JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 10, 2012

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcmg.2012.02.017

Mortality Rates in Smokers and Nonsmokers in the Presence or Absence of Coronary Artery Calcification

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OBJECTIVES The aim of this study was to further explore the interplay between smoking status, coronary artery calcium (CAC), and all-cause mortality.

BACKGROUND Prior studies have not directly compared the relative prognostic impact of CAC in smokers versus nonsmokers. In particular, although a calcium score of zero (CAC = 0) is a known favorable prognostic marker, whether smokers with CAC = 0 have as good a prognosis as nonsmokers with CAC = 0 is unknown. Given that computed tomography (CT) screening for lung cancer appears effective in smokers, the relative prognostic implications of visualizing any CAC versus no CAC on such screening also deserve study.

METHODS Our study cohort consisted of 44,042 asymptomatic individuals referred for noncontrast cardiac CT (age 54 ± 11 years, 54% men). Subjects were followed for a mean of 5.6 years. The primary endpoint was all-cause mortality.

RESULTS Approximately 14% (n = 6,020) of subjects were active smokers at enrollment. There were 901 deaths (2.05%) overall, with increased mortality in smokers versus nonsmokers (4.3% vs. 1.7%, $p < 0.0001$). Smoking remained a risk factor for mortality across increasing strata of CAC scores (1 to 100, 101 to 400, and >400). At each stratum of elevated CAC score, mortality in smokers was consistently higher than mortality in nonsmokers from the CAC stratum above. In multivariable analysis within these strata, we found mortality hazard ratios of 3.8 (95% confidence interval [CI]: 2.8 to 5.2), 3.5 (95% CI: 2.6 to 4.9), and 2.7 (95% CI: 2.1 to 3.5), respectively, in smokers compared with nonsmokers. However, among the 19,898 individuals with CAC = 0, the mortality hazard ratio for smokers without CAC was 3.6 (95% CI: 2.3 to 5.7), compared with nonsmokers without CAC.

CONCLUSIONS Smoking is a risk factor for death across the entire spectrum of subclinical coronary atherosclerosis. Smokers with any CAC had significantly higher mortality than smokers without CAC, a finding with implications for smokers undergoing lung cancer CT-based screening. However, the absence of CAC might not be as useful a "negative risk factor" in active smokers, because this group has mortality rates similar to nonsmokers with mild-to-moderate atherosclerosis. (J Am Coll Cardiol Img 2012;5:1037–45) © 2012 by the American College of Cardiology Foundation

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Smoking is a leading contributor to cardiovascular disease worldwide. Among Americans >18 years of age, 23% of men and 18% of women smoke (1). Although public health laws have helped curb smoking rates in Western populations (2), tobacco companies continue to aggressively advertise in Third World countries. Consequently, an estimated 1.3 billion people now smoke worldwide (1). Smokers have increased all-cause mortality, and it is estimated that up to 40% of this mortality is attributable to cardiovascular events (3).

Smoking exerts numerous pathological effects, including increases in endothelial dysfunction (4), platelet reactivity (5), and systemic markers of inflammation (including C-reactive protein) (6). These aberrations accelerate the development of both clinical and subclinical atherosclerosis in smokers (7). For instance, smoking has been strongly associated with both baseline coronary artery calcium (CAC) (8) and CAC progression (9,10), as measured by cardiac computed tomography (CT).

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CI = confidence interval

CHD = coronary heart disease

CT = computed tomography

EBT = electron beam tomography

HR = hazard ratio

However, the interaction between smoking and CAC has not been fully elucidated. Although it is known that smoking remains an independent risk factor for mortality after accounting for subclinical coronary atherosclerosis (8), a number of important questions remain. Is CAC a similarly good predictor of mortality among both nonsmokers and smokers? Prior studies have not specifically addressed this issue (8). Similarly, what are the relative risks of increasing levels of baseline CAC in smokers as compared with nonsmokers? Also, is mortality in smokers with a calcium score of zero (CAC = 0) higher than has been reported in the general population with CAC = 0 (11)?

With new evidence demonstrating a prognostic benefit for CT-based lung cancer screening in smokers (12), the mortality differences between the absence or presence of coronary calcification in smokers is of increasing clinical relevance. This question is particularly important, because smokers with CAC = 0 might harbor noncalcified plaque that is not visualized on calcium scoring protocols (13).

We sought to address these questions in the largest follow-up of CAC scanning yet undertaken.

METHODS

The study cohort consisted of 44,042 consecutive asymptomatic individuals, free of known coronary heart disease (CHD), referred by their physicians for electron beam tomography (EBT) to help refine individual CHD risk prediction. Patients were presumed to be free of clinical CHD on the basis of a clinical history, which was conducted by the referring physician. The dataset for this study represents the combination of data collected between 1991 and 2004 from 3 different centers in the United States (Nashville, Tennessee; Columbus, Ohio; and Torrance, California). The combined population was predominantly of Caucasian ethnicity.

All screened individuals provided informed consent to undergo EBT and for the use of their blinded data for epidemiologic research. The general study received approval from the Human Investigations Committee, and separate Committee approval was obtained for patient interviews, collection of baseline and follow-up data, and corroboration of the occurrence of death.

Risk factor data collection. All study participants were given a questionnaire for the collection of demographic characteristics as well as baseline cardiovascular risk factors. The following risk factors were considered in our study: 1) cigarette smoking was considered present if a subject was an active smoker at the time of scanning; 2) dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; 3) diabetes was defined as baseline use of oral anti-diabetes medications or insulin; 4) hypertension was defined as a self-reported history of high blood pressure or the use of antihypertensive medication; and 5) family history of premature CHD was determined by asking patients whether any member of their im-

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Manuscript received December 7, 2011; revised manuscript received January 31, 2012, accepted February 9, 2012.

mediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization in a male relative <55 years or a female relative <65 years in 36,010 (82% of the study population), whereas the age cutoff was <55 years of age in both male and female relatives in 8,042 participants recruited from the Columbus center (18% of the study population).

EBT screening protocol. All subjects underwent EBT on either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R-R interval.

A calcified lesion was defined as ≥3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored with the method developed by Agatston et al. (14) (Agatston units).

Follow-up and mortality ascertainment. Patients were followed for a mean of 5.6 ± 2.6 years (range 1 to 13 years). The primary endpoint was all-cause mortality. Ascertainment of mortality was conducted by individuals blinded to baseline historical data and EBT results, and was verified using the Social Security Death Index. The United States Social Security Death Index is a national registry of all deaths that occur within the United States, allowing for mortality ascertainment in 100% of study participants.

Statistical methods. The baseline characteristics of the study population are presented by smoking status. Age is presented as a continuous measure ± SD, and other risk variables are expressed as proportional frequencies. Age was compared across increasing CAC groups with analysis of variance techniques, and proportional frequencies of other risk variables were compared across increasing CAC groups with chi-square analysis. A p value <0.05 was considered statistically significant.

Annualized all-cause mortality rates were estimated by dividing the number of deaths by the number of person-years at risk. Mortality rates were first expressed for each CAC stratum group (0, 1 to 100, 101 to 400, and >400) and then stratified according to smoking status.

In addition, survival analysis was conducted with individual subject time to all-cause mortality data. Curves representing the cumulative probability of survival were generated with Kaplan-Meier estimates. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were calculated for each CAC stratum with the Cox proportional hazards regression model, with CAC = 0 as the reference group. Two hierarchical models were constructed: Model 1: adjusted for age and sex; and Model 2: adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, and family history of CHD. Schoenfeld residuals were calculated and visually interpreted to evaluate the validity of proportional hazards assumption. Interaction terms for sex and smoking in each CAC group were tested and discarded because of nonsignificance.

All statistical analyses were performed with STATA version 10 (StataCorp, College Station, Texas).

RESULTS

Clinical characteristics of the cohort. The final study population consisted of 44,042 asymptomatic individuals free of known cardiovascular disease before EBT. The average age was 54 ± 10 years. Approximately 14% of subjects were smokers (6,020 smokers, and 38,022 nonsmokers). Despite being younger on average, smokers had a greater number of cardiac risk factors as compared with nonsmokers (2.1 ± 1.2 vs. 0.8 ± 0.7, p < 0.0001) (Table 1).

All-cause mortality in smokers and nonsmokers. There were 901 deaths (2.05%) in the study cohort overall. A total of 258 (4.29%) smokers died over the mean follow-up of 5.6 years, as opposed to 643 (1.69%) nonsmokers (p < 0.0001). The mean annualized mortality rate was 10.99 deaths/1,000 person-years (95% CI: 9.63 to 12.30) for smokers versus 2.86 deaths/1,000 person-years (95% CI: 2.64 to 3.09) among nonsmokers. Furthermore, when the entire cohort was separated on the basis of

Table 1. Clinical Characteristics of Subjects With and Without a History of Cigarette Smoking

	Nonsmokers (n = 38,022, 86%)	Smokers (n = 6,020, 14%)	p Value
Age (yrs)	55 ± 11	53 ± 10	<0.0001
Female	45	57	<0.0001
Hypertension	33	41	<0.0001
Diabetes	5	10	<0.0001
Dyslipidemia	26	52	<0.0001
Family history of CHD	33	62	<0.0001

Values are mean ± SD or %
CHD = coronary heart disease.

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Table 2. All-Cause Mortality Rates by Cigarette Smoking Status as Stratified by Cardiac Risk-Factor Subsets

	Nonsmokers		Smokers	
	Rate/1,000 Person-Yrs at Risk	95% CI for Rate	Rate/1,000 Person-Yrs at Risk	95% CI for Rate
Entire cohort	2.86	2.64–3.09	10.99	9.63–12.30
Age				
<45 yrs	0.83	0.60–1.16	5.41	3.66–8.02
45–64 yrs	1.81	1.60–2.04	7.72	6.46–9.23
≥65 yrs	9.14	8.22–10.16	33.16	27.54–39.94
Sex				
Female	2.11	1.84–2.42	9.02	7.53–10.81
Male	3.44	3.13–3.78	13.15	11.15–15.53
HTN				
No	2.19	1.99–2.42	8.21	6.85–9.83
Yes	6.29	5.53–7.16	15.04	12.73–17.75
Diabetes mellitus				
No	2.42	2.22–2.63	9.93	8.67–11.35
Yes	14.78	12.34–17.69	20.37	15.16–27.38
Dyslipidemia				
No	2.67	2.45–2.93	11.86	10.07–13.97
Yes	3.64	3.10–4.25	9.84	8.18–11.84
Family history of CHD				
No	2.63	2.39–2.89	12.45	10.39–14.93
Yes	3.53	3.08–4.05	9.84	8.33–11.61

CHD = coronary heart disease; CI = confidence interval; HTN = hypertension.

cardiac risk-factor subsets, smokers had consistently higher mortality rates than nonsmokers (Table 2).

In age-sex adjusted analysis (model 1), smoking was associated with at least a 4-fold increase of mortality (HR: 4.39, 95% CI: 3.78 to 5.10, $p < 0.0001$). The HR for all-cause mortality among smokers was 3.73 (95% CI: 3.18 to 4.36), after adjustment for other relevant demographic data and cardiac risk-factors (model 2). There were no deviations from the proportional hazards assumption in any multivariable model.

All-cause mortality in smokers and nonsmokers, as stratified by CAC. As shown in Figure 1, CAC = 0 was found in 38% of smokers, as opposed to 46% of nonsmokers ($p < 0.0001$). CAC strata of 1 to 100, 101 to 400, and >400 Agatston units were found in 31%, 17%, and 14% of smokers, respectively. In comparison, the respective percentages were 32%, 12%, and 9% for nonsmokers.

We found that all-cause mortality rates were higher in both smokers and nonsmokers as baseline CAC score increased (Fig. 2). The lowest mortality was observed in nonsmokers with CAC = 0 (0.7 events/1,000 person years), whereas smokers with CAC >400 had the highest all-cause mortality rate (29.9/1,000 person years). Importantly, at each stratum of CAC score the mortality in smokers was noted to be higher than that of nonsmokers in the next highest CAC stratum (for example, smokers in the CAC stratum of 1 to 100 had higher all-cause mortality rates than nonsmokers in the CAC stratum of 101 to 400). Among smokers who died, CAC >400 was noted in 37% of participants at

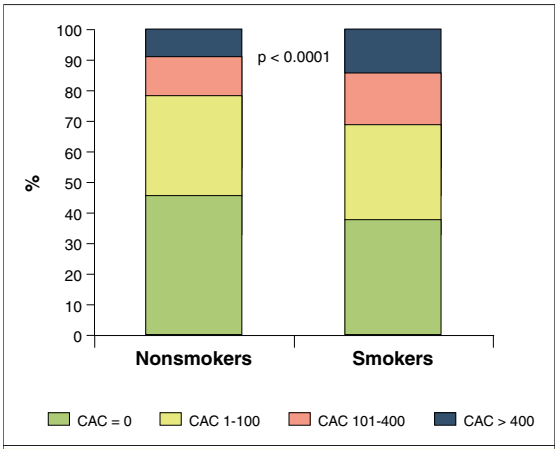

Figure 1. CAC Severity on the Basis of Smoking Status

On the basis of pre-specified coronary artery calcification (CAC) strata (1 to 100, 101 to 400, and >400 Agatston units), we found increased prevalence and severity of calcified subclinical atherosclerosis in smokers than in nonsmokers. These CAC strata of 1 to 100, 101 to 400, and >400 Agatston units were found in 31%, 17%, and 14% of smokers, respectively. In comparison, the respective percentages were 32%, 12%, and 9% for nonsmokers.

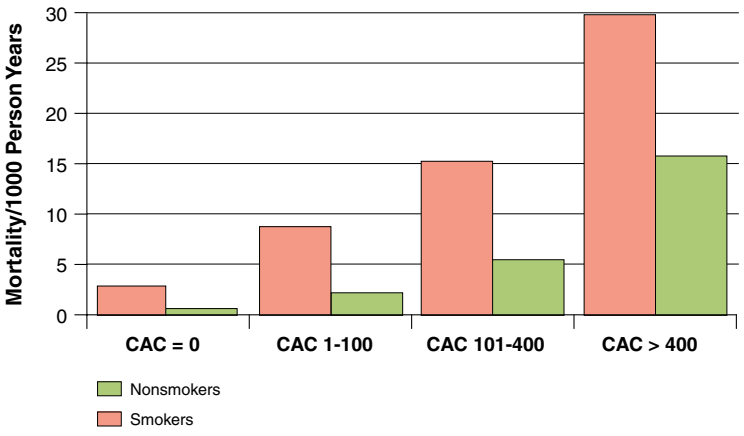

Figure 2. Mortality Rates (1,000 Person-Years) According to Smoking Status and CAC

The lowest mortality rate was observed in nonsmokers without coronary artery calcification (CAC) (0.7 events/1,000 person years), whereas smokers with CAC >400 had the highest all-cause mortality rate (29.9/1,000 person years). Importantly, at each stratum of CAC score, the mortality in smokers was noted to be higher than that of nonsmokers in the CAC stratum above (for example, smokers in the CAC stratum of 1 to 100 had higher all-cause mortality rates than nonsmokers in the CAC stratum of 101 to 400).

baseline as compared with 13% of smokers who survived ($p < 0.0001$).

With Cox proportional hazards regression, adjusting for demographic data and CHD risk factors, we found that increasing CAC scores (1 to 100, 101 to 400, and >400) were associated with increased hazard of all-cause mortality among both smokers as well as nonsmokers, compared with CAC = 0. However, the respective mortality HRs as CAC group increased were 2.0- to 4.3-fold among smokers and slightly higher at 2.6- to 8.0-fold among nonsmokers (Table 3). In keeping with this, the smoking-CAC group interaction term was negative (HR of 0.75, $p < 0.001$), suggesting that the association of smoking with mortality was weaker in higher CAC groups.

In Table 4 we take a different perspective. Instead of using CAC to stratify mortality in both smokers and nonsmokers as independent groups (Table 3), we now compare the mortality hazard of smoking compared to nonsmoking in each of the different strata of baseline CAC. This allows us to explore the potential effect of smoking at each level of CAC severity. We found that at each stratum of baseline CAC elevation, smokers had higher mortality HRs in multivariate analysis than nonsmokers (Table 4). Thus, baseline CAC accurately stratified HRs in both smokers and nonsmokers, but at each stratum of CAC score that hazard was higher in the smoking group when directly compared with the nonsmoking group. The CAC also added significantly to the prediction of all-cause mortality among smokers, beyond traditional risk factors (chi square = 47.80, $p < 0.0001$).

We found that the percentage of female smokers with CAC >0 was 65%, as opposed to 57% of male smokers. However, the multivariate-controlled all-cause mortality HR for female smokers was 3.80 (95% CI: 2.96 to 4.87) and for male smokers was 3.66 (95% CI: 2.98 to 4.48), compared with their respective nonsmoking counterparts. The smoking–

Table 3. All-Cause Mortality HRs in Subjects With Elevated Baseline CAC Compared With Baseline CAC = 0

	Nonsmokers (n = 38,022, 86%) HR (95% CI)	Smokers (n = 6,020, 14%) HR (95% CI)
CAC 0	Ref*	Ref†
CAC 1–100 vs. 0	2.62 (1.99–3.45)*	2.04 (1.10–1.83)†
CAC 101–400 vs. 0	4.15 (3.11–5.54)*	2.57 (1.62–4.05)†
CAC >400+ vs. 0	8.04 (6.09–10.61)*	4.25 (2.72–6.63)†

Stratified by cigarette smoking status. Adjusted for age, sex, dyslipidemia, diabetes mellitus, HTN, and family history of CHD. *Comparing strata of positive coronary artery calcification (CAC) with CAC = 0 in nonsmokers. †Comparing strata of positive CAC with CAC = 0 in smokers.
HR = hazard ratio; other abbreviations as in Table 2.

Table 4. All-Cause Mortality HRs in Smokers as Compared With Nonsmokers

	HR for Smoking (95% CI)
CAC 0	3.62 (2.28–5.75)
CAC 1–100	3.84 (2.82–5.22)
CAC 101–400	3.54 (2.57–4.89)
CAC >400	2.71 (2.12–3.48)

Stratified by baseline CAC scores. Adjusted for age, sex, dyslipidemia, diabetes mellitus, and family history of CHD.
Abbreviations as in Tables 2 and 3.

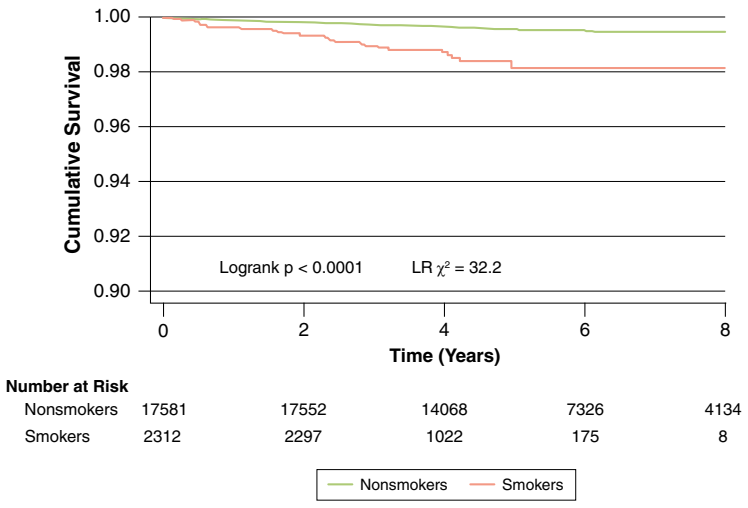

Figure 3. Survival in Nonsmokers and Smokers With CAC = 0

This is a Kaplan-Meier survival curve among those with coronary artery calcification (CAC) = 0, comparing nonsmokers with smokers. In the 19,898 individuals with CAC = 0, mean 5.6-year survival was 99.6% for nonsmokers and 98.7% for smokers ($p < 0.001$). The hazard ratio for mortality in smokers without CAC was 3.62 (95% confidence interval: 2.28 to 5.75) compared with nonsmokers without CAC. Although the event rates are low and the absolute survival differences between smokers and nonsmokers in the CAC = 0 subgroup are small, our results demonstrate that the absence of CAC might not be as reassuring in those who smoke. LR = log-rank.

sex interaction term was statistically nonsignificant ($p = 0.91$), suggesting similar effect across sex.

Outcomes in smokers with CAC = 0 at baseline. Smokers with CAC = 0 had an all-cause mortality rate of 3.31 deaths/1,000 person-years (95% CI: 2.31 to 4.74). This was in contrast to 0.67 deaths/1,000 person-years for nonsmokers with CAC = 0 (95% CI: 0.53 to 0.84). In the 19,898 individuals with CAC = 0, mean 5.6-year all-cause survival was 99.6% for nonsmokers and 98.7% for smokers ($p < 0.001$). Figure 3 demonstrates a Kaplan-Meier survival curve, on the basis of Cox proportional hazards cumulative survival, for nonsmokers and smokers among those with CAC = 0 (chi-square likelihood ratio = 32.2, $p < 0.0001$). In our multivariable analysis, the HR for mortality in smokers without CAC was 3.62 (95% CI: 2.28 to 5.75), compared with nonsmokers without CAC.

DISCUSSION

In this combined cohort of 44,042 middle-aged subjects, free of known CHD and followed for a mean of 5.6 years, we found that CAC is an independent predictor of all-cause mortality in both smokers and nonsmokers. Importantly, at each respective stratum of baseline CAC score, smokers were consistently found to have higher mortality rates than nonsmokers in the next highest CAC stratum. Sex did not influence the mortality effect of smoking on CAC in our study. However, smokers with CAC = 0 were also shown to have higher relative mortality than nonsmokers with CAC = 0. These findings highlight the importance of smoking cessation even in those without measurable evidence of subclinical atherosclerotic disease.

Smoking and atherosclerosis. Our findings are consistent with the known effect of smoking on mortality (3) and add to the findings of prior research evaluating the interplay between smoking and atherosclerosis. Prior studies have associated pack-years of smoking exposure with the severity of angiographically determined atherosclerosis (15). Cigarette smoking is a known independent predictor of new coronary atherosclerosis formation (16). Similarly, smoking is a well-documented risk factor for increased CAC, as assessed by cardiac CT (9).

Clinical effects of smoking and CAC. The largest study to date analyzed a patient registry of 10,377 asymptomatic individuals undergoing EBT, with a follow-up of 5 years (8). This cohort had a high prevalence of smoking (40%), considerably higher than our cohort and current national trends (1). Survival was 98.4% in nonsmokers, compared with 96.9% in smokers. Multivariable relative risk ratios for mortality in smokers were elevated 1.8-, 2.1-, 3.5-, and 4.5-fold higher for patients with CAC scores of 11 to 100, 101 to 400, 401 to 1,000, and >1,000, respectively (as compared with CAC

scores of 0 to 10). However, this study did not focus on those with CAC = 0 (8). In addition, we provide CAC-stratified mortality data for nonsmokers as well as smokers, facilitating a direct comparison between these 2 groups.

Although we found that HRs for mortality did increase with each stratum of increasing baseline CAC in smokers, we also found that these increases were smaller in magnitude than the respective HRs for nonsmokers in our cohort (Table 3). This finding is likely due to the increased all-cause mortality rates in the HR comparator groups of CAC = 0 in smokers than in nonsmokers (3.3 vs. 0.7 deaths/1,000 patient years, respectively) (Fig. 2). Also contributing to this was the finding of a negative interaction between smoking status and CAC group. In such, smoking has less effect on mortality as baseline CAC increases. We hypothesize that this is because much of the bad effects of smoking over a lifetime are "taken into account" by the high baseline CAC.

Importantly, baseline CAC severity does not fully explain the mortality risk of smoking. Indeed, when we controlled for baseline CAC in the multivariate analysis, we found that the HR for mortality remained significantly elevated at 3.31 (95% CI: 2.83 to 3.87, $p < 0.00001$) for smokers compared with nonsmokers. This finding should be interpreted in the context of our study endpoint of all-cause mortality, which incorporates noncardiac causes of death. However, direct comparison of mortality HRs between smokers and nonsmokers found a similar magnitude of excess relative risk in smokers as each stratum of baseline CAC score increased (Table 4). This suggests that the relative effect of smoking was similar at each stratum of baseline CAC score.

Smoking in the absence of subclinical atherosclerosis. Although CAC = 0 might be thought of as a "negative" cardiac risk factor (11), our results demonstrate that the absence of CAC might not be as reassuring in those who smoke. Although the event rates are low and the absolute survival differences between smokers and nonsmokers in the CAC = 0 subgroup are small (Fig. 3), the calculated HR of 3.62 for mortality is highly statistically significant and might translate into ongoing separation of the Kaplan-Meier survival curves over longer follow-up. Factors associated with an increased relative risk of mortality in smokers without CAC might be partly attributed to the potential presence of noncalcified plaque, which might be more prone to rupture than calcified plaque (13).

Other explanations include the increased incidence of malignant arrhythmias and stroke in smokers as well as death from other causes, in particular malignancies. Future study (which includes cause-of-death data) is needed to further elucidate the importance of cardiac events related to noncalcified plaque in smokers (as opposed to noncardiac causes of death).

Clinical implications. Our findings have a number of broad implications for risk prediction and preventive efforts in cardiology. Figure 2 demonstrates that the mortality rates in smokers at a given stratum of baseline CAC are higher than in nonsmokers in the next-higher CAC stratum. As such, risk among smokers should be considered equivalent to those with higher subclinical atherosclerosis burden in the absence of smoking. Thus, we hope that the same sense of clinical foreboding extended by physicians to smokers with asbestos exposure also be extended to smokers found to have a moderate-large burden of CAC on testing.

Our findings also extend to those without calcified subclinical atherosclerosis. Given the potential for increased future use of CAC quantification to assess individual cardiac risk (17) as well as the expected increase in CT-based lung cancer screening in smokers (12), it is important to evaluate whether all those with CAC = 0 are uniformly at low risk for future events. Although longer follow-up will be needed to confirm our finding of increased mortality in smokers with CAC = 0 compared with nonsmokers with CAC = 0, it seems prudent that the former group not be presently considered as low risk as the latter. Similarly, those smokers found to have any coronary calcification on chest CT imaging (for example, on the basis of lung cancer CT screening) are at significantly increased future mortality risk compared with those without coronary calcification and should have their cardiac risk factors aggressively treated (Fig. 4).

We hope our findings might help animate smoking cessation discussions in those who have undergone CAC testing. However, whether CAC measurement can improve smoking cessation rates remains to be seen. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial (18) did not demonstrate improved smoking cessation in those randomized to undergo CAC testing. Unfortunately, the study was underpowered for this particular issue, because the number of active smokers was small (<6% of the total study cohort).

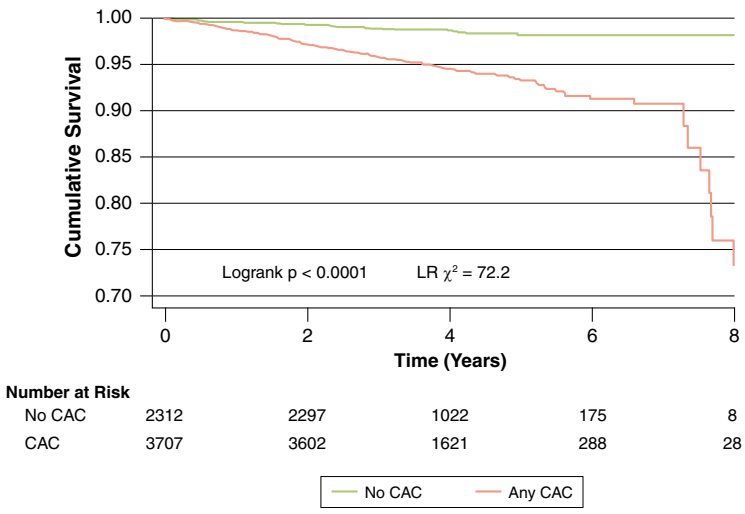

Figure 4. Survival in Smokers Without CAC Versus Smokers With Any CAC

Trial evidence demonstrates a prognostic benefit for computed tomography-based lung cancer screening in smokers, and such screening might become much more widespread. Thus, the relative prognostic implications of visualizing any coronary calcification versus no coronary calcification on such screening are of clinical significance. Smokers with any CAC elevation are at significantly increased future mortality risk compared with those without CAC and would likely benefit from more aggressive cardiac risk factor modification. Abbreviations as in Figure 3.

Study limitations. This is a post-hoc analysis, which cannot assess causality. All patients were referred for CAC screening and therefore do not represent a random sample of the population.

Another potential weakness is the self-reporting of risk factors. Data gathered by self-report are limited by patient recall and thus subject to recall bias. Although Hoff et al. (19) have shown a good reliability of self-reported histories of CHD risk factors in self-referred individuals for EBT scanning, potential "residual confounding" (which would possibly diminish the strength of association of risk factors with mortality) cannot be ruled out. Similarly, although the lack of a continuous risk variable might decrease the precision of point estimates of risk, the use of categorical risk factor data has been validated as an approach to clinical risk stratification (20).

Unfortunately, we also do not have cardiac-specific mortality available. However, the examination of death from all causes might allow for a more reliable prediction model without the possibility for cause of death misclassification (21). We know from prior population-based studies that cardiac mortality accounts for approximately 35% of deaths in smokers and 27% of deaths in nonsmokers in our cohort age group (3).

In addition, we do not have data with regard to the number of pack-years smoked and whether or not nonsmokers were ex-smokers or never smoked in the past. Such data might have provided further insight into any dose-response relationship in this cohort. We plan to study this relationship further in the MESA (Multi-Ethnic Study of Atherosclerosis) study. It is of interest that several large epidemiological studies have failed to find a significant dose-dependent correlation between cardiovascular risk and the pack-years of smoking exposure (22,23).

Finally, we hypothesize that our results likely represent an underestimation of the effect of smoking. Population studies have shown that ex-smokers have higher cardiovascular event rates than never-smokers. Thus, the event rates reported in our nonsmoking group might be higher than would be truly seen in those who never smoked. The event rates in our smoking group might also be an underestimation of the effect of continuous smoking exposure, because we were unable to distinguish those who gave up smoking during our follow-up from those who continued to smoke. This potential underestimation of the effects of smoking in our analysis adds poignancy to the adverse findings we report above.

CONCLUSIONS

Smoking is an important mortality risk factor across the entire spectrum of subclinical atherosclerosis, including those with CAC = 0. The absence of

CAC in smokers should not be regarded as a "negative risk factor" until smoking cessation occurs. Despite this, coronary artery calcification remains an excellent way of risk stratifying both nonsmokers and smokers. Whether CAC quantification can motivate smoking cessation efforts deserves future study. Our data reinforce the notion that all smokers, including those without subclinical coronary atherosclerosis but especially those with increased CAC, should be strongly encouraged to quit.

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Key Words: cardiac CT ■ coronary artery calcification ■ prognosis ■ smoking ■ subclinical atherosclerosis