Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers

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Introduction

Smoking continues to be the principal cause of premature death in the USA and the second cause of death worldwide.1,2 The World Health Organization estimates that nearly half of the current smokers (n = 650 million) will die as a result of tobacco use.2 In the USA, it is estimated that ~5.6 million years of potential lives lost each year as a result of cigarette smoking.3 The effect of smoking on the cardiovascular system is pervasive with unfavourable effects on lipids, blood pressure, inflammation, and subclinical disease markers of non-cardiac atherosclerosis.3 Several reports have examined the association of smoking with coronary calcium scoring,4,5 and data are available on the effect of smoking on the severity of angiographic coronary stenosis;6,7 however, to date, no prior report has focused on the prognostic value of computed tomographic measurements of coronary artery calcium. Thus, we sought to explore the relative prognostic differences by smoking status in the prevalence and extent of coronary artery calcium in a large registry of 10 377 asymptomatic individuals, 40% of whom were current smokers.

Methods

Patient selection

A consecutive series of 10 377 asymptomatic individuals who were referred for evaluation of cardiac risk factors by their primary care physician were followed for the occurrence of death from all-causes at 5 years. This cohort included a consecutive series of patients and, therefore, 100% of the available cohort was included in this analysis. All referred patients were available for study entry and enrolled in this registry. All patients gave informed consent for the procedure and follow-up portion of this study. Results from this cohort study have been reported in several prior series.8–10 All patients without a prior history of coronary artery disease (CAD) were included in this registry.

KEYWORDS

Prognosis; Smoking; Coronary calcium; Cardiovascular screening

Aims To determine the extent and prognostic significance of coronary artery calcium in asymptomatic smokers and non-smokers. Population data are available on the prognostic impact of smoking on atherosclerotic imaging measurements of the carotid and peripheral arteries. Limited data are available on the impact of cigarette smoking on the prognostic value of coronary calcium.

Methods and results A referred patient registry of 10 377 asymptomatic individuals (40% were current smokers) was followed for death from all-causes at 5 years. Univariable and multivariable Cox proportional hazard models were calculated to estimate time to all-cause mortality. Cumulative 5-year survival was 96.9 and 98.4% for smokers when compared with non-smokers (P < 0.0001). Using a stratified Cox proportional hazards survival analysis, survival for non-smokers ranged from 99.7 to 89.6% with calcium score of 0–10 and >1000 (P < 0.0001). In comparison, smokers had survival rates ranging from 99.5 to 81.4% for calcium score of 0–10 to >1000 (P < 0.0001). When further evaluating the effect of age on prognosis by coronary calcium, there was an additive relationship between age and calcium that was exacerbated with smoking, resulting in higher relative risk ratios for older smokers with coronary calcium (P < 0.0001). For smokers <50 years of age, a calcium score >1000 was associated with a relative risk ratio that was elevated 8.9-fold (P = 0.029). Thus, resulting in an expected reduction in life expectancy of 4.8 years for smokers <50 years of age with a calcium score >400 (P < 0.0001).

Conclusion The prognostic value of coronary artery calcium scoring was accurate in identifying a high-risk cohort of asymptomatic smokers and non-smokers. Young smokers with high-risk calcium scores have a four- to nine-fold increased risk of dying when compared with similarly aged non-smokers. When prospectively applied, evidence of a high-risk calcium score may be useful in educating patients as to their expected risk of dying over the next 5 years.

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Data collection

As part of the referral process, data collection included information on categorical risk factors. These data were collected through patient interview by an experienced nurse practitioner and reviewed by two experienced cardiologists (T.Q.C. and P.R.). Additionally, each patient’s primary care physician also provided risk factor data at the time of referral to electron beam tomography (EBT). Collected risk factor data were corroborated by referring physician contact and cross-referenced to existing medical records. For the risk factors, systemic arterial hypertension was defined as a documented history of high blood pressure or concomitant treatment with medication, diet, and/or exercise. Additionally, an elevated blood pressure was defined as measurement of systolic blood pressure $>130$ mmHg or diastolic blood pressure $>85$ mmHg. Current smoking status was defined as ongoing cigarette smoking. Hypercholesterolaemia was determined on the basis of patient queries regarding medical treatment for high cholesterol and current cholesterol-lowering medication usage. Patients were also classified as diabetic if they had a prior diagnosis of diabetes mellitus by blood glucose measurement $>126$ mg/dL or treatment with diet, insulin, oral hypoglycaemic agents, or insulin-sensitizing agents (alone or in combination).

Electron beam tomography

Each patient gave informed consent to undergo screening with EBT. EBT imaging was performed on an Imatron C-100 or C-150 scanner (GE-Imatron, So. San Francisco, CA, USA). Approximately, 40 contiguous 3 mm thick tomographic sections were obtained beginning at the level of carina and extending through to the diaphragm; scan time was 100 ms per section. EBT imaging was electrocardiographically trigged at $\sim60$–80% of the R–R interval. Coronary calcification was calculated by measuring plaque in at least three contiguous pixels (i.e. voxel size $= 1.03$ mm$^3$) using an attenuation coefficient $>130$ Hounsfield units. We employed quantitative coronary calcium scoring using the methods previously described by Agatston et al.11 For routine EBT imaging, all scans were reviewed by experienced investigators (P.R. and T.Q.C.) in random order on a NetraMD workstation (Scilimage, Los Altos, CA, USA).

Follow-up procedures

Death from all causes was verified by searching the National Death Index.12 Our Human Investigations’ Committee approved the procedures for follow-up and collection of death data from the National Death Index. Patients were followed for 5 years for the collection of death data. The median time of follow-up for surviving patients was 4.5 (25th, 75th percentiles = 2.1, 5.0) years.

Statistical methods

Death from all causes was the primary endpoint for this registry. For comparisons of smokers vs. non-smokers, categorical risk factors and coronary calcium score subsets were compared using a $\chi^2$ statistic. We compared continuous variables, such as age, with smoking status, using a $t$-test.

Time to death from all causes was estimated using a Cox proportional hazards model. For the Cox model, univariable and multivariable models were developed and included an evaluation of traditional cardiac risk factors and coronary calcium score measurements in smokers and non-smokers. It was our intention to evaluate the relationship between calcium measurements and smoking, and to do so, we evaluated both the prognostic value of continuous and categorical coronary calcium scores. A receiver operating characteristic (ROC) curve was calculated for continuous and categorical measures estimating death from all-cause.

Cumulative differences in survival were compared for smokers and non-smokers using an unadjusted Cox survival analysis. In each case, we evaluated the proportional hazards assumption by determining whether the hazard ratio was constant across time or if the proportionality of hazard from one case to another did not vary over time. We visually inspected the survival curves for linearity in decrementally worsening survival across time. In no cases, did the survival curves for calcium scores cross over time.

From the Cox models, relative risk ratios and 95% confidence intervals (CI) were calculated. A first-order test for interaction of smoking by the coronary calcium score was calculated in a Cox regression model. Relative risk ratios (95% CI) for calcium subsets of 11–100, 101–400, 401–1000, and >1000 were calculated in smokers aged <50, 50–59, 60–69, 70–79, and $\leq$80 years. Furthermore, a stratified Cox survival analysis plotted 5-year survival by coronary calcium subsets from 0–10, 11–100, 101–400, 401–1000, and >1000, respectively, for smokers and non-smokers. Survival rates were rounded to the nearest tenth of a percent.

Risk-adjusted or multivariable prognostic models were also employed to assess the independent prognostic value of coronary calcium in smokers as compared with non-smokers while controlling for other cardiac risk factors including age, hypertension, hyperlipidaemia, diabetes, and a family history of premature coronary disease. The justification for this model was to include traditional cardiac risk factors that were components of global risk scores and effect modifiers of adverse outcome.

Based upon a patient’s age at the time of EBT screening, average life expectancy was estimated based upon published national normative statistics for age and gender subsets (www.cdc.gov/nchs/fastats/lifeexpect.htm, date accessed: August 2004). Each patient’s life expectancy was adjusted for the observation of death during follow-up. We have previously published our methodology for estimating life expectancy.13,14 In this case, the observed time to death was used as their individual life expectancy. In addition, age and gender estimates of life expectancy were further revised based upon an age-, calcium-, and other risk factor-adjusted predicted survival function. The final estimate is derived using a product of predicted survival by the normative life expectancy estimate. Life expectancy estimates for smokers were then compared with non-smokers by their coronary calcium score subset using non-parametric tests including k-independent samples using the Kruskal–Wallis and median statistic. Both statistical tests resulted in concordant results and the P-values included were those of the Kruskal–Wallis test. Life expectancy estimates were also further stratified by age groups.

Results

Clinical characteristics of the asymptomatic smokers and non-smokers

Of the 10 377 patients, 40% were current smokers. When compared with non-smokers (Table 1), smokers were younger, more often male, with a greater prevalence of cardiac risk factors, with exception hyperlipidaemia.

Smokers also had a greater number of cardiac risk factors as compared with non-smokers (2.9 ± 0.9 vs. 1.8 ± 1.0, $P < 0.0001$). Overall, smokers had a greater odds of calcium scores from 11–100, 101–400, 400–1000, and >1000 ($P < 0.0001$), respectively (Figure 1). Smokers had, on average, a calcium score 72 points higher than non-smokers ($P < 0.0001$). Nearly two-thirds of non-smokers had no calcium on EBT imaging as compared with approximately half of current smokers ($P < 0.0001$). Coronary artery calcium was reported in 11.6, 4.4, and 2.4% of non-smokers with scores of 101–400, 401–1000, and >1000, respectively. In comparison, 17.2, 8.4, and 4.4% of current smokers had calcium scores of 101–400, 401–1000, and >1000, respectively.
All-cause survival in smokers and non-smokers

A total of 249 deaths were reported during 5 years of follow-up. Cumulative 5-year survival was 96.9 and 98.4% for smokers as compared with non-smokers (Figure 2, P < 0.0001). As reported in Table 2, survival differed by smoking status and the co-occurrence of various cardiac risk factors. For patients <55 years of age, smokers had a 5-year survival of 97.8% as compared with 99.3% for non-smokers (P < 0.0001). Similarly, among smokers, worsening survival was noted for females (P < 0.001), hypertensive patients (P < 0.0001), hyperlipidaemic patients (P < 0.0001), and smokers with a family history of premature CAD (P < 0.0001). Because of the limited sample size of diabetics, only a trend toward worsening survival was noted for diabetic smokers (P = 0.066).

Smokers who died during follow-up had an average calcium score of 505 ± 722 as compared with smokers who survived and had an average score of 164 ± 393 (P < 0.0001). For smokers, univariable relative risk ratios were elevated 2.4-, 3.4-, 5.6-, and 10.9-fold higher, respectively, for patients with coronary artery calcium scores (CACS) of 11–100, 101–400, 401–1000, and >1000 as compared with scores of 0–10 (Table 3, P < 0.0001). The univariable relative risk ratio using the continuous CACS was 1.001 (95% CI = 1.001–1.001, P < 0.0001).

Multivariable model estimating death from all causes

Significant multivariable estimators of death from all causes include age (P < 0.0001), such that a patient’s risk of death increased ~7% for every year of increasing age. In this model, hypertension (P < 0.0001) and diabetes mellitus (P = 0.001) were also significantly associated with worsening survival, with risk-adjusted relative risk ratios of 1.7 (95% CI = 1.3–2.4) (Table 4). In comparison, due to their age of evaluation and current treatment, both family history of premature CAD and hyperlipidaemia exhibited negative coefficients noting a lower risk in the presence of these stated risk factors. In addition, a first-order interaction of coronary calcium scores by smoking status was statistically significant in a model controlling for other cardiac risk factors (continuous and categorical coronary calcium scores P < 0.0001 for both). In this model, smokers with varying calcium scores had higher relative risk ratios ranging from 1.8- to 4.5-fold as compared with patients with scores of 0–10 (P < 0.0001). Using a stratified Cox proportional hazards survival analysis (Figure 3), survival for non-smokers ranged from 99.7 to 89.6% with calcium score of 0–10 and >1000 (P < 0.0001). In comparison, smokers had survival rates ranging from 99.5 to 81.4% for calcium score of 0–10 to >1000 (P < 0.0001).

Relative risk ratios for all-cause mortality in smokers of varying age groups

On further evaluation of the prognostic significance of coronary calcium in varying age groups of smokers, we revealed a trend towards higher relative risk ratios for older smokers with more extensive coronary calcium (Figure 4, P < 0.0001). For example, in patients with a calcium score of 101–400, the relative risk ratios ranged from 1.2 (P = 0.001) to 7.1 (P < 0.0001) in patients who are in the age group of 50–59 and ≥80 years.
However, for the 100 smokers with a high-risk calcium score >1000, the relative risk ratio was elevated 8.9-fold higher ($P = 0.029$). For patients in their 50s, relative risk ratios were elevated 3.6- and 3.8-fold for those with calcium score of 401–1000 ($P = 0.001$) and > 1000 ($P = 0.027$).

### Effect of coronary artery calcium on predicted life expectancy in smokers
Smoking was estimated to decrease a patient’s life expectancy by nearly one year for whom CACS were >400 ($P < 0.0001$). When compared across age groups (Table 5), there was a graded relationship between age and calcium scores with changes in predicted life expectancy. Generally, patients with low-risk calcium scores were predicted to live ~5.0–6.9 years longer than in patients with larger calcium scores ($P < 0.0001$). By comparison, in patients with high-risk calcium scores greater than 400, the expected loss in life expectancy was 4.8 years for patients <50 years of age; this decreased to 2.0 years for those >80 years of age ($P < 0.0001$).

### Discussion
Pathology studies have repeatedly shown a clear and strong association between smoking and atherosclerotic disease for younger and older patients. Smoking is the single greatest risk factor for acute coronary thrombosis in cases of sudden cardiac death. Population studies are available on the prognostic impact of smoking on more progressive atherosclerotic disease in the carotid and peripheral arteries. Although the prognostic value of CACS has been reported, limited data are available on the utility of computed tomographic measurements in key patient subsets and importantly note an inconsistent relationship between smoking and subclinical disease.

Although it is a prominent cardiovascular risk factor, smoking has been variably related to worsening prognosis in asymptomatic cohorts undergoing coronary heart disease screening. In many cases, prior reports on the prognostic value of coronary heart disease screening have focused on the comparative predictive accuracy of global risk scores, such as the Framingham risk score, and have not evaluated the interactive relationship between coronary calcium scores and smoking. A key element that may explain the difference between the current study and prior reports may be related to a substantially higher proportion of smokers in the current series as compared with the limited predictive accuracy of smoking in younger, healthier cohorts from prior reports.
To our knowledge, this is the first analysis to evaluate the impact of cigarette smoking on the prognostic value of coronary calcium. These results could be generalizable to a large segment of the USA and European population who currently smoke. In the USA, recent data from the Centers for Disease Control and Prevention reveal that nearly one in five adults report being current smokers. In our large clinical registry of 10,377 asymptomatic individuals, nearly 40% reported being current smokers.

Coronary disease prevalence rates
The Framingham study reported that 10-year coronary heart disease rates were 27 and 37% for female and male smokers. From a recent study by Danesh et al., the odds of coronary heart disease were elevated approximately two-fold for smokers as compared with non-smokers. In our study, current smokers had significantly more coronary artery calcium than non-smokers with nearly two-thirds having calcium scores >10 as compared with only half of non-smokers having notable coronary calcification. Approximately, 13 and 7% of smokers and non-smokers had a high-risk calcium score >400 ($P < 0.0001$); the higher frequency and frequent atherosclerotic disease in smoking patients is likely the result of repeated smoking-induced endothelial damage with subsequent coronary thrombosis and enhanced arterial plaque deposition.

In two prior studies, a history of smoking was significantly associated with the presence of coronary calcium in multivariable regression analyses. Using a combined subclinical atherosclerosis index (constructed using an electrocardiogram, echocardiogram, carotid intima media thickness, ankle arm index, and responses to an angina questionnaire) in participants (aged $\geq 65$ years) from the Cardiovascular Health Study, current smokers were more than twice as likely to have evidence of atherosclerotic disease even when adjusting for other major risk factors.

Comparative prognostic studies
Smoking was not predictive of outcome in two recent reports evaluating coronary heart disease screening strategies including risk factors and coronary calcium measures. The limited representation of smokers may have precluded prior reports from evaluating the prognostic...
value of smoking as a prominent effect modifier interacting with subclinical disease measures. The focus of prior reports has also been on the prognostic value of coronary calcium when compared with global risk scores; thus, diverting analyses away from the interactive relationship between subclinical disease and smoking. Two critical factors appear to be influential in discerning the incremental risk of smoking by coronary calcium extent measures. It appears that in referral populations evaluated in fitness clinics or for those undergoing health screenings, the prevalence of smoking may be low obscuring its inter-relationship to CACS measurements. Furthermore, prognostic results from healthier cohorts would be less generalizable to patient populations where higher rates of smoking are reported. The prevalence of smoking in our cohort was nearly four-fold higher than that noted in the LaMonte, Arad, and Taylor series. Thus, it may be in certain settings with a low prevalence of smoking that its predictive relationship affecting subclinical disease markers may be diminished. As a result of a limited number of smokers from prior series, the effective sample size and ensuing statistical power of an interaction of smoking by coronary artery calcium scoring may be suboptimal.

In our sample of 10,377 patients, study results reveal that female smokers and those with hypertension and other cardiac risk factors have worsening survival as compared with similarly matched non-smokers (P < 0.01). A recent report from the surgeon general of the US noted that cigarette smoking has been linked with sudden death of all types in women and men. Our data also revealed a graded and somewhat linear relationship between prognosis by age and coronary calcium; such that, elderly patients had a higher risk of dying and that, in the setting of significant subclinical disease, their mortality risk was further increased if they smoked and had a large burden of subclinical atherosclerosis. For smokers age 80 or older, their risk of dying was elevated 5.3- to 11.0-fold for calcium scores ranging from >100 to >1000 as compared with non-smokers. Relative risk ratios were even higher for smokers of age 80 or older ranging from 10 to 22.9 for the same categories of calcium score.

Other investigators have noted significantly higher restenosis and progressive CAD rates in patients who continue to smoke as compared with non-smokers. Specifically, restenosis rates were nearly 20% higher following percutaneous coronary intervention (PCI) and repeat coronary bypass graft surgery rates were more than three-fold higher in smokers as compared with non-smokers. More relevant to the current series is the published evidence on the prognostic value of imaging non-cardiac vascular beds and their association with coronary heart disease events. Although little data is available on the role of computed tomography in the evaluation of a smoker’s risk of atherosclerotic disease, there is considerable data on the use of other imaging tests for subclinical disease including carotid intima media thickness and ankle brachial index. Carotid thickening and plaque occurred more often in smokers vs. non-smokers and a carotid stenosis was approximately three-fold more likely in female and male smokers. These studies reveal a consistently strong positive association between smoking and carotid intima media thickness. Importantly, cigarette smoking was associated with a greater baseline carotid intima media thickness and higher incidence of coronary heart disease events. From a pooled analysis using the atherosclerotic risk factors in the Community Study and Cardiovascular Health Study, smoking was strongly and independently associated with carotid atherosclerosis when controlling for age. In the same report, a stronger association was noted in older adults. When evaluating the utility of ankle brachial index measurements, smoking accelerates the rate of peripheral arterial disease. But also, smokers with abnormal ankle brachial measurements have an increased risk of coronary as well as cerebrovascular events.

High-risk, young smokers

It is only of late that computed tomographic imaging allowed for a direct assessment of subclinical coronary atherosclerosis for measurement of coronary calcification and, thus, the unveiling of prognostic evidence has only been reported in the last decade. Our analysis revealed that young smokers with evidence of extensive subclinical disease had 5-year survival rates significantly lower than that of young non-smokers. The results of our study show that young smokers with high-risk calcium scores have an elevated risk of dying from four- to nine-fold higher than young, non-smokers. In models estimating life expectancy, patients <50 years of age with a high-risk calcium score were predicted to live ~5 years less than that of similarly aged asymptomatic, non-smokers. This evidence is concerning, given the higher growth rates for smoking in younger populations. Moreover, this data is in concert with pathologic series showing that young smokers may be particularly prone to acute coronary thrombosis.

These results are, however, in apparent contrast to prior reports noting that younger age, higher LDL-cholesterol, diabetes, and active smoking were associated with a greater frequency of non-calcified plaques; as reported in 40 consecutive patients with acute coronary syndromes. This report noted an inverse relationship between smoking and the presence of coronary calcium. In a related report from 618 relatively low-risk (mean age = 48 years) men enrolled in an employee health program, no association was found between smoking status and coronary calcium. These prior reports were limited because of smaller sample sizes as compared with the current analysis that focused on prognosis and was undertaken in a sufficiently statistically powered sample. In the latter report by Simon et al., a lower frequency of detectable calcium and the use of calcium subsets of 0, 1-9, 10-99, and ≥100 may have undervalued the association between smoking and computed tomographic measurements of subclinical disease. Differences between the prior and current results may also be the result of variable risk in an employee vs. clinical population. Resulting in a lower prevalence of significant calcium where only 11% (17%) of the 681 asymptomatic employees had a calcium score ≥100 as compared with nearly one in four of our patient cohort. Moreover, the authors did not evaluate the long-term effects of smoking but only current use that may be lessened because of the younger age of their low-risk employee cohort. However, the possibility remains that subclinical disease testing may
have a greater incremental value in higher risk, clinical populations; at least for smokers with more frequent risk factors.

Study limitations
Although, we do not have available cardiac specific mortality, the examination of death from all causes allows for a more reliable prediction model without the possibility for cause of death misclassification. Furthermore, prior reports often utilize coronary-specific death rates, and the inclusion of other vascular events encompass nearly 40% of all deaths in this middle-age to elderly cohort; as based upon data from the Centers for Disease Control and Prevention. Only categorical risk factor data were available thus diminishing the predictive value of cardiac risk factors. We further did not document the patient’s number of pack years smoked that may provide further insight into a dose response relationship in this cohort. Finally, it is notable that the prevalence of smoking varies by ethnicity that may further confound the current results.

Conclusion
From a large cohort of patients referred to EBT, the prognostic value of coronary calcium scoring was particularly useful for identifying a high-risk cohort of asymptomatic individuals who persist in smoking. To our knowledge, this is the first analysis of the impact of cigarette smoking on the prognostic value of coronary artery calcium. Although prognostic data are available for carotid intima media thickness and ankle brachial index measurements, prior reports have been mixed as to the association between smoking and coronary calcium. Unique to this study are the results reporting that young smokers with high-risk calcium scores have an elevated risk of dying from four- to nine-fold higher than similarly-aged, non-smokers. In models estimating patient life expectancy, patients ~50 years of age with a high-risk calcium score would be expected to live nearly 5 years less than that of younger, non-smokers. When prospectively applied, evidence of a high-risk calcium score may be particularly useful in educating patients as to their risk of death over the ensuing 5 years. This information may provide the necessary motivation to promote lifestyle changes, because of more direct evidence of advanced CAD burden, to achieve higher quit rates when other population health policy efforts have been less successful. The current evidence with coronary calcium taken in conjunction with prior data on an elevated event risk with peripheral arterial disease reveals a similar pattern that the risk for clinical complications in the patient with high-risk subclinical atherosclerotic disease in smokers is high. It is then possible that serial measurements of coronary artery calcium may provide a means to improve the assessment and monitoring of disease risk in smoking patients. Coronary artery calcium measurement provides a direct measurement of subclinical coronary disease and may be an effective test to be used in conjunction with screening of smoking populations and to improve smoking cessation rates by finding potential at-risk patient subsets.

Conflict of interest: The authors have neither conflicts of interest nor financial disclosures to make.

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