

Prognostic importance of extensive coronary calcium on lung cancer screening chest computed tomography

Marcella Cabral Caires MSc MD, Keren Mbondo Kasuku BSc, Bethlehem Mengesha MD, Habibat Garuba MD, Angeline Law MD, Christopher Johnson MD, David Ian Paterson MD, Carole Dennie MD, Elena Pena MD, Li Chen MSc, Benjamin J.W. Chow MD PhD, Gary R. Small MBChB PhD

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Abstract

Background: Low-dose chest computed tomography (CT) is used for lung cancer screening, but can also detect coronary artery disease as coronary artery calcium. We sought to determine the prevalence and prognostic utility of coronary artery calcium in a population at high risk of cancer.

Methods: We reviewed CT scans from consecutive participants screened for lung cancer between March 2017 and November 2018 as part of the Ontario Health Lung Cancer Screening Pilot for People at High Risk. We quantified coronary artery calcium using an estimated Agatston score. We identified the composite

primary outcome of all-cause death and cardiovascular events using linked electronic medical record data from The Ottawa Hospital to December 2023.

Results: Among 1486 people who underwent screening CT, coronary artery calcium was detected in 1232 (82.9%) and was extensive in 439 (29.5%). On multivariable analysis, extensive coronary artery calcium was associated with the composite primary outcome (hazard ratio [HR] 2.13, 95% confidence interval [CI] 1.35–3.38), all-cause death (HR 2.39, 95% CI 1.34–4.27), and cardiovascular events (HR 2.06, 95%

CI 1.13–3.77). Extensive coronary artery calcium remained predictive of cardiovascular events after we adjusted for noncardiovascular death as a competing risk (HR 2.05, 95% CI 1.09–3.85).

Interpretation: Among people undergoing low-dose chest CT for lung cancer screening, extensive coronary artery calcium was an independent predictor of all-cause death and cardiovascular events, even after adjustment for noncardiovascular death. The opportunity to identify and reduce risks from coronary artery disease may represent an additional benefit of lung cancer screening.

Cancer is the leading cause of death in Canada, and lung cancer is the most frequent cause of cancer death.¹ Initiatives have begun across the Canadian provinces to introduce low-dose lung cancer screening chest computed tomography (CT) for at-risk people, as part of multidisciplinary programs to screen for lung cancer.² Lung nodules may not, however, be the only important findings on lung cancer screening CT; coronary calcification, a marker of coronary artery disease that carries similar weight to other recognized cardiovascular risk factors, is also readily detectable.³

Heart disease is second only to cancer as the leading cause of death in Canada, and coronary artery disease is the most common cause of cardiac death.⁴ Thus, if appropriate therapeutic responses are instituted, lung CT findings could affect survival from 2 leading causes of death: lung cancer and coronary artery disease.

Coronary artery calcium detection on lung screening CT is expected, owing to shared risk factors for coronary artery disease

and lung cancer in the population being screened. The expectation for a high prevalence of coronary artery calcium on lung cancer CT has not always materialized and appears to vary from country to country.^{5–8} In Canada, if it were highly prevalent, there could be a significant opportunity to improve cardiovascular health. When coronary artery calcium is detected in asymptomatic people who are otherwise at low or intermediate cardiovascular risk, addition of risk reduction therapies (e.g., a statin) may be indicated, according to national and international guidelines.^{9–12}

Whereas coronary artery calcification detection might appropriately trigger risk prevention therapy, whether coronary artery calcification alone should prompt further downstream testing for obstructive coronary artery disease is unclear. As such there is a further need to understand risk stratification in patients with asymptomatic coronary artery calcification, to avoid unnecessary investigations.

This is especially so in people with an extensive smoking history where competing risks exist, such as cancer death or other

noncardiovascular death. In this scenario, premature death from other causes could diminish the clinical relevance of potential risks from cardiovascular events.^{13,14}

We sought to establish the prevalence of coronary artery calcium on lung screening CT at The Ottawa Hospital and determine whether coronary artery calcium might predict all-cause death, cardiovascular events despite cancer, and other smoking-associated risks.

Methods

Study population

In the analysis, we included consecutive asymptomatic people who underwent a CT scan for lung cancer screening between March 2017 and November 2018 as part of the High-Risk Lung Cancer Screening Pilot based at The Ottawa Hospital (this became an official program in April 2021). The Ottawa Hospital is an academic health sciences centre with 2 primary sites serving 1.3 million people across Eastern Ontario.

Participants eligible for screening were aged 55–74 years and currently or formerly smoked cigarettes daily for at least 20 years, and had a 2% or higher risk of developing lung cancer in the next 6 years, according to a risk prediction model. They could be either self-referred or referred by their health care providers. Patients with a previous diagnosis of lung cancer were not

eligible for screening. If patients underwent more than 1 CT procedure during the study period, we analyzed only the first scan.

We collected participant demographics, cardiovascular risks, and previous cardiac history from electronic medical records at The Ottawa Hospital. We excluded patients with previous coronary revascularization or myocardial infarction. To obtain a summary measure of cardiovascular risk, we extracted data on age, sex, hypertension, diabetes, dyslipidemia, and smoking status to calculate the Framingham Risk Score.

Computed tomography imaging

A low-dose (100–120 kVp, 60–80 mA), noncontrast, ungated helical chest CT scan was performed in a single inspiratory breath hold (Revolution EVO, or Discovery CT 750 HD, GE Healthcare, Mississauga, Ontario). Images were reconstructed in 1.25-mm axial section thickness in both standard and lung windows.

We reviewed axial images (Change Healthcare Picture Archiving and Communication System 12.3, Change Healthcare LCC, Nashville, Tennessee) for coronary artery calcium¹⁵ (Figure 1). We visually quantified both the presence and extent of coronary artery calcium using an estimated Agatston score.^{12,13}

The Agatston score was originally calculated from gated cardiac CT images using specialized software. Greater Agatston values indicate more extensive calcification and carry greater risk of coronary events.¹⁶ An estimated equivalent (estimated Agatston score)

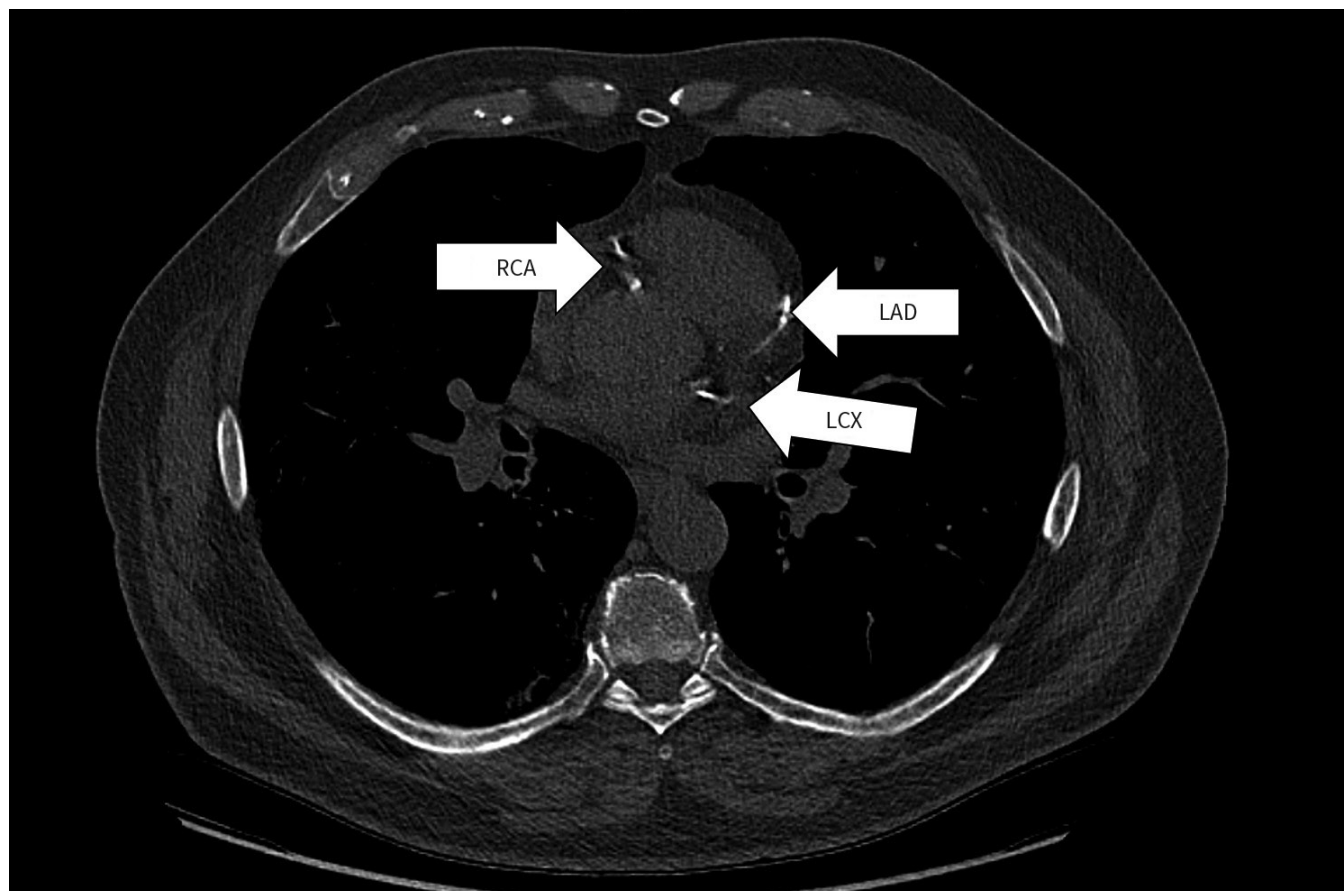


Figure 1: Coronary artery calcification on low-dose chest computed tomography (CT). Transaxial image of a lung cancer screening CT scan, showing coronary artery calcium in all 3 coronary arteries. Note: LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.

using visual assessment and nongated cardiac images has been validated against the original version.^{15,17–19}

For the estimated Agatston score, we divided the major coronary arteries (left main, left anterior descending, left circumflex, and right coronary arteries) into thirds and classified branch vessels with their parent arteries. The presence of calcium in each segment scored 1 point, with a maximum possible score of 12.¹⁷ We categorized participants into no coronary artery calcium (0 points), mild–moderate coronary artery calcium (1–5 points; estimated Agatston score 1–400), and extensive coronary artery calcium (≥ 6 points; estimated Agatston score > 400).^{6,17}

Clinical events

We identified lung cancer, cardiovascular events (nonfatal myocardial infarction, elective revascularization, stroke), and death from the text of each patient's Ottawa Hospital electronic medical record with a census date of Dec. 21, 2023. We used Epic, The Ottawa Hospital's electronic medical record system. We examined inpatient and outpatient visits to determine last date of follow-up. When a patient experienced a study clinical event (identified by M.C., K.K., or B.M.), the medical record text was further interrogated to verify the clinical diagnosis and confirm the validity of the event (G.S.). The primary outcome was a composite of all-cause death and cardiovascular events. We also analyzed cardiovascular events and all-cause death separately as secondary outcomes.

Lung cancer diagnoses had to be confirmed by biopsy. We identified physician-diagnosed causes of death and nonfatal cardiovascular events from the primary diagnosis indicated on the discharge summary, corroborated by review of the clinical chart. Further details are provided in Appendix 1 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.231602/tab-related-content). In the absence of an in-hospital death, we assumed that patients who were managed palliatively with a terminal diagnosis of cancer in a hospice setting had died from a cancer cause.²⁰

Medical assistance in dying

Medical assistance in dying could affect survival analysis; thus, for competing risk survival assessment, we performed sensitivity analyses with and without such patients.

Statistical analysis

We analyzed continuous variables for skewedness and expressed normally distributed data as means with standard deviation (SD). We expressed categorical variables as counts and percentages, and determined statistical significance by the χ^2 statistic, whereas for continuous variables, we used one-way analysis of variance.

Previous work had indicated that a sample size of 1600 would have adequate power to determine the influence of coronary calcium on the primary outcome in this population, and study enrolment continued until this sample size was achieved (November 2018).^{8,21–23} This sample size anticipated a potential 10% rate of exclusions owing to previous coronary revascularization.²⁴

We used adjusted Cox proportional hazards analysis to evaluate the association between any coronary calcium or extensive

coronary artery calcium and the primary composite outcome. Model covariates included Framingham Risk Score or clinically relevant cardiovascular risk variables.²⁵

We performed univariable survival analyses using Kaplan–Meier curves. We calculated annualized event rates for the primary outcome, all-cause death and cardiovascular events.²²

We performed a competing risk survival analysis for cardiovascular events using noncardiovascular death (cancer death and other noncardiac deaths) for extensive coronary artery calcium and adjusted it for differential cardiovascular risk using the Framingham Risk Score. We used the subdistribution hazard model proposed by Fine and Gray to compare the cumulative incidence rates between groups and generate hazard ratios.²⁶ We carried out the statistical analysis using SPSS for Windows, version 29 (Chicago, Illinois). We used $p < 0.05$ to indicate statistical significance.

Ethics approval

The Ottawa Health Science Network Research Ethics Board reviewed the protocol and waived the need for ethics approval and patient consent (Quality Improvement Project No. 185).

Results

We followed 1486 patients for a mean ($\pm$ SD) of 50 ± 9.6 months, and none were lost to follow-up. The mean age was 66 ± 5.4 years, 765 (51.5%) were male, and 1017 (68.4%) currently smoked (Table 1). Cardiovascular risk among participants, as defined by the Framingham Risk Score, was high in 945 (63.6%) participants, intermediate in 479 (32.2%), and low in 62 (4.2%). Lung cancer screening CT scans identified mild–moderate coronary artery calcium in 793 (53.4%) participants, extensive coronary artery calcium in 439 (29.5%), and no coronary artery calcium in 254 (17.1%).

At follow-up, 78 (5.2%) participants experienced the primary composite outcome, including 39 (8.9%) with extensive coronary artery calcium, 32 (4.0%) with mild–moderate coronary artery calcium, and 7 (2.8%) with no coronary artery calcium (Table 2). There were 49 deaths, including 16 cardiovascular deaths and 19 cancer deaths, of which 10 were from lung cancer. Cardiovascular events included sudden cardiac death ($n = 8$), fatal stroke ($n = 6$), heart failure ($n = 1$), and peripheral vascular disease ($n = 1$). Fourteen patients died of noncancer, noncardiovascular causes (Appendix 1, Table 1). The noncancer and noncardiovascular deaths included 4 patients who received medical assistance in dying.

Annualized rates of the primary composite outcome were higher in patients with extensive coronary artery calcium (2.11 events per 100 patient-years, 95% confidence interval [CI] 2.07–2.15) and mild–moderate coronary artery calcium (0.96 events per 100 patient-years, 95% CI 0.95–0.97) than in patients with no coronary artery calcium (0.64 events per 100 patient-years, 95% CI 0.62–0.65) (Appendix 1, Table 2). In unadjusted analyses, extensive coronary calcium was more likely to be present in patients who went on to experience the

Table 1: Patient demographics according to extent of coronary artery calcification

Variable	Total no. (%)* of participants n = 1486	No. (%)* of participants with extensive CAC n = 439	No. (%)* of participants with mild-moderate CAC n = 793	No. (%)* of participants with no CAC n = 254	p value
Age, yr, mean $\pm$ SD	66.21 $\pm$ 5.5	67.5 $\pm$ 5.5	66.1 $\pm$ 5.4	64.1 $\pm$ 5.1	< 0.001
Sex					< 0.001
Male	765 (51.5)	276 (62.9)	403 (50.8)	86 (33.9)	–
Female	721 (48.5)	163 (37.1)	390 (49.2)	168 (66.1)	–
Smoking history					0.60
Formerly smoked	469 (31.6)	143 (32.6)	252 (31.8)	74 (29.1)	–
Currently smokes	1017 (68.4)	296 (67.4)	541 (68.2)	180 (70.9)	–
Hypertension	571 (38.4)	228 (51.9)	263 (33.2)	80 (31.5)	< 0.001
Dyslipidemia	634 (42.7)	257 (58.5)	283 (35.7)	94 (37.0)	< 0.001
Diabetes	222 (14.9)	94 (21.4)	100 (12.6)	28 (11.0)	< 0.001
Framingham Risk Score					< 0.001
Low: < 10%	62 (4.2)	8 (1.8)	29 (3.7)	25 (9.8)	–
Intermediate: 10%–19%	479 (32.2)	83 (18.9)	286 (36.1)	110 (43.3)	–
High: $\geq$ 20%	945 (63.6)	348 (79.3)	478 (60.3)	119 (46.9)	–

Note: CAC = coronary artery calcification, SD = standard deviation.
*Unless otherwise specified.

Table 2: Study outcomes according to extent of coronary artery calcification

Outcome	Total no. (%) of participants n = 1486	No. (%) of participants with extensive CAC n = 439	No. (%) of participants with mild-moderate CAC n = 793	No. (%) of participants with no CAC n = 254	p value
Primary outcome	78 (5.2)	39 (8.9)	32 (4.0)	7 (2.8)	< 0.001
Secondary outcomes					
All-cause death	49 (3.3)	24 (5.5)	21 (2.6)	4 (1.6)	0.007
CV events	45 (3.0)	24 (5.5)	16 (2.0)	5 (2.0)	0.002
CV death	16 (1.1)	9 (2.1)	5 (0.6)	2 (0.8)	0.06
Nonfatal MI	11 (0.7)	7 (1.6)	3 (0.4)	1 (0.4)	0.045
Elective PCI	5 (0.3)	3 (0.7)	2 (0.3)	0 (0.0)	0.30
Nonfatal stroke	13 (0.9)	5 (1.1)	6 (0.8)	2 (0.8)	0.80
Cancer outcomes					
Cancer death	19 (1.3)	8 (1.8)	9 (1.1)	2 (0.8)	0.40
Lung cancer death	10 (0.7)	4 (0.9)	5 (0.6)	1 (0.4)	0.70
Lung cancer diagnosis	42 (2.8)	13 (3.0)	20 (2.5)	9 (3.5)	0.70

Note: CAC = coronary artery calcification, CV = cardiovascular, MI = myocardial infarction, PCI = percutaneous coronary intervention.

primary outcome than in those who did not (50.0% v. 28.4%, hazard ratio [HR] 2.30, 95% CI 1.47–3.59) (Table 3 and Figure 2). Results were similar for any coronary artery calcification (91.1% v. 82.5%, HR 2.19, 95% CI 1.00–4.75). Framingham Risk Score, hypertension, dyslipidemia, diabetes, lung cancer, and all cancers were also associated with the primary outcome (Table 3).

In Cox proportional hazards regression, after we adjusted for clinical cardiovascular risks, extensive coronary artery calcification was an independent predictor of the primary outcome (adjusted HR 2.13, 95% CI 1.35–3.38) (Table 3).

The association of any coronary artery calcium with the primary outcome was smaller and not statistically significant

Table 3: Unadjusted and adjusted associations of coronary artery calcium and other variables with the primary composite outcome (all-cause death and cardiovascular events)

Variable	Total no. (%) [*] participants with events n = 78	Total no. (%) [*] participants with no events n = 1408	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Extensive artery coronary calcium, n = 439†	39 (50.0)	400 (28.4)	2.30 (1.47–3.59)	2.13 (1.35–3.38)¶
Any coronary artery calcium, n = 1232†	71 (91.1)	1161 (82.5)	2.19 (1.00–4.75)	1.99 (0.91–4.35)**
Covariates				
Age, yr, mean ± SD, per additional year	66.6 ± 5.3	66.2 ± 5.5	1.01 (0.97–1.05)	1.00 (0.96–1.04)††
Male sex, n = 765	43 (55.1)	722 (51.3)	1.17 (0.75–1.82)	1.02 (0.65–1.61)††
Diabetes mellitus, n = 222	18 (23.1)	204 (14.5)	1.65 (0.97–2.78)	1.29 (0.74–2.26)††
Hypertension, n = 571	42 (53.8)	529 (37.6)	1.79 (1.15–2.80)	1.37 (0.82–2.30)††
Dyslipidemia, n = 634	44 (56.4)	590 (41.9)	1.69 (1.08–2.65)	1.18 (0.71–1.98)††
Currently smokes, n = 1014	57 (73.1)	960 (68.2)	1.27 (0.77–2.09)	1.30 (0.78–2.20)††
Framingham Risk Score‡, mean ± SD, per 1% increase	24.8% ± 6.8%	22.8% ± 7.7%	1.03 (1.00–1.07)	1.02 (0.99–1.06)¶
Cancer outcomes§				
All cancers, n = 80	21 (26.9)	59 (4.2)		
Lung cancer, n = 42	12 (15.4)	30 (2.1)		

Note: CI = confidence interval, HR = hazard ratio, SD = standard deviation.
^{*}Unless otherwise specified.
[†]The comparison is no coronary artery calcium.
[‡]Framingham Risk Score represents the 10-year risk of clinical cardiovascular events.
[§]Cancer outcomes occurred during follow-up and had not been identified at or before the time of computed tomography screening. Accordingly, they were not included in the multivariable models reported here.
[¶]Variables in the model included extensive coronary calcium and Framingham Risk Score.
^{**}Variables in the model included any coronary calcium and Framingham Risk Score.
^{††}Variables in the model included extensive coronary calcium, age, sex, diabetes mellitus, hypertension, dyslipidemia, and smoking status.

(adjusted HR 1.99, 95% CI 0.91–4.35) (Table 3). Cardiovascular risk factors, either individually or combined as the Framingham Risk Score, were not associated with the primary outcome after adjustment for other covariates (Table 3 and Appendix 1, Tables 3 and 4).

In secondary analyses, extensive coronary artery calcium was associated with all-cause death (HR 2.39, 95% CI 1.34–4.27) and cardiovascular events (HR 2.06, 95% CI 1.13–3.77) (Appendix 1, Tables 5–8). When the Framingham Risk Score was replaced with individual cardiovascular risk factors in the model, associations of extensive coronary calcium (HR 2.34, 95% CI 1.28–4.25) and any coronary artery calcium (HR 2.03, 95% CI 0.92–4.49) with the primary composite outcome were similar to the main analysis.

Extensive coronary artery calcium remained predictive of cardiovascular events after we adjusted for noncardiovascular death (cancer death and other noncardiovascular death) as a competing risk (HR 2.05 95% CI 1.09–3.85). The association of any coronary artery calcium with cardiovascular events after we adjusted for noncardiovascular death was smaller and not statistically significant (HR 1.38, 95% CI 0.55–3.47). Exclusion of events related to medical assistance in dying did not alter the results of the competing risk analysis (extensive coronary calcium, HR 2.07, 95% CI 1.10–3.87; any coronary calcium, HR 1.38, 95% CI 0.55–3.45).

Interpretation

We present data from a large consecutive cohort from a Canadian lung cancer screening program and report cardiovascular and cancer outcomes. We confirmed a high prevalence of asymptomatic coronary atherosclerosis in this population and found that the risk of death and nonfatal cardiovascular events was highest in people with extensive coronary artery calcium. Estimated Agatston scores of more than 400 predicted the primary outcome of death and nonfatal cardiovascular events. Extensive coronary artery calcium was predictive of the primary outcome and all-cause death despite increased cancer risk and noncardiovascular death in this population with an extensive smoking history.¹⁴

Most previous studies considering the prognostic importance of coincidental coronary artery calcium on lung screening CT scans did not include competing risk analysis.^{6,19,21–23,27} The persistence of coronary artery calcium to predict events in survival models that included cancer-related and noncardiovascular death indicates the clinical importance of this coincidental finding. The relevance of using comprehensive competing risks is that extensive smoking increases the risks of premature death from other causes and not solely lung cancer.^{14,28}

Previous work has suggested that in the presence of advanced cancer, coronary artery calcium may be less predictive

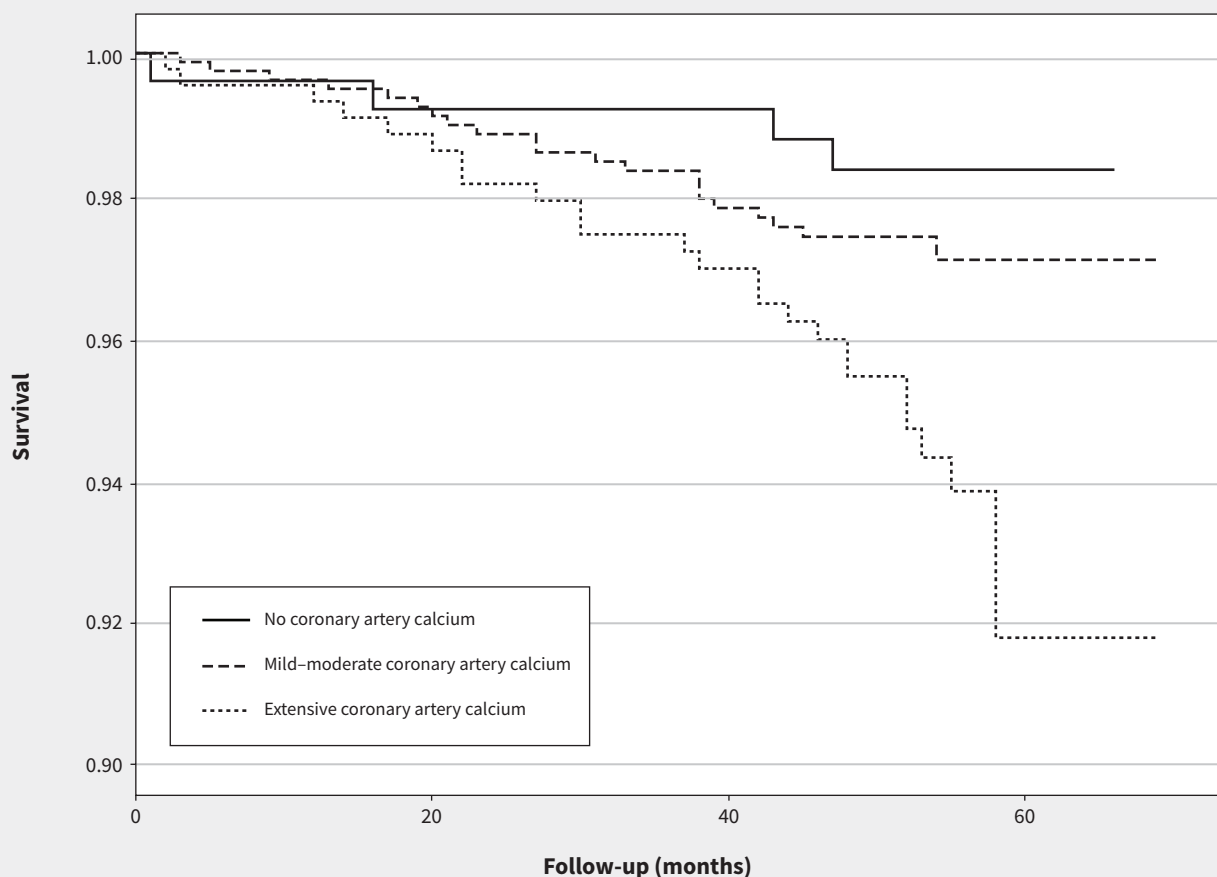


Figure 2: Kaplan–Meier survival curves for all-cause death according to extent of coronary artery calcium.

of clinical events.²⁰ Such observations were likely a result of the occurrence of cancer-related events before development of an adverse cardiovascular event. In contrast, the lung screening participants in the current study represented a lower risk population with good prognosis. And because they presented for screening, this population may be amenable to primary cardiovascular prevention strategies.

The prevalence of coronary artery calcium in lung cancer screening populations has varied depending upon the origin of the study. Rasmussen and colleagues studied a Danish population, finding that coronary artery calcium was present in 47% of participants, and 7% of participants had an Agatston score greater than 400 for coronary artery calcium.⁶ This population was younger and had lower prevalence of hypertension, dyslipidemia, and diabetes than our cohort. In contrast, where cardiovascular risk profiles were similar to that of the current study, the prevalence of coronary artery calcium was similar²¹ (Appendix 1, Table 9).

The prevalence and extent of coronary artery calcium appear to be unique to the population studied, and reflective of differences in atherosclerotic risks. Geographical differences in prevalence and extent of coronary artery calcium emphasize the importance of local data to determine potential health care consequences of incidental findings on lung screening CT.

Annualized event rates were low in patients without coronary calcium and consistent with the findings of others.²² In patients with coronary artery calcium, event rates were comparable to those seen in previously studied asymptomatic populations with similar coronary artery calcium extent and 3 or more cardiovascular risk factors.²⁹

How clinicians interpret and manage incidental findings on low-dose lung screening CT will affect the success of the program. We and others have noted that extensive coronary artery calcium does carry prognostic significance with medium-term follow-up and is a valid health care target. Lesser degrees of coronary artery calcium would be expected to have prognostic significance with longer follow-up, and guideline-directed risk reduction therapy for these findings would be recommended.³⁰

A potential negative impact of coincidental detection of coronary artery calcium is the possibility that inappropriate investigations could occur. Caution but diligence will therefore be required in managing incidental coronary artery calcium findings on lung screening CT, to ensure the prognostic benefit from this initiative can be fully realized. Lung cancer screening, although primarily seeking to reduce death from lung cancer, also has an opportunity to help tackle the second most common cause of premature death in middle-aged adults, through the identification and risk stratification of coronary atherosclerosis.

Limitations

This is a single-centre, retrospective study, and as such, the population may not be representative of other sites. It is possible some nonfatal events were managed at community sites and not recorded on The Ottawa Hospital electronic record. We believe the likelihood for this is low, given that the regional stroke centre and coronary angiography site are at The Ottawa Hospital. It is also possible that fatal events may not have been accounted for. We obtained survival follow-up from the electronic hospital record. For the 4 out-of-hospital deaths during the study, the patients' deceased status was captured in the electronic record.

We did not perform a standardized gated coronary calcium score using the Agatston method.¹⁶ The ordinal scoring used in the current study was limited to 3 categories. We defined extensive calcium at an estimated Agatston score higher than 400. Patients with extensive coronary calcium were not further risk stratified to identify those at highest risk; e.g., Agatston score higher than 1000. In the future, artificial intelligence algorithms to detect coronary artery calcification on nongated CT scans may be able to offer more precise estimated Agatston scores, to better delineate patients at highest risk.

Conclusion

We present cardiovascular outcome data from Canadian participants screened for lung cancer and highlight the relevance of coincidental coronary artery calcification that is seen on thoracic CT. We have shown that even in the presence of cancer and other noncardiovascular deaths, extensive coronary artery calcium predicts cardiovascular events and all-cause death. Prospective studies to investigate appropriate clinical response to coincidental coronary artery calcium are needed. While these data are awaited, continued attention to cardiovascular disease prevention is warranted and could be amalgamated into lung cancer screening initiatives to promote health.

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Affiliations: Medicine Division of Cardiology, (Cabral Caires, Mbondo Kasuku, Mengesha, Paterson, Chen, Chow, Small), University of

Ottawa Heart Institute; Department of Cardiology (Garuba, Law, Johnson), The Ottawa Hospital; Department of Radiology (Dennie, Pena), University of Ottawa, Ottawa, Ont.

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Correspondence to: Gary Small, gsmall@ottawaheart.ca