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%,...
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

---

**Figure. Kaplan-Meier Survival Curves and Adjusted Hazard Ratios.**

Kaplan-Meier survival curves of incident (A) atherosclerotic cardiovascular disease (ASCVD) and (B) lung cancer stratified by lung cancer screening computed tomography eligibility. C, Adjusted hazard ratios for ASCVD and lung cancer events. Incident ASCVD was more frequent than lung cancer for both eligible and ineligible groups (\(P<0.001\)).
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 10.7% 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.

SOURCES OF FUNDING
This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contracts N01-HC-25195, HL076784, AG028321, HL070100, HL060040, HL080124, HL071039, HL077447, and HL107385). Dr Lu was supported by National Institutes of Health grant T32 HL076136 and the American Roentgen Ray Society Scholarship. The National Institutes of Health and American Roentgen Ray Society had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

DISCLOSURES
Dr Hoffmann reports receipt of grants from HeartFlow Inc, Siemens Healthcare, Genentech, and the American College of Radiology Imaging Network and personal fees from the American Heart Association (all significant). No other disclosures were reported.

AFFILIATIONS
From Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA (M.T.L., U.H.); Cardiology Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA (O.K.O.); The Framingham Heart Study of the National Heart, Lung and Blood Institute (NHBLI) and Boston University, Framingham, MA (O.K.O., J.M.M., R.B.D., C.J.O., U.H.); Department of Biostatistics, Boston University School of Public Health, Boston, MA (J.M.M.); Department of Mathematics and Statistics, Boston University, Boston, MA (R.B.D.); Division of Intramural Research, NHBLI, Bethesda, MD (C.J.O.), and Cardiology Section, Department of Medicine, Boston Veteran’s Administration Healthcare System, Harvard Medical School, Boston, MA (C.J.O.).

FOOTNOTES
Received April 20, 2016; accepted August 8, 2016.
Circulation is available at http://circ.ahajournals.org.

REFERENCES
Lung Cancer Screening Eligibility in the Community: Cardiovascular Risk Factors, Coronary Artery Calcification, and Cardiovascular Events
Michael T. Lu, Oyere K. Onuma, Joseph M. Massaro, Ralph B. D'Agostino, Sr., Christopher J. O'Donnell and Udo Hoffmann

Circulation. 2016;134:897-899
doi: 10.1161/CIRCULATIONAHA.116.023957

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/134/12/897

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/