Lung Cancer Screening Eligibility in the Community
Cardiovascular Risk Factors, Coronary Artery Calcification, and Cardiovascular Events

The Centers for Medicare & Medicaid Services (CMS) recently approved lung cancer screening with computed tomography (CT); smoking is a risk factor for lung cancer and atherosclerotic cardiovascular disease (ASCVD). Data are needed regarding the cardiovascular risk of patients who are eligible for lung cancer screening, including implications of coronary artery calcification (CAC) visible on lung cancer screening CT.

In a longitudinal primary prevention cohort study, we determined lung cancer screening eligibility in the community and its association with statin eligibility, CAC, and incident ASCVD events. A total of 3000 asymptomatic FHS (Framingham Heart Study Offspring Cohort) participants aged 55 to 77 years and free of prevalent cardiovascular disease or lung cancer were divided based on eligibility for lung cancer screening CT by CMS criteria: (1) aged 55 to 77 years (all by definition), (2) current or recent (≤15 years) former smoker, and (3) ≥30 pack-year cigarette smoking history. Participants were enrolled at examinations 3 (1984-1987) and 7 (1998-2001) and followed for the primary outcome of incident ASCVD (myocardial infarction, death due to coronary heart disease, or ischemic stroke) and the secondary outcome of lung cancer. Participants were contacted annually with suspected ASCVD or lung cancer events adjudicated by a panel of 3 physicians based on review of medical records, histopathology reports, and death certificates. A subgroup of 980 from examination 7 had electrocardiography-gated calcium score multidetector CT. The institutional review boards of Boston University Medical Center and Massachusetts General Hospital approved the study. All participants provided written informed consent.

Hazard ratios for incident ASCVD and lung cancer were compared between lung cancer screening eligible and ineligible groups using multivariable Cox proportional hazards regression. Interaction of enrollment examination on these associations was assessed with separate Cox models. Secondary analyses assessed statin eligibility by the 2013 American College of Cardiology/American Heart Association guidelines, predicted versus observed 10-year ASCVD risk, and the extent of CAC and association with ASCVD. Multivariable models were adjusted for age, sex, body mass index, systolic blood pressure, high-density lipoprotein, low-density lipoprotein, total cholesterol, lipid-lowering therapy, antihypertensive treatment, and diabetes mellitus. Statistical analysis was performed with SAS version 9.4.

Of 3000 participant visits (mean age 62.8±5.9 years; 54.6% female), 20% (596; 62.1±5.4 years; 49.0% female) were eligible for lung cancer screening. Eligible participants were more likely male (51% versus 44%, P=0.002) or current smokers (56% versus 4%, P<0.001), but otherwise had similar age (62 versus 63 years) and risk profile to ineligible participants. The participants who were screening eligible had a median of 50.1 (quartiles: 39.4–65.7) pack-years of cigarette smoking.

During a median follow-up of 11.4 (9.7–12.0) years, screening eligible participants had more incident ASCVD than ineligible persons (12.6% versus 8.0%, P=0.001).
multivariable-adjusted hazard ratio 1.8 (95% confidence interval, 1.4–2.3), \( P < 0.001 \), Figure). ASCVD was more frequent than lung cancer in both groups (eligible: 12.6% versus 7.2%, \( P = 0.002 \); ineligible: 8.0% versus 1.0%, \( P < 0.001 \)). There was no interaction between when the participant was enrolled and the association with incident ASCVD or lung cancer (\( P > 0.3 \)).

In the lung cancer screening eligible group, predicted and observed 10-year ASCVD risk were similar (predicted 11.4% versus observed 11.7%, \( P = 0.31 \)). In contrast, the screening ineligible group had higher predicted than observed risk (9.6% versus 6.9%, \( P = 0.001 \)). According to the 2013 American College of Cardiology/American Heart Association guidelines, 78.9% (470 out of 596) of the screening eligible participants qualified for a statin.

Among 980 with calcium score CT, the 13.6% participants who were screening eligible were more likely to have any or high CAC (Agatston Score [AS] >0: 90.2% versus 78.0%, \( P = 0.010 \) and AS >300: 39.1% versus 27%, \( P = 0.045 \)). Overall, 94.7% of the screening eligible participants either qualified for statin or had CAC. In the screening eligible group, ordinal calcium score categories were associated with ASCVD, with 0% (0 out of 13) for AS=0, 4.7% (2 out of 43) for AS 1 to 100, 12.0% (3 out of 25) for AS 101 to 300, and 19.2% (10 out of 52) for AS >300 (adjusted \( P = 0.003 \)).

Prior research in lung cancer screening trials demonstrates that standard low-dose nonelectrocardiography gated lung cancer screening CT accurately assigns CAC to semiquantitative ordinal categories that predict future ASCVD.\(^3\)\(^4\) We extend these findings, demonstrating that in a community cohort aged 55 to 77 years and eligible for primary cardiovascular prevention, 20% met CMS eligibility criteria for lung cancer screening CT with \( \approx 60\% \) greater incident ASCVD than the ineligible participants during 11.4 years of follow-up. Nearly all (95%) of the screening eligible participants had CAC or were statin eligible; 39% had AS >300. CMS requires a consultation for shared decision-making and smoking cessation before lung cancer screening CT.\(^1\) Given the substantial risk of ASCVD, we propose that cardiovascular prevention counseling should be considered as part of this consultation.

Reporting CAC on lung cancer screening CT personalizes risk and may improve compliance with cardiovascular prevention as a supportive measure.\(^4\) Although
nonelectrocardiography-gated lung cancer screening CT does not discriminate between 0 and very low AS in 10% compared with gated CT, most events in our study occurred with AS >100. Our results suggest that considering long-term heavy smoking may improve risk prediction. The ASCVD risk calculator performed well in the screening eligible group (predicted 11.4% versus observed 11.7% at 10 years, P=0.31). In contrast, ASCVD risk was overestimated substantially in the screening ineligible participants (predicted 9.6% versus observed 6.9%, P=0.001) concordant with other population-based studies. Thus knowledge of lung cancer screening eligibility may give physicians greater confidence in the projected ASCVD risk. Our study limitations include enrollment periods ending 29 and 15 years ago during a period of lower statin awareness. Nevertheless, an interaction analysis found no difference in results based on when participants enrolled. Furthermore the screening eligible participants had cumulative pack years (50 versus 48 in the National Lung Screening Trial) representative of the contemporary US screening population.

In conclusion, in a community-based primary prevention cohort, 20% aged 55 to 77 years are eligible for lung cancer screening CT. The lung cancer screening eligible participants are at high risk for ASCVD events, even greater than the risk of lung cancer, and have a high prevalence of subclinical atherosclerosis. Cardiovascular prevention should be considered as part of the consultation for lung cancer screening.

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**FOOTNOTES**

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