Center of Excellence, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157. E-mail: jyeboah@wakehealth.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The addition of CAC scores to the PCE in smokers who are LCSE by the USPSTF poorly improved discrimination for ASCVD events. Statins or other lipid-lowering therapy should be considered in all LCSE smokers irrespective of their calculated 10-year ASCVD risk or CAC score, to reduce the high rate of observed ASCVD events in the NLST. Absence of CAC should not be used to downgrade ASCVD risk in smokers who are LCSE according to the USPSTF recommendations.

TRANSLATIONAL OUTLOOK: Our study results need further validation in other, larger prospective cohorts but suggest that the current recommended approach for 10-year ASCVD risk assessment including the use of CAC scores may not be adequate in persons who are LCSE. Their very high 10-year ASCVD risk demonstrated in this study and also in the NLST trial should be an active area of further research.

REFERENCES

1. Centers for Medicare & Medicaid Services. Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT). 2015. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274. Accessed January 11, 2018.

2. US Preventive Services Task Force. Final Recommendation Statement: Lung Cancer: Screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lung-cancer-screening. Accessed December 7, 2016.

3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

4. National Lung Screening Trial Research Team, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013;368:1980–91.

5. Mozaffarian D, Benjamin EJ, Go AS, et al. heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.

6. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004;43:1731–7.

7. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.

8. Isgum I, Prokop M, Niemeijer M, Viergever MA, van Ginneken B. Automatic coronary calcium scoring in low-dose chest computed tomography. IEEE Trans Med Imaging 2012;31:2322–34.

9. Htwe Y, Cham MD, Henschke CI, et al. Coronary artery calcification on low-dose computed tomography: comparison of Agatston and ordinal scores. Clin Imaging 2015;39:799–802.

10. Arcadi T, Maffei E, Sverzellati N, et al. Coronary artery calcium score on low-dose computed tomography for lung cancer screening. World J Radiol 2014;6:381–7.

11. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American

College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am Coll Cardiol 2014;63:2889–934.

12. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.

13. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005; 234:35–43.

14. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935–59.

15. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44: 837–45.

16. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27: 157–72.

17. Mets OM, Vliegenthart R, Gondrie MJ, et al. Lung cancer screening CT-based prediction of cardiovascular events. J Am Coll Cardiol Img 2013; 6:899–907.

18. Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. Radiology 2015;276: 82–90.

19. Jacobs PC, Prokop M, Van der Graaf Y, et al. Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers. Atherosclerosis 2010;209:455–62.

20. Shemesh J, Henschke CI, Shaham D, et al. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. Radiology 2010;257:541–8.

21. Sverzellati N, Cademartiri F, Bravi F, et al. Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial. Radiology 2012;262:460–7.

22. Jacobs PC, Gondrie MJ, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events in low dose CT screening for lung cancer. AJR Am J Roentgenol 2012;198:505–11.

23. Takx RA, Isgum I, Willemink MJ, et al. Quantification of coronary artery calcium in nongated CT predicts cardiovascular events in male lung cancer participants: results of the NELSON study. J Cardiovasc Comput Tomogr 2015;9:50–7.

24. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J 2017; 38:598–608.

25. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66: 1657–68.

26. Martin SS, Blaha MJ, Blankstein R, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation 2014;129: 77–86.

27. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Association between hsCRP≥2, coronary artery calcium, and cardiovascular events—implications for the JUPITER population: Multi-Ethnic Study of Atherosclerosis (MESA). Lancet 2011;378: 684–92.

28. McEvoy JW, Blaha MJ, Rivera JJ, et al. Mortality rates in smokers and nonsmokers in the presence or absence of coronary artery calcification. J Am Coll Cardiol Img 2012;5:1037–45.

KEY WORDS atherosclerotic cardiovascular disease, cigarette smokers, coronary artery calcium, pooled cohort equation

APPENDIX For supplemental figures, please see the online version of this paper.