Coronary Artery Calcium Can Predict All-Cause Mortality and Cardiovascular Events on Low-Dose CT Screening for Lung Cancer

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OBJECTIVE. Performing coronary artery calcium (CAC) screening as part of low-dose CT lung cancer screening has been proposed as an efficient strategy to detect people with high cardiovascular risk and improve outcomes of primary prevention. This study aims to investigate whether CAC measured on low-dose CT in a population of former and current heavy smokers is an independent predictor of all-cause mortality and cardiac events.

SUBJECTS AND METHODS. We used a case-cohort study and included 958 subjects 50 years old or older within the screen group of a randomized controlled lung cancer screening trial. We used Cox proportional-hazard models to compute hazard ratios (HRs) adjusted for traditional cardiovascular risk factors to predict all-cause mortality and cardiovascular events.

RESULTS. During a median follow-up of 21.5 months, 56 deaths and 127 cardiovascular events occurred. Compared with a CAC score of 0, multivariate-adjusted HRs for all-cause mortality for CAC scores of 1–100, 101–1000, and more than 1000 were 3.00 (95% CI, 0.61–14.93), 6.13 (95% CI, 1.35–27.77), and 10.93 (95% CI, 2.36–50.60), respectively. Multivariate-adjusted HRs for coronary events were 1.38 (95% CI, 0.39–4.90), 3.04 (95% CI, 0.95–9.73), and 7.77 (95% CI, 2.44–24.75), respectively.

CONCLUSION. This study shows that CAC scoring as part of low-dose CT lung cancer screening can be used as an independent predictor of all-cause mortality and cardiovascular events.

Keywords: all-cause mortality, cardiovascular events, coronary artery calcium score, low-dose CT, lung cancer screening

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Tobacco use causes both lung cancer and cardiovascular disease (CVD) and is the most important preventable cause of death worldwide [1]. Early diagnosis is considered an important goal for both diseases. The effectiveness of CT screening to reduce mortality from lung cancer has yet to be established and is currently being investigated [2]. Coronary artery calcium (CAC) screening has been proposed as an attractive addition to screening for lung cancer [3]. Adding CAC screening at baseline could lead to improved detection of high-risk individuals and, consequently, the improved primary prevention of cardiovascular events, through optimized medical treatment of cardiovascular risk factors. Furthermore, it is likely to offer benefits in terms of efficiency and radiation dose reduction. Dedicated CAC screening is usually performed with ECG synchronization, which is considered a necessary part of the scanning protocol to reduce motion artifacts. Two recent reports, however, have shown the feasibility of accurate CAC screening using nongated low-dose CT compared with dedicated cardiac CT [4, 5].

The predictive properties of CAC above and beyond those of traditional risk factors for CVD have been described in a number of prospective cohort studies, mostly using electron beam tomography (EBT) [6–8]. One of several factors that has been shown to influence the predictive value of CAC is the variability of underlying risk profiles across different populations studied [9]. This calls for a separate evaluation of the usefulness of CAC screening in different types of study populations. Currently, no outcome data are available on the association of CAC with all-cause mortality or risk of future cardiovascular events from a high-risk asymptomatic lung cancer screening population using nongated low-dose CT.

Within the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) study, a randomized controlled population-based lung cancer screening trial among former or current heavy smokers 50 years old

or older, we investigated whether CAC is an independent predictor of all-cause mortality, fatal and nonfatal cardiovascular events, and fatal and nonfatal coronary events. Furthermore, we investigated the possible effect that this approach could have on the management of CVD risk factors within this screening population.

Subjects and Methods

Patient Selection

The NELSON study is a randomized controlled population-based trial comprising 15,822 men and women 50 years old or older. Its overall aim is to investigate the beneficial effects of screening for lung cancer with low-dose CT. In 2003–2004, in four distinct geographic areas (147 municipalities), all people born between 1928 and 1953 were invited by mail to participate in this study. A more detailed description of patient selection and data collection has been published elsewhere [10]. Every participant had a history of 15 or more pack-years of smoking. From 2004 to 2006, baseline CT scans were performed in 7557 participants randomly allocated to the screen group. All analyses in the current study are derived from the screen group of the NELSON Study. The Medical Ethics Committees of all four participating hospitals approved the NELSON Study protocol, and written informed consent was obtained from all participants.

Study Design

We used a case-cohort design [11] in which a random baseline sample is drawn from the total screen group of the NELSON trial at the beginning of the study (so-called subcohort, $n = 925$). Cases are defined as all participants from the baseline screen group experiencing an outcome of interest (all-cause death or cardiovascular events) during follow-up. All cases ($n = 226$) were ascertained through linkage with the national death registry and the national registry of hospital discharge diagnoses (Fig. 1). The choice of the sample fraction (~ 11%) was calculated to correspond to approximately four control subjects per case detected. The major advantage of this design is that it enables the performance of survival analyses that produce valid estimates for the total study population without the need to perform time-consuming CAC scoring in all study participants.

Through linkage with the national registry of hospital discharge diagnoses, we first excluded participants with a known history of CVD (cases, $n = 72$; subcohort, $n = 97$). In this registry, all diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9-CM). One research physician selected and excluded all subjects with a cardiovascular discharge diagnosis before the start of this study (January 2004) (ICD-9 codes 410–414, 428, 430–438, 440, 441, 443, and 444). Then, we excluded those participants who had missing baseline CT scans (cases, $n = 4$; subcohort, $n = 17$) or a baseline CT scan performed after follow-up had ended (cases, $n = 0$; subcohort, $n = 3$). This resulted in a final study cohort for this study of 958 subjects (cases, $n = 150$; subcohort, $n = 808$). Baseline CAC scores were measured in all 958 subjects.

Low-Dose Chest CT Protocol

Baseline low-dose CT scans were conducted with a 16-MDCT scanner (Mx8000 IDT, Philips Healthcare in two participating hospitals; and Sensation-16, Siemens Healthcare in the third hospital). The following parameters were applied: collimation, 16 × 0.75 mm; pitch, 1.3–1.5; scan direction, caudocranial; and smallest FOV to include the outer rib margins. Transverse images with 1.0-mm section thickness and 0.7-mm increment were acquired from the level of the lung bases to the lung apices. No ECG triggering was performed; no contrast agent was administered. Low-dose exposure settings were applied according to body weight: 30 mAs at a tube voltage of 120 kVp for subjects weighing 80 kg or less and 140 kVp for subjects weighing more than 80 kg. This corresponds to an effective radiation dose of 0.6–1.1 mSv.

All 958 CT scans were equally divided between two observers with 2 and 3 years of experience in reading cardiac CT who subsequently performed calcium scoring of the coronary arteries. The readers were blinded to each participant's age, sex, and name. Before the start of the study, interobserver variability of coronary calcium scoring was measured in a subset of 50 baseline scans not included in this study (intraclass $R = 0.97$). To reduce image noise and to use data comparable to that of previously published studies, all scans were reconstructed to 3.1-mm-thick slices with an increment of 1.4 mm by averaging four neighboring slices. Calcium scoring was performed in these reconstructed images using software written in C++ [12]; all regions of three or more adjoining voxels (0.7 mm^3) with attenuation greater than 130 HU were shown with a colored overlay. An investigator identified a point in each calcified lesion. Subsequently, 3D component labeling using 26-connectivity was automatically performed to mark all connected voxels as calcification. Care

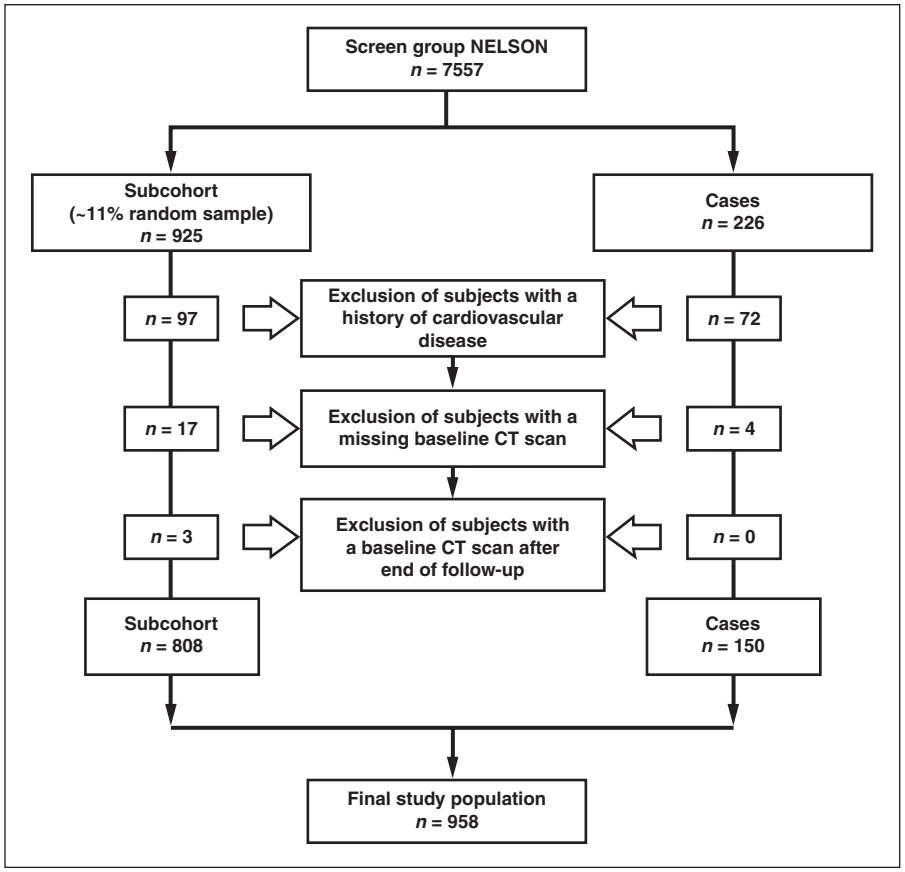

Fig. 1—Flowchart of case-cohort design. NELSON = Dutch-Belgian Randomized Lung Cancer Screening Trial.

was taken not to include noncoronary calcifications (e.g., valve calcifications) or hyperattenuating foci due to image noise. Agatston scores were computed as outlined by Ulzheimer and Kalendar [13] and Agatston et al. [14]. Apart from being considered as a continuous measure, the Agatston score for coronary calcium was categorized into four well-defined risk categories: CAC of zero denotes very low risk, reference category; CAC more than but less than or equal to 100 denotes low risk; CAC more than 100 but less than or equal to 1000 denotes moderate to high risk; and CAC greater than 1000 denotes very high risk [15].

Classification of Endpoints

All participants in the screen group of the NELSON Study ($n = 7557$) were linked with the national death registry and the national registry of hospital discharge diagnoses. This database linkage was performed on the basis of birth date, sex, and postal code with a validated probabilistic method [16].

All-cause mortality was chosen as the primary endpoint for this study. Through linkage with the national death registry for the years 2004–2006, a total of 56 deaths were detected. Secondary endpoints were defined as a composite CVD endpoint consisting of cardiovascular deaths and all nonfatal cardiovascular hospital admissions and a composite coronary heart disease (CHD) endpoint consisting of all fatal myocardial infarctions and nonfatal CHD admissions. To retrieve information on cardiovascular hospital admissions, all participants from the screen group were linked with the national registry of hospital discharge diagnoses for the years 2004–2005. One research physician selected all cardiovascular discharge diagnoses and classified them as CHD (codes 410–414) or other CVD hospitalizations, including peripheral arterial occlusive disease (codes 440 and 443–444), aortic aneurysm or dissection (code 441), cerebrovascular disease (codes 430–438), heart failure (code 428), and nonrheumatic valvular disease (code 424). All other codes included in the ICD-9-CM as diseases of the circulatory system were not included as valid endpoints. Through this linkage, a total of 94 nonfatal cardiovascular events could be identified.

Follow-up started after the baseline CT scan. Follow-up time differed for primary and secondary endpoints because of the differential availability of the two registries used. For all-cause mortality, follow-up was complete until January 1, 2007 (median, 21.5 months), and for both secondary endpoints, follow-up was complete until January 1, 2006 (median, 9.5 and 10.0 months). For all participants who experienced an event, follow-up ended at the date of diagnosis or death. Participants with a CVD hospital admission before death were counted as all-cause mortality. In participants with multiple cardiovascular hospital admissions during follow-up, the first hospital discharge diagnosis was used as the endpoint.

Assessment of Covariates

At baseline, all participants from the NELSON Study were asked to return a questionnaire containing information on prior and current smoking behavior. For those subjects drawn into the final study cohort, a research physician collected information from their general practitioners (GPs) using a standardized questionnaire. The obtained information included the current use of drugs—specifically, the use of antihypertensive drugs (defined as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers, or calcium channel blockers), lipid-lowering drugs, oral hypoglycemic agents, insulin, and other drugs prescribed for cardiovascular purposes (most commonly antiplatelet drugs such as acetylsalicylic acid and clopidogrel)—systolic and diastolic blood pressure (BP), and nonfasting blood glucose, HbA1c, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels. The overall response rate was 70%. For all covariates obtained through the GP, missing values were imputed using regression methods implemented in SPSS software (version 14.0, SPSS) [17]. We defined diabetes mellitus as a nonfasting glucose level 11.1 mmol/L or higher or the use of oral hypoglycemic agents or insulin. Hypertension was defined as a diastolic BP greater than 90 mm Hg, systolic BP greater than 140 mm Hg, or the use of antihypertensive drugs. Hypercholesterolemia was defined as a total cholesterol level greater than 5.0 mmol/L, a low-density lipoprotein level greater than 3.0 mmol/L, or the use of lipid-lowering drugs.

Statistical Methods

Baseline characteristics were summarized for the subcohort and the three different case groups separately. Categoric variables were compared with a chi-square statistic; continuous variables were compared with Student *t* tests. Means and SDs were computed for normally distributed variables; medians and interquartile ranges were computed for variables with skewed distributions. Annualized event rates for all three endpoints in the full cohort were calculated as follows: 100% × (total no. of events / ∑ person-days in the subcohort) × 365. Adjusting for the case-cohort design was performed by weighting the number of person-days contributed by the subcohort by the inverse of the sampling fraction.

The association of CAC with all-cause mortality, the composite CVD endpoint, and CHD was evaluated with Cox proportional hazard analyses with modification of the standard errors based on robust variance estimates. We used the method of Prentice [11], in which all subcohort members are equally weighted. Cases outside the subcohort are not weighted before failure and at failure receive the same weight as members of the subcohort [11]. This method has been shown to resemble estimates from a full-cohort analysis most accurately [18].

We classified participants using a four-level risk stratification based on the Agatston scoring algorithm [14] and used the lowest level (Agatston score = 0) as the reference category. First, Cox proportional hazard models for all three endpoints were performed for Agatston score risk categories unadjusted for covariates (model 1). In model 2, we adjusted for age and sex. In model 3, current smoking and history of hypertension, diabetes, and hypercholesterolemia were added. We tested the interaction of CAC risk categories with smoking status by entering this interaction term in the models. Unadjusted and risk-adjusted Cox proportional hazard survival curves were drawn to show the effects of CAC per risk category.

All analyses were performed with the statistical software package SPSS (version 14.0, SPSS) and the cch(survival) package (standard available in R software, version 6.2, The R Project).

Results

Table 1 shows the baseline characteristics of the subcohort and the all-cause mortality for CVD and CHD cases. At the time of baseline screening, mean (± SD) age of the members in the subcohort was 59.5 ± 5.6 years. Current cigarette smoking was recorded for 56%, diabetes for 7%, hypercholesterolemia for 75%, and hypertension for 64% of subjects. A CAC score of 0 was detected in 24% of participants: CAC scores of 1–100, 100–1000, and greater than 1000 were detected in 29%, 30%, and 17% of participants, respectively (median CAC score, 74).

As presented in Table 2, there is a strong association between increasing categories of CAC and the annualized event rate for all three endpoints. The mortality for all participants increased in a linear fashion from 0.08% to 0.2%, 0.6%, and 1.1% with increasing CAC categories of 0, 1–100, 101–1000, and greater than 1000, respectively ($p < 0.001$).

During a median follow-up of 21.5 months (range, 1–1003 days), 56 subjects died. CAC score was associated with risk of all-cause mortality (Table 3). Compared with the reference category (CAC score, 0), crude hazard ratios (HRs) for CAC scores of 1–100, 101–

TABLE 1: Baseline Characteristics for Subjects in the Subcohort, All-Cause Mortality, Fatal and Nonfatal Cardiovascular Disease (CVD) Events, and Fatal and Nonfatal Coronary Heart Disease (CHD) Events Case-Groups

Variable	Subcohort (*n* = 808)	All-Cause Mortality[a] (*n* = 56)	CVD Endpoint[a] (*n* = 127)	CHD Endpoint[a] (*n* = 61)
Age (y), mean ± SD	59.5 ± 5.6	63.7 ± 5.8	61.0 ± 5.9	60.1 ± 5.6
Male sex, %	83	95	97	93
Hypertension, %	64	63	87	93
Hypercholesterolemia, %	75	77	80	85
Diabetes, %	7	13	15	18
Current smoker, %	56	68	63	62
CAC score (Agatston score), %				
0	24	4	8	7
1–100	29	14	21	13
101–1000	30	39	25	29
> 1000	17	43	46	51
CAC score (Agatston score) continuous, median (interquartile range)	74 (591)	685 (1828)	769 (2063)	1055 (2017)

Note—Categoric variables are expressed as percentage. CAC = coronary artery calcium.
[a]Median follow-up per case-group was 21.5 months for all-cause mortality, 9.5 months for CVD events, and 10.0 months for CHD events.

1000, and greater than 1000 were 3.03, 8.26, and 16.17, respectively. After adjustment for age and sex, the strength of the association was attenuated. Compared with a CAC score of 0, HRs for scores of 1–100, 101–1000, and greater than 1000 were 2.82, 5.96, and 10.24, respectively. After adjustment for additional cardiovascular risk factors, the association of CAC with all-cause mortality remained statistically significant.

During a median follow-up of 10.0 months (range, 1–638 days), 127 incident fatal and nonfatal CVD events occurred, of which 61 were fatal or nonfatal coronary events (see Table 2 for specification of endpoints). CAC showed a graded association with the risk of all fatal and nonfatal CVD events and with only coronary events. In case of fatal or nonfatal coronary events, crude HRs for scores of 1–100, 101–1000, and higher than 1000 compared with a CAC score of 0 were 1.42, 3.13, and 9.97, respectively (Table 3). After adjustment for all cardiovascular risk factors, the corresponding HRs were 1.38, 3.04, and 7.77, respectively. Attenuation of these HRs was mainly caused by adjustment for hypertension. Compared with all-cause mortality, adjustment for age did not materially influence the association for these two endpoints. The models for all CVD events showed a similar pattern, although the strength of the association was slightly less than that for coronary events alone (Table 3). No interaction was present between CAC and current smoking ($p = 0.9$ for interaction) in relation to all three endpoints. Most probably this is because the entire study population consisted of former and current heavy smokers.

To illustrate the possible benefits in terms of improved primary prevention when adding CAC screening to lung cancer screening, we summarized the percentage of subjects treated and not treated with antihypertensive drugs and statins stratified into CAC categories (Table 4). In subjects with an intermediate-to-high risk of CVD events (CAC score, 100–1000), 55% of participants were not treated with antihypertensive drugs and 64% were not treated with statins. In subjects at very high risk (CAC score, > 1000), still 43% and 48% of people were not treated with antihypertensive drugs and statins, respectively.

TABLE 2: Annualized Event Rates for All-Cause Mortality, Fatal and Nonfatal Cardiovascular Disease (CVD) Events and Fatal and Nonfatal Coronary Heart Disease (CHD) Events According to Coronary Artery Calcium (CAC) Risk Categories

CAC Risk Category[a]	All-Cause Mortality (*n* = 56)	CVD Endpoint[b] (*n* = 127)	CHD Endpoint[b] (*n* = 61)
0	0.08 (2)	0.7 (10)	0.3 (4)
1–100	0.2 (8)	1.5 (27)	0.4 (8)
101–1000	0.6 (22)	1.7 (32)	1.0 (18)
> 1000	1.1 (24)	6.1 (58)	3.2 (31)

Note—Data are percentage annualized event rate (no. of cases). Annualized event rates were calculated as follows: 100% × [no. of total events / (∑ person-days subcohort × 1/0.107)] × 365. The ∑ person-days of the subcohort was weighted by the inverse of the sampling fraction (~ 11%) for the subcohort (1/0.107).
[a]Median follow-up per case-group was 21.5 months for all-cause mortality, 9.5 months for CVD events, and 9.8 months for CHD events.
[b]CVD endpoint (*n* = 127) consists of 10 fatal events (myocardial infarction, *n* = 5; stroke, *n* = 3; aortic aneurysm, *n* = 1; and peripheral arterial occlusive disease, *n* = 1) and 117 nonfatal events (myocardial infarction, *n* = 13; angina pectoris, *n* = 43; aortic valve stenosis, *n* = 24; stroke, *n* = 14; aortic aneurysm, *n* = 12; and peripheral arterial occlusive disease, *n* = 11). Of these 127 events, all fatal and nonfatal myocardial infarctions (*n* = 18) and angina pectoris (*n* = 43) events were included in the CHD endpoint (*n* = 61).

Discussion

The current study shows that CAC is an independent predictor of all-cause mortality, fatal and nonfatal cardiovascular events, and fatal and nonfatal coronary events in a lung cancer screening population. These associations are independent of traditional cardiovascular risk factors.

To our knowledge, this is the first study that shows the predictive value of CAC in a cohort of former and current heavy smokers participating in a lung cancer screening trial using low-dose nongated CT. One previous study similarly reported good predictive value of CAC in a

TABLE 3: Hazard Ratios (HRs) for Events According to Coronary Artery Calcium (CAC) Risk Categories

Group, CAC Risk Category	Model 1	Model 2	Model 3
All-cause mortality (*n* = 56)			
0	1.00	1.00	1.00
1–100	3.03 (0.62–14.92)	2.82 (0.57–13.95)	3.00 (0.61–14.93)
101–1000	8.26 (1.86–36.68)	5.96 (1.32–26.88)	6.13 (1.35–27.77)
> 1000	16.17 (3.64–71.75)	10.24 (2.25–46.56)	10.93 (2.36–50.60)
Cardiovascular disease endpoint (*n* = 127)			
0	1.00	1.00	1.00
1–100	1.92 (0.89–4.18)	1.88 (0.86–4.08)	1.76 (0.80–3.87)
101–1000	2.23 (1.04–4.76)	2.09 (0.97–4.52)	1.93 (0.88–4.21)
> 1000	7.51 (3.60–15.68)	6.88 (3.22–14.67)	5.33 (2.45–11.60)
Coronary heart disease endpoint (*n* = 61)			
0	1.00	1.00	1.00
1–100	1.42 (0.41–4.92)	1.49 (0.43–5.19)	1.38 (0.39–4.90)
101–1000	3.13 (1.01–9.69)	3.45 (1.10–10.84)	3.04 (0.95–9.73)
> 1000	9.97 (3.32–29.89)	11.45 (3.70–35.45)	7.77 (2.44–24.75)

Note—Data are HR (95% CI). Model 1 shows crude HRs. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, smoking, hypertension, hypercholesterolemia, and diabetes.

TABLE 4: Proportion of Patients Treated and Untreated with Antihypertensive Drugs or Statins in the Subcohort per Coronary Artery Calcium Category (*n* = 808)

	Antihypertensive Drugs		Statins	
CAC Risk Category	Not Treated	Treated	Not Treated	Treated
0 (*n* = 197)	70 (137)	30 (60)	76 (149)	24 (48)
1–100 (*n* = 231)	67 (154)	33 (77)	74 (170)	26 (61)
101–1000 (*n* = 239)	55 (131)	45 (108)	64 (154)	36 (85)
> 1000 (*n* = 141)	43 (60)[a]	57 (81)	48 (68)[b]	52 (73)

Note—Data are percentage (no. of patients).
[a]Of the 60 participants with a CAC score > 1000 not treated with antihypertensive drugs, 26 participants (43%) actually had hypertension (diastolic blood pressure > 90 mm Hg or systolic blood pressure > 140 mm Hg).
[b]Of the 68 participants with a CAC score > 1000 not treated with statins, 42 (62%) actually had elevated lipid levels (total cholesterol > 5.0 mmol/L or low-density lipoprotein > 3.0 mmol/L).

large cohort of former and current smokers using higher-dose ECG-gated EBT imaging [19]. However, their patients were derived from a cohort of asymptomatic individuals referred for evaluation of cardiac risk by their GPs, which, when we compare baseline characteristics, has resulted in a younger and healthier population than in our study. As a consequence, our population has higher CAC scores and is therefore at higher risk of all-cause mortality and CVD events. Consequently, we report higher risk ratios than those reported by Shaw et al. [19].

We think that the importance of our results is threefold. First, this study shows that CAC, when measured on nongated low-dose CT as part of a lung cancer screening program in heavy smokers, can predict all-cause mortality and cardiovascular events in a comparable way as when using a normal-dose gated CT protocol. Subjects in the highest risk category had an almost sixfold risk of coronary events compared with those without detectable CAC. These results are comparable with those of several different prospective cohort studies [6–8, 19–24]. In general, these studies found strong and independent associations between CAC and poor clinical outcome with, for example, risk-adjusted HRs of 9.4 for all-cause mortality for participants with a score higher than 1000 (HR = 10.9 in the present study) [6]. Younger patients (mean age, 43 years) were analyzed in the Prospective Army Coronary Calcium Project, and they reported an 11-fold increased risk for hard coronary events (HR = 7.8 in present study) [8]. We think that these minor differences can be explained by the different underlying risk profiles of various study populations. One study that specifically selected participants with a high-risk profile (≥ 2 coronary risk factors; mean age, 66 years), and therefore more closely resembling our population, reported a much weaker association (risk ratio = 2.3 for CAC score above the median) [25]. Our results are somewhere in between those described previously in this article, reflecting in one respect the high-risk profile of our participants, but on the other hand that mean age in our study is approximately 7 years lower than in the former example [25]. As outlined above, these studies invariably used EBT imaging protocols for CAC scoring with, typically, an effective radiation dose of 1.0–1.3 mSv; effective radiation dose of calcium scoring with MDCT, which is the technique most often used nowadays in clinical practice, ranges between 1.5 and 6.2 mSv [26]. Our study shows that comparable risk estimates can be obtained with low-dose CT, typically involving an effective radiation dose of only 0.6–1.1 mSv. We consider the potential reduction of radiation dose as an important strength of this study.

Second, this is the first study, to show the very high proportion of asymptomatic former and current heavy smokers with excessively high CAC scores (> 1000). By comparison, the two largest cohorts of asymptomatic people followed-up so far have reported a prevalence of CAC scores higher than 1000

of 3–4% [6, 7] compared with 17% of participants in our population. Conversely, although our study population consists of people with a minimum of 15 pack-years of smoking, still 24% of participants have no detectable calcium (CAC score, 0), corresponding to a low risk.

Third, this study shows that approximately 55% of study participants with intermediate-to-high risk (CAC score, 100–1000) and 43% of participants with very high risk (CAC score, > 1000) of CVD events do not receive optimal treatment of CVD risk factors. Apart from the fact that around 50% of these subjects actually had elevated BP or lipid levels or both and should have been treated anyway, all these subjects are likely to benefit from risk factor treatment because of their extremely high CAC score (> 1000). They currently do not receive it for reasons unknown. This indicates that extra information from CAC scores could have a great impact on changing the management of CVD risk factors in these particular subjects. For example, when performing CAC scoring as part of baseline lung cancer screening in 1000 participants without a history of CHD, one would detect 175 subjects with a CAC score greater than 1000 (massively increased risk), and of these 175 subjects, 84 subjects (1 in 12 of all participants screened) could benefit from starting secondary preventive medical treatment of cardiovascular risk factors by initiating antihypertensive or lipid-lowering drugs, or both, that they did not receive before. A scenario analysis and cost-effectiveness study will be needed to calculate the exact contribution of incorporating CAC screening into lung cancer screening.

Several possible limitations of our study need to be considered. This study has a rather limited follow-up, especially for cardiovascular and coronary events; despite this fact, a substantial number of events did occur. In our cohort, only 17% of participants were female. This could limit the generalizability of our results to women. However, CAC has previously been shown to be a comparable predictor of CVD risk in men and women [23]. In the current study, most baseline information has been obtained through GPs. A response rate by GPs of 70% may be a limitation, yet we did not observe a differential pattern of missing values for cases and control subjects. Imputation of missing covariate information, taking into account the 100% completeness of follow-up for all endpoints, has been shown to be superior to a complete case analysis [17, 27, 28]. Although risk stratification of subjects has been shown to be accurate using our low-dose nongated CT protocol, making it a valid tool for identification of high-risk CT screening participants, interscan variability of absolute Agatston scores in individual patients is still considerable. For this reason, the low-dose CT protocol will be optimized during the next screening round. Finally, assessment of a history of CVD before the start of this study was unavailable for years before 1995. Linkage of patient characteristics with the registry of hospital discharge diagnoses was not possible before that date. This will have resulted in an underestimation of participants with a history of CVD. We believe that, given the mean age of our population in 1995 and the fact that the vast majority of CVD events take place after age 45 years, this underestimation will not have influenced the results of our study substantially.

Our results show that CAC is a strong and independent predictor of all-cause mortality and cardiovascular events in a population of former and current heavy smokers participating in lung cancer screening using a low-dose CT protocol. Our results further suggest that adding CAC scoring to lung cancer screening could be a clinically useful tool for detection of people at risk for CVD and for improving primary prevention of CVD events by optimizing risk factor management in these patients.

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