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

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Abstract

Objective—We assess 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 eligible for lung cancer screening.

Background—The U.S. Preventive Service Task Force (USPSTF) recommended and the Center for Medicare and Medicaid currently pays for annual screening for lung cancer with low-dose computer tomography in a specified group of cigarette smokers. CAC can be obtained from these low dose CT scans. The incremental utility of CAC for ASCVD risk stratification remains unclear in this high risk group.

Methods—Of 6814 Multi-Ethnic Study of Atherosclerosis (MESA) participants 3,356 (49.2% of total cohort) were smokers (2,476 former and 880 current) and 14.3% were lung cancer screening eligible (LCSE). Kaplan Meier, Cox proportional hazard, AUC and net reclassification improvement (NRI) analyses were used to assess the association between PCE and or CAC and

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incident ASCVD. Incident ASCVD defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke.

Results—Smokers had a mean age of 62.1 years, 43.5% were females, and had a mean of 23.0 pack-years of smoking. The LCSE sample had a mean age of 65.3 years, 39.1% female, and had a mean of 56.7 pack-years of smoking. After a mean of 11.1 years of follow-up 13.4% of smokers and 20.8% of LCSE had ASCVD events. 6.7% of all smokers and 14.2% of LCSE smokers with CAC=0 had an ASCVD events during the follow up. One standard deviation increase in the PCE 10yr. risk was associated with a 68% increase risk for ASCVD events in all-smokers [HR (95% CI): 1.68(1.57–1.80)] and a 22% increase in risk for ASCVD event in the LCSE smokers [HR (95%): 1.22(1.00–1.47)]. CAC was associated with increased ASCVD risk in all-smokers and LCSE in all the Cox models. The C-statistic of the PCE for ASCVD was higher in all-smokers compared with LCSE (0.693 vs. 0.545). CAC significantly improved the C-statistics of the PCE in all-smokers but not in LCSE. The event and non-event NRI for all smokers and LCSE were: 0.018 and −0.126 vs. 0.16 and −0.196, respectively.

Conclusion—In this well-characterized multi-ethnic US cohort, CAC was predictive of ASCVD in all-smokers and LCSE but modestly improve discrimination over and beyond the PCE. However, 6.7% of all-smokers and 14.2% of LCSE with CAC=0 had an ASCVD event during follow up.

Keywords

Cigarrete smokers; coronary artery calcium; atherosclerotic cardiovascular disease; Pooled Cohort Equation

Introduction

In 2015, the Center for Medicare and Medicaid Services (CMS) published a decision memo paying for annual low dose computed tomography 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 computed tomography in smokers who met the CMS criteria but with an expanded age range (Grade B)[2]. In order to be eligible for lung cancer screening per the CMS[1] , a person must be between the ages of 55–77, 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 based largely on the results from the National Lung Screening Trial (NLST) which showed a significant reduction in mortality in the low dose computed tomography 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 the general population[5,6] and highlighted the need to reduce cardiovascular risk in this subgroup of smokers.

Presently most radiologists provide data on coronary artery calcium (CAC), a marker of subclinical atherosclerosis associated with heightened risk of ASCVD events[7], qualitatively or quantitatively on the report of this lung cancer screening test. These data often presents a dilemma to clinicians in terms of ASCVD risk assessment since the value of CAC in this

unique population is understudied. The gold standard for the assessment of CAC is via cardiac gated computed tomography (CT) scanning however assessments can also be made from non-gated CT scans with a high degree of agreement.[8–10]

In 2013, the ACC/AHA guidelines on the treatment of blood cholesterol recommended statins for ASCVD risk reduction in 4 main statin benefit groups: those with prior ASCVD, low-density lipoprotein (LDL) cholesterol ≥ 190mg/dl, diabetes mellitus and those with a 10yr. 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 recommends the use of additional markers to improve ASCVD risk assessment and medical decision making, especially in individuals in whom 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 for lung cancer screening(LCSE), a subgroup of smokers who have been shown in the NLST[3,4] trial to have a significantly high cardiovascular risk. It also remains unclear if CAC (qualitative or quantitative) is as informative for ASCVD risk assessment in smokers especially those LCSE similar to that demonstrated in the general population for primary prevention. In this report we assess 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 but also in the LCSE subgroup of participants who are part of the ongoing Multi Ethnic Study of Atherosclerosis (MESA).

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 age 45 to 84 years 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 four specific race 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 (TIA) or who had undergone an invasive procedure for ASCVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) 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 based on the review of prescribed medication containers. Resting blood pressure was measured 3 times in a seated position, and the average of the second and third readings was used. Hypertension was defined as a systolic blood pressure(SBP) ≥140 mm Hg, diastolic blood pressure(DBP) ≥90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height^2 (m^2). Total and high-density lipoprotein(HDL) cholesterol were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein(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 via 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 greater 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) X (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 define a sub-sample of smokers as LCSE using the USPSTF criteria namely: ages of 55–80, 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.

Measurement of Coronary Artery Calcium (CAC) score

Details of the MESA CT scanning and interpretation methods have been reported previously[13]. Scanning centers assessed CAC by non-contrast 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 absense of calcium and a three-level variable (CAC of 0, 1–300, and >300). The three-level variable was based on the ACC/AHA recommendations for using CAC >300 as a non-traditional 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 non-fatal myocardial infarction, other fatal and non-fatal coronary heart disease, fatal and non-fatal 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 9–12 months, participants were contacted via 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 exam as well as the sub-sample who were deemed to have met eligibility criteria for lung cancer screening. Mean and standard deviation or percent 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 compared using log rank test. Cox proportional hazard regression analysis was used to assess the association between CAC and incident ASCVD in multivariable models adjusting for the confounders such as age, gender, race / ethnicity, SBP, DBP, LDL & HDL cholesterol, body mass index, diabetes mellitus, statin use, antihypertensive medication use and smoking status. Receiver operator curve (ROC) 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) [16] analysis was also used to assess the potential for CAC to improve discrimination over and beyond the PCE in individuals classified into low (≤ 5%), intermediate(5–7.5%), and high(≥ 7.5%) ASCVD risk categories based on the clinically determined ASCVD risk cut –offs.[11] We additionally eliminated participants who were on statins(15.2%) at the baseline MESA exam and repeated the above 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, NC).

Results

A total of 3,356/6814(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, 481/3356 (14.3%) were LCSE per the USPSTF criteria for lung cancer screening. After a mean of 11.1 ±2.9 years of follow up, 445/3356(13.4%) of all- smokers and 100/481(20.8%) of the LCSE MESA participants had an adjudicated ASCVD event. Only 117/3356(3.5%) and 20/481(4.2%) of the adjudicated events in all smokers and LCSE smokers were strokes. Thus majority of the events that occurred in this cohort were fatal and non-fatal 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, were more likely to be on statins, have diabetes mellitus, be current smokers, have higher mean 10 year ASCVD risk score and have high CAC.

Figure 1 shows the percent 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 percent of ASCVD events, 6.7% of CAC=0 participants in all-smokers and 14.2% of LCSE CAC=0 participants had an event during the follow up. Figure 2 is a display of tertiles of pack year of cigarette smoking by CAC categories and percent ASCVD in smokers in this cohort. Within the strata of CAC=0 and CAC 1–300, higher pack-years of smoking correlated to higher ASCVD events, but in the strata of CAC>300, higher pack-years correlated to fewer events

Based on 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), 397/481(82.5%) of the LCSE participants in our study were eligible. 99/397(24.9%) of the statin eligible LCSE had CAC=0 and 14/99(20.6%) of the statin eligible LCSE per the 2013 ACC/AHA cholesterol guidelines who had CAC= 0 had an adjudicated ASCVD event during the follow up. 89/481 (18.5%) of the LCSE had calculated 10yr ASCVD risk (PCE) 7.5–15%, the so called “ intermediate risk”. 37/89(41.6%) of the LCSE with PCE 7.5–15% had a CAC = 0. Figure 3(A & B) shows the ASCVD event-free survival of all –smokers (3A) and the LCSE smokers (3B) over the follow up period by CAC categories. Compared with smokers with absent CAC, smokers with the presence of CAC, CAC 1–300 or CAC > 300 had lower ASCVD event -free survival (Log rank $p < 0.01$ for all comparisons). One standard deviation increase(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 [HR (95% CI): 1.68(1.57–1.80)] and a 22% increase in risk for ASCVD event in the LCSE smokers [HR (95%): 1.22(1.00–1.47)]. CAC was significantly associated with future ASCVD events in all smokers and in LCSE smokers in both univariate and multivariable Cox models (Table 2). Table 3 is a frequency table of clinically relevant categories of the Pooled Cohort Equation risk categories and CAC categories in all smokers and those eligible for lung screening per the USPSTF guidelines.

The PCE had a significantly higher discriminative ability in all-smokers compared with those 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) (Supplemental Figure I&II). The Harrell’s C statistic of the PCE and PCE + 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 + 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 0–5, 5–7.5% and ≥ 7.5%, the event NRI when ln (CAC+1) was added to the PCE for all smokers and LCSE smokers were 0.018 and 0.160 respectively. The non-event NRI when ln (CAC + 1) was

added to the PCE for all- smokers and LCSE were −0.126 and −0.196 respectively. Thus CAC improved reclassification in those who had events but not in those who did not have events during the follow up period. Overall CAC did not improvement the net reclassification in all smokers and those who were LCSE(−0.108 vs. −0.036 respectively).

Our sensitivity analyses eliminating the ~15% of participants who were taking statin during the MESA baseline exam(All smokers N= 2846; LCSE N=389) yielded similar point estimates and conclusions albiet slightly wider confidence intervals(data not shown). For example out of the 389 LCSE smokers not on statins at baseline,, 19.3% had an adjudicated ASCVD events during the follow up, 29.6% had CAC=0, 21% of those 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 per the USPSTF guidelines. Our study showed that the PCE has a good discriminative ability assessed using AUC in all smokers but modest/poor in the sub-sample of participants who were LCSE. The addition of CAC significantly improved the discrimination of the PCE in all –smokers but marginally (non-significant) in the LCSE sub-sample. In the NRI analysis, CAC improved the discriminative ability of the PCE in smokers/LCSE who had events but not in those who did not have events during the follow up period.

The U.S. Preventive Services Task Force recommends screening for those who meet the Medicare criteria but aged 55–80 (Grade B)[2]. These recommendations were based largely on results from the NLST, a randomized double blind study which compared survival of smokers who were screened for lung cancer with either annual chest radiography or low dose computed tomography[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 those 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 better assess ASCVD risk in this population and to better target lifestyle changes and therapeutics to reduce this heightened risk in this subgroup of smokers.

Limited data exist on the value of CAC assessed from non gated low dose CT scans for ASCVD risk assessment [17–23]. Jacobs et al used data from a Dutch-Belgian randomized lung cancer screening trial (NELSON) to show that Agatston scores of CAC measured from low dose CTscans 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 used a case-cohort design to examine the relationship between multiple CAC scoring methods, coronary heart disease mortality and all – cause mortality.[22] The authors showed that overall subjective assessment of CAC, coronary artery segment CAC totals and Agatson scores based strata of CAC were all associated with coronary heart disease death and all-cause

mortality.[22] Sverzellati et al used data from the Multicentric Italian Lung Detection (MILD) trial to show that modified CAC from low dose CT scans is a better predictor of cardiovascular events and all-cause mortality than FEV1 and emphysema extent and may contribute to the identification of high risk individuals in a lung cancer screening setting.[21] Shemesh et al used CAC quantified from low dose CT scans from 8782 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.[20] These studies[17–23] were however limited by the paucity of cardiovascular disease risk factor profile and non-fatal ASCVD events information collected in the studies/trials. In addition, the limited reporting of CVD risk factor profile in these studies/ clinical trials made it impossible for the authors to assess the clinical utility of CAC over and above current risk scores as recommended by current guidelines[11]. The presented study used a well characterized but relatively small cohort of population based adults to show that; LCSE identifies a high risk subset of smokers in whom the PCE may have significant limitations for ASCVD risk assessment. Even though CAC showed a trend towards improving the C-statistics of the LCSE subgroup in this analysis, the overall C-statistics of PCE+ CAC was still modest/poor. Our study needs replication in larger cohorts but will support treating the current LCSE smokers per the USPSTF recommendation as high risk and therefore statin eligible to possibly reduce the high observed risk found in the NLST study.

Current data suggests[24–27] that individuals with CAC of zero have a low risk for future ASCVD and therefore some authors 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. Twenty-five percent(25%) of the LCSE who were statin eligible per the 2013 ACC/AHA cholesterol guidelines for primary prevention and 41.6% of LCSE with calculated 10year ASCVD risk 7.5–15%(intermediate risk) had CAC=0. Moreover 21% of the LCSE participants who were eligible for statin therapy per the 2013 ACC/AHA cholesterol guidelines and CAC=0 had an adjudicated ASCVD event during follow up. Thus the notion that CAC = zero 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 per the USPSTF recommendations. Our findings if confirmed in larger cohorts will have significant implications for the estimated 9 million Americans eligible for lung cancer screening annually per the USPSTF recommendations.[2,3] Larger studies on the observed ASCVD risk in smokers especially in those LCSE per the USPSTF recommendations are needed.

Our study has several limitations. First, in the MESA study, all CT scans used in this analysis were performed using ECG-gating. While this is the preferred method for a detailed assessment of CAC, non-gated protocols are used in the low dose CTs performed for lung cancer screening. While the difference in protocol is significant, there is a wealth of evidence showing high degree of concordance between gated and non-gated scan.[8–10] In addition we also assessed categories of CAC which 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 most well characterized sample so far used to assess this important question. Approximately 15% of our cohort were on statins at baseline and it is plausible that even more may have been prescribed statins during the follow up period. Our sensitivity analyses suggest similar findings and conclusions when those on statins at baseline are eliminated but does not account for those not on statins at baseline but may have been prescribed statins during the follow up. Nonetheless statin use reduces ASCVD events and hence the significantly high ASCVD event rate observed in the lung cancer screening eligible sub-sample (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 with CAC =0 supports the notion that LCSE should be considered a statin eligibility criteria. More studies using larger well characterized LCSE cohorts are needed. This is an observational study and so our results may be due to residual confounding.

Conclusion

CAC is a predictor of future ASCVD events in all smokers and LCSE smokers in this multi –ethnic study. The USPSTF recommended lung cancer screening eligibility criteria identify a subgroup of smokers with high ASCVD risk which 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/poorly improved the discriminative ability for future ASCVD events in our cohort. Additional larger studies assessing the observed ASCVD risk, utility of the PCE, PCE + CAC in individuals eligible lung cancer screening per the USPSTF lung cancer screening guidelines are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CMS	Center for Medicare and Medicaid Services
USPSTF	United States Preventive Service Task Force
LCSE	Lung cancer screening eligible
CAC	Coronary artery calcium
PCE	Pooled Cohort Equation

ASCVD Atherosclerotic Cardiovascular disease

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Perspectives

Competency in Medical Knowledge

1. The addition of coronary artery calcium(CAC) scores to the PCE in smokers eligible for the lung cancer screening by the USPSTF poorly improved discrimination for ASCVD events
2. Statins/lipid lowering therapy should be considered in all smokers eligible for lung cancer screening irrespective of their calculated 10 year ASCVD risk or CAC score in order to reduce the high observed ASCVD events in the National Lung Screening Trial (NLST).
3. Absence of CAC should not be used to downgrade ASCVD risk in smokers eligible for lung cancer screening per the USPSTF recommendations.

Translational Outlook

Our study results needs further validation in other larger prospective cohorts but suggests the current recommended approach for 10 year ASCVD risk assessment including the use of coronary calcium scores may not be adequate in persons eligible lung cancer screening. 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.

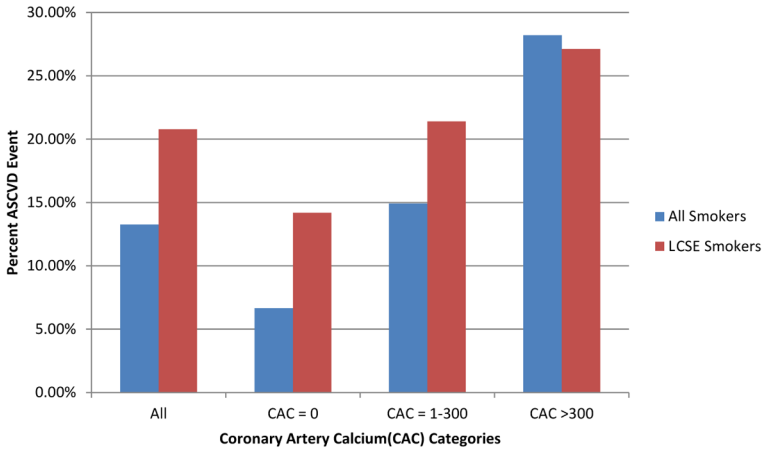


Figure 1. CAC categories by ASCVD events in smokers

Percent of all smokers and lung cancer screening eligible smokers within coronary calcium score categories with Atherosclerotic Cardiovascular Disease event after a mean of 11.1 years of follow up.

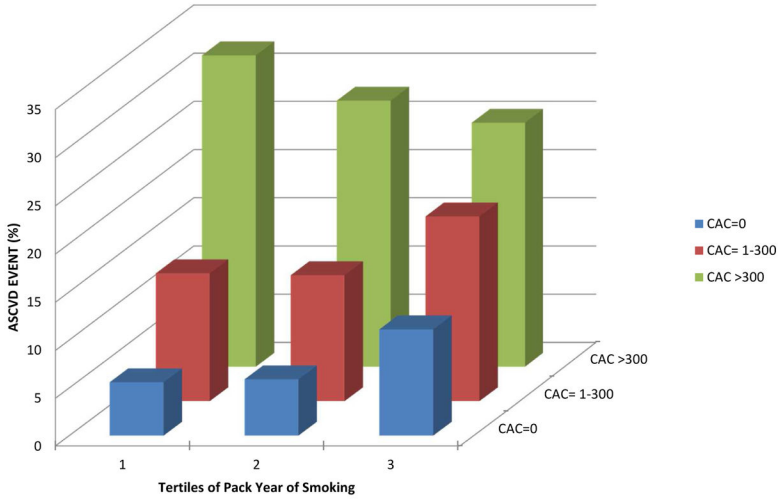
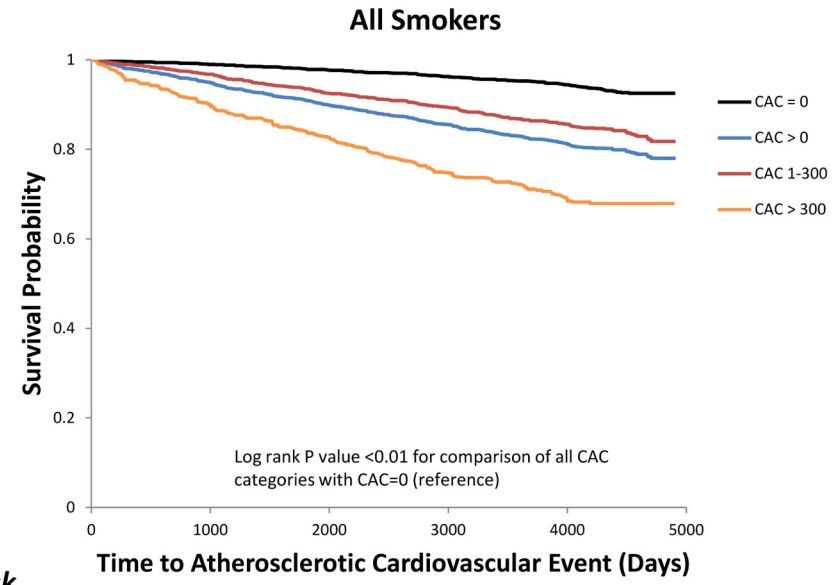


Figure 2. Degree of smoking by CAC categories and ASCVD events

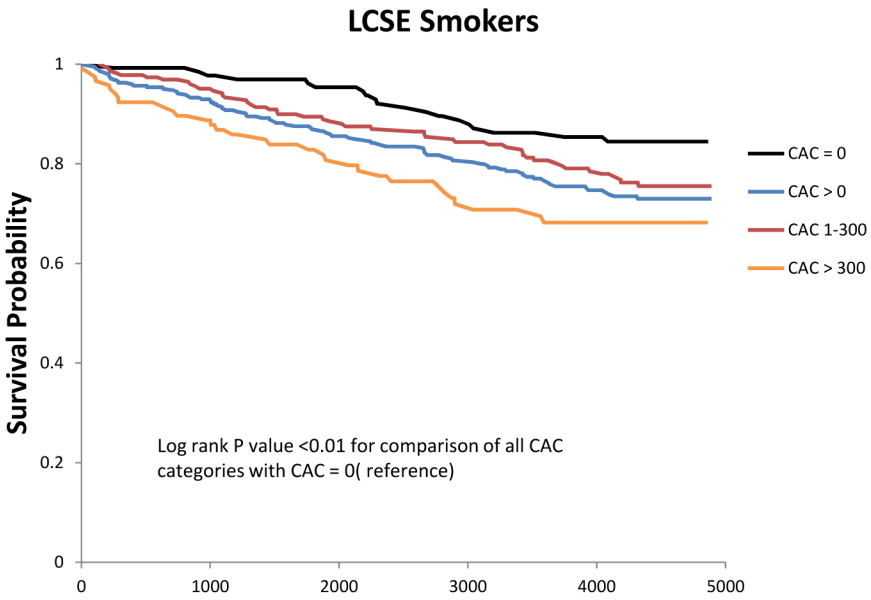
Display of tertiles of pack year of cigarette smoking by coronary artery calcium (CAC) scores categories and atherosclerotic cardiovascular disease (ASCVD) events in MESA.

Figure 3 A



# at Risk					
CAC =0	1488	1427	1359	1308	1254
CAC > 0	1868	1690	1501	1360	1229
CAC =1-300	2849	2687	2501	2362	2225
CAC > 300	507	430	359	306	258

Figure 3B



# at Risk					
CAC =0	134	126	118	106	97
CAC > 0	347	303	254	224	187
CAC =1-300	363	332	294	267	234
CAC > 300	118	97	78	63	50

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) score / CAC categories and those with CAC absent at baseline MESA exam. B: Survival Curves showing the Atherosclerotic Cardiovascular Disease Event -free survival of lung cancer screening eligible smokers with coronary artery calcium (CAC) score / CAC categories and those with CAC absent at baseline MESA exam

Table 1

Demographic and cardiovascular risk factors distribution of All-smokers and lung cancer screening eligible(LCSE) smokers per the United States Preventive Service Task Force(USPSTF).

Variables	Total MESA Cohort N=6814 Mean± SD/ %	All – Smokers (N=3356) Mean± SD/ %	LCSE Smokers (N=481) Mean ±SD/ %	P value (all-smokers vs. LCSE)
Age (years)	62.2±10.2	62.1± 9.9	65.3± 6.9	<0.001 *
Female	47.2	43.5	39.1	0.07 †
Race/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(mmHg)				
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	
Coronary Artery Calcium (CAC)				

Variables	Total MESA Cohort N=6814 Mean± SD/ %	All – Smokers (N=3356) Mean± SD/ %	LCSE Smokers (N=481) Mean ±SD/ %	P value (all-smokers vs. LCSE)
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	

*t-test,

†Chi-squared

Table 2

The Hazard ratios (HR) and the 95% confidence intervals (CI) of the association between coronary artery calcium variables and incident ASCVD events

Variable	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, gender, race/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.

Table 3

Frequency Table of Pooled Cohort Equation(PCE) risk categories and coronary artery calcium score (CAC) categories in all smokers and those eligible for lung screening(LCSE) per the USPSTF guidelines

PCE Risk Categories	**CAC Categories**			
All Smokers	**0 (n=1488)**	**> 0 (n=1868)**	**1–300 (n=1363)**	**>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=2082)	652(31.3%)	1430(68.7%)	969(46.5%)	461(22.1%)
LCSE Smokers	**(n=134)**	**(n=347)**	**(n=229)**	**(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%)

Table 4

Net reclassification improvement afforded by the addition of coronary artery calcium(CAC) scores to the Pooled Cohort Equation (PCE) for all smokers and lung cancer screening eligible (LCSE) smokers.

Variable		Risk Category			% Reclassified		Net Correct Reclassified (%)	NRI
		Low	Intermediate	High	Down	Up		
All Smokers								
PCE Alone PCE +[In CAC +1)]	Events	31 8	32 58	382 379	10.6	12.4	1.8	−0.108
	No Events	841 301	370 938	1700 1672	19.7	32.3	− 12.6	
LCSE Smokers								
PCE Alone PCE +[In CAC +1)]	Events	5 0	11 0	84 100	0	16.0	16.0	−0.036
	No Events	34 0	39 0	308 381	0	19.2	−19.6	