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Coronary artery calcium is associated with increased risk for lung and colorectal cancer in men and women: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Aims This study explored the association of coronary artery calcium (CAC) with incident cancer subtypes in the Multi-Ethnic Study of Atherosclerosis (MESA). CAC is an established predictor of cardiovascular disease (CVD), with emerging data also supporting independent predictive value for cancer. The association of CAC with risk for individual cancer subtypes is unknown.

Methods and results We included 6271 MESA participants, aged 45–84 and without known CVD or self-reported history of cancer. There were 777 incident cancer cases during mean follow-up of 12.9 ± 3.1 years. Lung and colorectal cancer (186 cases) were grouped based on their strong overlap with CVD risk profile; prostate (men) and ovarian, uterine, and breast cancer (women) were considered as sex-specific cancers (in total 250 cases). Incidence rates and Fine and Gray competing risks models were used to assess relative risk of cancer-specific outcomes stratified by CAC groups or Log(CAC+1). The mean age was 61.7 ± 10.2 years, 52.7% were women, and 36.5% were White. Overall, all-cause cancer incidence increased with CAC scores, with rates per 1000 person-years of 13.1 [95% confidence interval (CI): 11.7–14.7] for CAC = 0 and 35.8 (95% CI: 30.2–42.4) for CAC ≥400. Compared with CAC = 0, hazards for those with CAC ≥400 were increased for lung and colorectal cancer in men [subdistribution hazard ratio (SHR): 2.2 (95% CI: 1.1–4.7)] and women [SHR: 2.2 (95% CI: 1.0–4.6)], but not significantly for sex-specific cancers across sexes.

Conclusion CAC scores were associated with cancer risk in both sexes; however, this was stronger for lung and colorectal when compared with sex-specific cancers. Our data support potential synergistic use of CAC scores in the identification of both CVD and lung and colorectal cancer risk.

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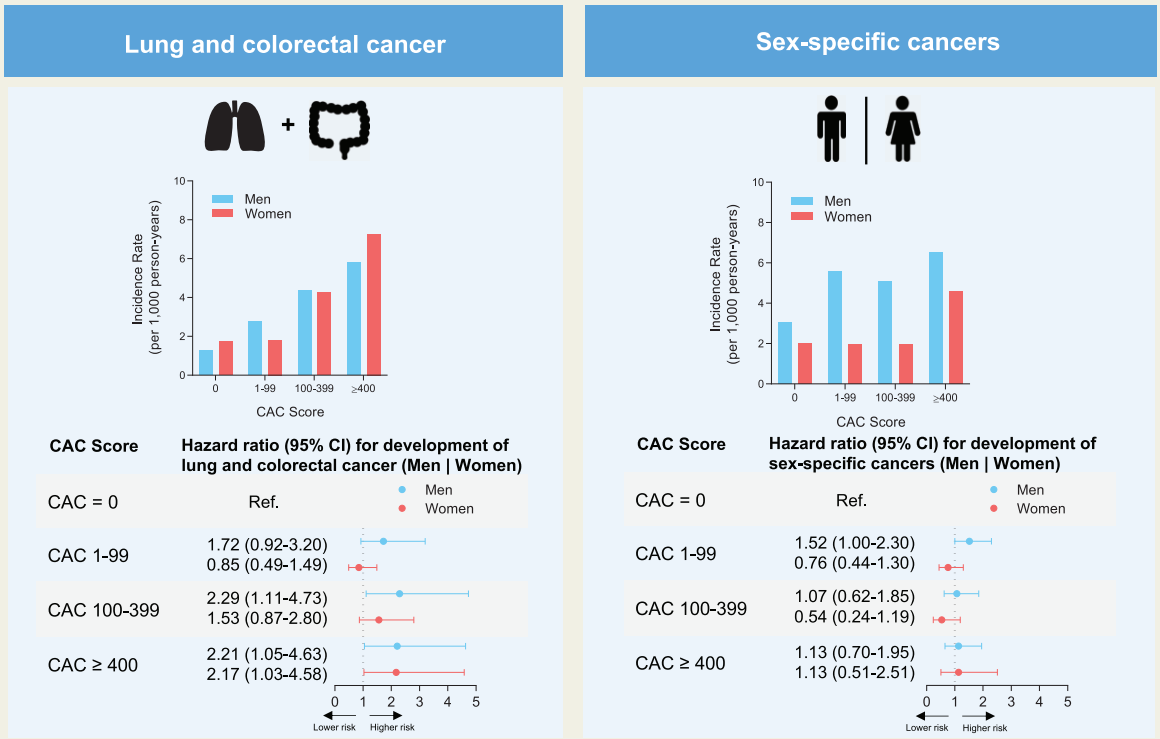
Graphical Abstract



Association of coronary artery calcium with cancer subtypes. (*Top left*) Incidence rates per 1000 person-years for lung and colorectal cancer by sex. (*Top right*) Incidence rates per 1000 person-years for sex-specific cancers = prostate (men); ovarian, endometrial, and breast cancer (women). (*Bottom left*) Hazard ratios for development of lung and colorectal cancer and (*Bottom right*) sex-specific cancers by CAC score group and sex. CAC, coronary artery calcium score; CI, confidence interval.

Keywords coronary arterial calcium • cancer • cardiovascular disease • risk prediction • prevention

Introduction

Coronary artery calcium (CAC) is a well-established tool for quantifying cardiovascular risk using non-contrast computed tomography.[1–3] As a crude marker of total coronary atherosclerotic plaque burden, CAC reflects lifetime exposure to cardiovascular risk factors (known as well as unknown) and thus represents an excellent predictor for cardiovascular disease (CVD) outcomes.[1,4,5] Increased CAC levels are also associated with an increased risk for incident cancer and cancer mortality.[6–8] However, the extent to which CAC is associated with specific cancer subtypes is unknown.

Links between CVD and cancer are emerging.[6,7,9,10] A substantial proportion of cancer deaths can be attributed to modifiable risk factors and, interestingly, many of the cancer-related risk factors overlap with CVD risk factors.[11–13] Tobacco is related to the incidence of several malignancies and still represents the most common modifiable risk among all cancer cases.[11,14] Similarly, obesity is a highly relevant modifiable risk factor that is associated with colorectal cancer prevalence. Since both CVD and cancer share numerous risk factors, we hypothesized that there may be a particular association of CAC with cancers related to modifiable risk factors. Thus, by categorizing cancers according to underlying associations with modifiable CVD/cancer risk factors (lung and colorectal cancers) and sex-specific entities with relation to hormonal processes (breast, ovarian, uterine and prostate cancer), we aimed to evaluate the predictive value of CAC for these cancer subgroups.[15,16]

Therefore, we evaluated whether baseline CAC scores in the well-characterized Multi-Ethnic Study of Atherosclerosis (MESA) cohort were predictive of risk for the respective cancer entities over long-term follow-up. We believe that results from our study might contribute to a better understanding of the cancer subtypes most strongly associated with CAC and may be helpful in exploring potential synergistic approaches to CVD and cancer risk assessment.

Methods

Study population

MESA is a prospectively observed cohort including 6814 individuals at 45–84 years of age without known CVD at enrolment that has been described in detail elsewhere.[17] Participants were enrolled from July 2000 through September 2002 at 6 US field centres (Baltimore, MA; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). The study

protocol was approved by the local institutional review boards and all subjects gave their informed consent. The data that support the findings of this study are available on reasonable request to the corresponding author.

The analysis was prespecified and included all MESA participants with Visit 1 CAC evaluation, no self-reported history of cancer at baseline, and available long-term follow-up for new cases of cancer ($n = 6271$). Also, we included two additional sensitivity analyses:

(1) exclusion of participants with self-reported lung emphysema, liver disease, or prior blood clots, all of which might be suggestive of undiagnosed cancer at baseline ($n = 419$);
(2) exclusion of participants with new cancer diagnoses within the first 180 days after baseline assessment ($n = 54$). Case numbers for individual cancer entities are summarized in Supplementary data online, *Table S1*.

Baseline characteristics and risk factors

Ethnicity was self-assessed as White, Black, Chinese, or Hispanic at the time of enrolment. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or antihypertensive medication use. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or use of diabetes medication. Smoking status was determined by a self-completed questionnaire as published elsewhere.[18] In brief, assessment was conducted to classify as current/former smoker or no smoker. In case of a positive smoking status, burden of smoking was calculated as pack-years. Family history of coronary heart disease was assessed using standardized questionnaires and defined as positive if any first-degree relative had any history of myocardial infarction with or without coronary revascularization. Physical activity was measured by using a detailed, semiquantitative questionnaire as reported previously.[19] Healthy diet was defined as self-assessed dietary patterns with favourable impact on CVD incidence as previously published and guideline-recommended.[20–22]

CAC scoring and assessment

Non-contrast cardiac-gated computed tomography (CT) scanning and interpretation were performed as previously described.[23] CAC was assessed at Visit 1 by using either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, and New York Field Centres) or a multidetector CT system (Baltimore, Forsyth County, and St. Paul Field Centres). CAC was determined from two scans and was calculated for all analyses using the Agatston method.[24] Further details on the MESA computed tomographic scanning protocol have been previously described.[24] We defined the following CAC groups: CAC = 0, CAC 1–99, CAC 100–399, and CAC ≥400 as well as a log-transformed continuous (Log(CAC + 1)) form.

Outcome definitions and event ascertainment

Mean patient follow-up time was 12.9 years [95% confidence interval (CI): 8.0–17.8 years]. The outcomes of interest for the present study were time to incident cancer diagnosis. Cancer diagnosis was determined utilizing data gathered during prespecified annual phone calls after baseline examination inquiring about interim hospital admissions, CVD diagnoses, medical procedures, and deaths. For this purpose, International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes from hospitalization records were ascertained. ICD-9 codes associated with cancer were extracted from the records and re-coded into the specific cancer entity (Supplementary data online, *Table S2*). The hospitalization date was defined as date of cancer diagnosis.

Based on the known predominant underlying risk factors from the cancer literature and due to the overlap with CVD risk profile, lung and colorectal cancer were grouped for the analyses. These two cancer entities are, based on large data sets from the Centers for Disease Control and Prevention and the National Cancer Institute, at the top of cancer deaths linked to modifiable risk factors.[11] Additionally, prostate cancers in men were considered as 'sex-specific cancers'; and accordingly ovarian, endometrial and breast cancers in women.[25] The defined group term 'All Cancers' included all registered and defined cancer type groups within the MESA cohort, i.e. in addition to the above stated cancer entities, melanoma, bladder, thyroid, brain, non-melanoma skin cancer, liver, kidney, lymphoma, other gastrointestinal cancer, multiple myeloma, and other cancers.

Statistical analyses

Baseline characteristics were stratified by lung and colorectal cancer versus sex-specific cancers (main analysis) or sex (supplemental analysis) and shown as mean ± standard deviation for continuous variables, and as frequencies and percentages for categorical variables where appropriate. Cancer type-specific incidence rates were calculated and presented per 1000 person-years, both before and after stratification by sex.

Fine and Gray's sub-distribution hazard models were used to assess the relative cancer-specific hazards across CAC groups, using CAC = 0 as the reference group, defining 'other' cancer and CVD as competing events. Fully adjusted model considered age, sex, ethnicity, and other conventional cardiovascular risk factors including body mass index, physical activity, socioeconomic status, education, health insurance, pack-years of smoking, and healthy diet. In order to further demonstrate the relative association of CAC groups with specific cancer type risk across age, sub-hazard distributions as a function of age (*x*-axis) were used with fully adjusted sub-distribution hazard ratios (*y*-axis). All calculations were performed in Stata version 15.0 software (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

Baseline characteristics of individuals meeting the inclusion criteria are shown in *Table 1*. Overall, the mean age of participants was 61.7 ± 10.2 years, 52.7% were women, 36.5% were White and 51.1% had CAC score = 0. In total, there were 777 new first cancer events during follow-up, of which 436 were grouped as either lung and colorectal cancer ($n = 186$) or sex-specific cancers ($n = 250$). The distribution of conventional cardiovascular risk factors in the entire cohort across cancer groups sexes is depicted in *Table 1* and Supplementary data online, *Table S3*.

Incidence rates of distinct cancer subtypes by CAC scores

The incidence of cancer-specific outcomes increased with higher CAC scores as shown in *Figures 1 and 2* and *Graphical abstract*. The incidences of lung and colorectal cancer increased progressively with CAC score (*Figure 2* and *Graphical abstract*). For sex-specific cancers (prostate cancer, breast cancer, ovarian, cancer, and endometrial cancer), we did not observe such a trend of incidence rates across CAC score groups (*Figure 2*).

A similar pattern could be detected for individual cancer entities (*Figure 1*). Lung and colorectal cancer incidences showed a clear increase with CAC in both sexes. The incidence rate per 1000-person years in women was 1.8 (95% CI: 1.3–2.3) in the CAC = 0 group and

Table 1 Baseline characteristics of cancer patients

Characteristics	Total cohort (*n* = 6271)	Lung cancer + colorectal cancer (*n* = 186, 3.7%)	Sex-specific cancers (*n* = 250, 4.0%)	
			Men (*n* = 154, 100%)	Women (*n* = 93, 100%)
Age, mean ± SD (years)	61.7 ± 10.2	66.2 ± 9.9	65.1 ± 9.1	64.3 ± 10.0
Sex				
Men	47.3	51.6	100	
Women	52.7	48.4		100
Ethnicity				
White-Caucasian	36.5	37.1	40.3	37.6
Chinese-American	12.5	9.7	4.6	8.6
African-American	28.3	35.5	35.1	37.6
Hispanic	22.7	17.8	20.1	16.1
High school education	81.4	78.0	85.7	80.7
Hypertension	44.3	47.3	49.3	49.5
Antihypertensive medication	36.6	37.1	44.8	37.6
Lipid lowering medication	15.8	16.1	13.0	18.2
Diabetes mellitus	12.8	15.1	11.0	12.9
Body mass index, mean ± SD	28.4 ± 5.5	27.9 ± 5.0	28.1 ± 4.7	30.1 ± 6.8
Healthy diet	46.6	43.3	46.3	40.0
Family history of heart attack	42.0	42.6	39.9	47.2
Cigarette smoking, pack-years ± SD	11.0 ± 20.6	26.0 ± 31.8	30.8 ± 36.3	21.1 ± 25.7
Mean CAC	137.7 ± 402.0	310.5 ± 659.6	271.4 ± 558.3	91.7 ± 308.3
CAC = 0	51.1	34.4	29.2	61.3
CAC 1–99	26.1	24.2	35.1	21.5
CAC 100–399	13.4	22.0	18.9	8.6
CAC ≥400	9.3	19.4	16.9	8.6

Values are column percentages (%) or as indicated. Sex-specific cancers = prostate (men); ovarian, endometrial, and breast cancer (women).
CAC, coronary artery calcium score.

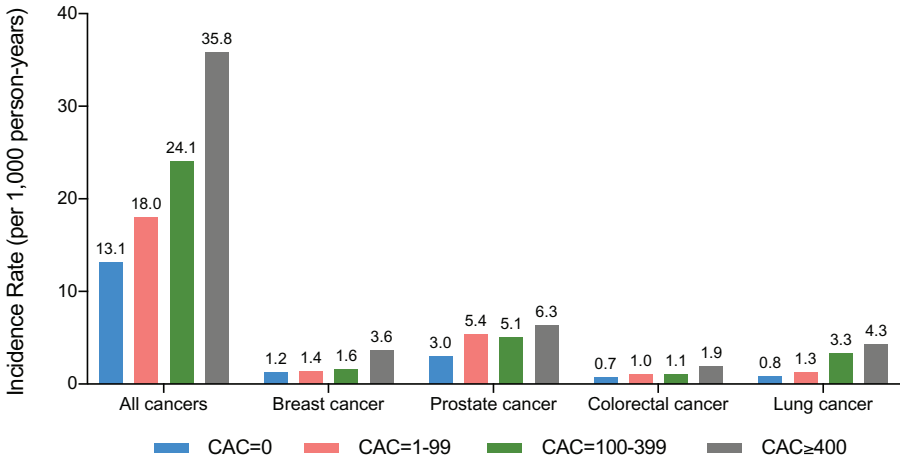


Figure 1 Incidence rates for all cancers and distinct cancer subtypes by CAC score groups. Incidence rates per 1000 person-years for all cancers and distinct cancer subtypes. Rates increased with CAC score groups. Numbers indicate incidence rates. CAC, coronary artery calcium score.

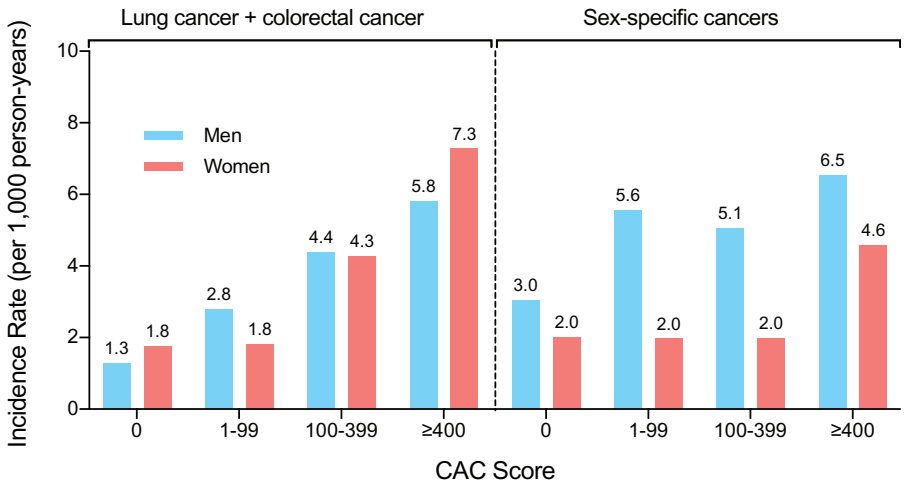


Figure 2 Incidence rates for lung and colorectal cancer, and sex-specific cancers by CAC score group and sex. Sex-specific cancers = prostate (men); ovarian, endometrial, and breast cancer (women). CAC, coronary artery calcium score.

Table 2 Hazard ratios for development of lung and colorectal cancer, and sex-specific cancers by CAC score group and sex.

Lung cancer + colorectal cancer

	CAC score, HR (95% CI)				
	CAC = 0	**CAC 1–99**	**CAC 100–399**	**CAC ≥ 400**	**Log(CAC + 1)**
All					
Unadjusted	Ref.	1.42 (0.97–2.09)	2.59 (1.75–3.83)	3.51 (2.33–5.28)	1.20 (1.13–1.26)
Adjusted[a]	Ref.	1.20 (0.81–1.78)	1.87 (1.20–2.92)	2.01 (1.20–3.35)	1.11 (1.03–1.19)
Men					
Unadjusted	Ref.	2.10 (1.18–3.76)	3.20 (1.76–5.80)	4.03 (2.21–7.35)	1.22 (1.27–1.32)
Adjusted[a]	Ref.	1.72 (0.92–3.20)	2.29 (1.11–4.73)	2.21 (1.05–4.63)	1.12 (1.01–1.24)
Women					
Unadjusted	Ref.	1.01 (0.58–1.78)	2.27 (1.27–4.06)	3.83 (2.03–7.23)	1.18 (1.08–1.29)
Adjusted[a]	Ref.	0.85 (0.49–1.49)	1.56 (0.87–2.80)	2.17 (1.03–4.58)	1.09 (0.99–1.21)

Sex-specific cancers

	CAC score, HR (95% CI)				
	CAC = 0	**CAC 1–99**	**CAC 100–399**	**CAC ≥ 400**	**Log(CAC + 1)**
Men					
Unadjusted	Ref.	1.77 (1.20–2.62)	1.56 (0.98–2.49)	1.88 (1.17–3.02)	1.10 (1.03–1.16)
Adjusted[a]	Ref.	1.52 (1.00–2.30)	1.07 (0.62–1.85)	1.13 (0.65–1.95)	1.02 (0.95–1.10)
Women					
Unadjusted	Ref.	0.95 (0.57–1.58)	0.90 (0.43–1.88)	1.93 (0.92–4.02)	1.03 (0.94–1.13)
Adjusted[a]	Ref.	0.76 (0.44–1.30)	0.54 (0.24–1.19)	1.13 (0.51–2.51)	0.95 (0.86–1.05)

[a]Adjusted for: age, sex, race, body mass index, physical activity, income >40K, completed high school, health insurance, pack-years of smoking, healthy diet.
Sex-specific cancers = prostate (men); ovarian, uterine and breast cancer (women).
CAC, coronary artery calcium score; CI, confidence interval; HR, hazard ratio.

Table 3 Hazard ratios for development of individual cancer entities by CAC score group

Cancer types	CAC score groups, HR (95% CI)				
	CAC = 0	CAC 1–99	CAC 100–399	CAC ≥ 400	Log(CAC + 1)
Breast (*n* = 60)					
Unadjusted	Ref.	1.12 (0.59–2.14)	1.25 (0.52–3.00)	2.76 (1.15–6.63)	1.10 (0.98–1.23)
Adjusted[a]	Ref.	0.98 (0.48–2.02)	0.83 (0.32–2.15)	1.91 (0.70–5.22)	1.04 (0.98–1.05)
Prostate (*n* = 155)					
Unadjusted	Ref.	1.73 (1.16–2.56)	1.60 (1.01–2.56)	1.89 (1.17–3.06)	1.10 (1.04–1.17)
Adjusted[a]	Ref.	1.53 (1.01–2.31)	1.11 (0.64–1.90)	1.17 (0.68–2.02)	1.03 (0.96–1.10)
Colorectal (*n* = 71)					
Unadjusted	Ref.	1.35 (0.77–2.39)	1.35 (0.66–2.77)	2.32 (1.16–4.64)	1.09 (0.99–1.21)
Adjusted[a]	Ref.	1.02 (0.59–1.77)	0.77 (0.36–1.67)	1.22 (0.58–2.53)	1.00 (0.90–1.10)
Lung (*n* = 115)					
Unadjusted	Ref.	1.52 (0.91–2.55)	3.83 (2.36–6.21)	4.87 (2.92–8.13)	1.27 (1.19–1.37)
Adjusted[a]	Ref.	1.44 (0.83–2.49)	3.34 (1.88–5.94)	3.22 (1.61–6.46)	1.22 (1.11–1.34)

[a]Adjusted for: age, sex, race, body mass index, physical activity, income >40K, completed high school, health insurance, pack-years of smoking, healthy diet.
CAC, coronary artery calcium score; CI, confidence interval; HR, hazard ratio.

7.3 (95% CI: 4.1–12.8) in the CAC ≥400 group when compared with men with 1.3 (95% CI: 0.8–2.0) and 5.8 (95% CI: 3.9–8.6), respectively (*Figure 2*). We observed similar results when excluding participants with additional potential indicators of undiagnosed cancer or self-reported cancer within the first 180 days after baseline assessment (Supplementary data online, *Figure S1*).

Unadjusted and multivariate-adjusted hazard ratios by CAC scores

The unadjusted hazards for lung and colorectal cancer, sex-specific cancers as well as for individual cancer entities with the reference group CAC = 0 are shown in *Tables 2 and 3*. These analyses showed a progressive increase in hazards across CAC score groups as well as for log-transformed CAC scores as a continuous variable, exclusively for lung and colorectal cancer. Adjusted for conventional cardiovascular risk factors, when compared with the CAC = 0 group, risks for lung and colorectal cancer in the CAC ≥400 group were significantly higher in all participants with a subdistribution hazard ratio (SHR) of 2.0 (95% CI: 1.2–3.4). Considering CAC as a continuous variable, there remained a statistically significant association with an SHR of 1.1 (95% CI: 1.0–1.2). The predictive value of CAC for lung and colorectal cancer could be detected for both men and women (*Table 2*). For sex-specific cancer risks, the adjusted model did not reveal a significant CAC-related association (*Table 2*). Additional analyses for the CAC related risks after removing those participants with potential indicators of undetected cancer at baseline or cancer diagnosis within the first 180 days of follow-up revealed similar results (Supplementary data online, *Figure S1, Tables S4* and *S5*).

Exploratory analyses looking at individual cancer-specific hazards for breast, prostate, colorectal, and lung cancer are shown in *Table 3*. Here, unadjusted hazard ratios indicate an increased risk for the CAC ≥400 group for all entities which corresponds with respective incidence rates as shown in *Figure 1*. After adjusting for traditional risk factors, only lung cancer risk remained significantly increased for CAC ≥100 (*Table 3*).

Figure 3 shows the relationship of CAC groups with cancer type-specific risk, considering age as the *x*-axis variable and age 60 years and CAC = 0 as the reference group. The multivariable-adjusted risks for lung and colorectal cancer increased with age in both men and women (*Figure 3A and B*). Curves for CAC score groups show a clear separation, thus indicating for the highest prevalence of these cancers in the CAC ≥400 group; for sex-specific cancers, the curves for CAC score groups did not clearly separate (*Figure 3C and D*).

Discussion

There were three main findings in this study. First, we describe an independent association of CAC with incidence of lung and colorectal cancer, but not for sex-specific cancers such as prostate (men), breast, uterine and ovarian cancer (women). Second, the predictive value of CAC for lung and colorectal cancer was observed for both men and women (for women at CAC ≥400), and in exploratory analysis appeared strongest for lung cancer. Finally, we displayed the joint effects of CAC, age, and sex on the long-term risk of lung and colorectal cancer, underscoring the importance of considering all three of these variables in the prediction of cancer type-specific risks. Our findings support our hypothesis that CAC is predominately associated with lung and colorectal cancer, both of which relate to modifiable risk factors that in turn show strong overlap with CVD risk factor profiles.

While CVD mortality has declined over the past decades, cancer mortality has been predicted to become the leading cause of death.[26] However, guideline recommendations for combined cancer and CVD prevention strategies are lacking. By dividing cancer entities into (i) cancers related to modifiable risk factors (lung and colorectal cancer) and (ii) sex-specific cancers, we believe we have further elucidated the potential predictive role of CAC in those cancers that are likely to be most responsive to preventive approaches. Modifiable risk factors such as tobacco use, obesity, alcohol consumption and physical activity account for almost half of cancer-related deaths in

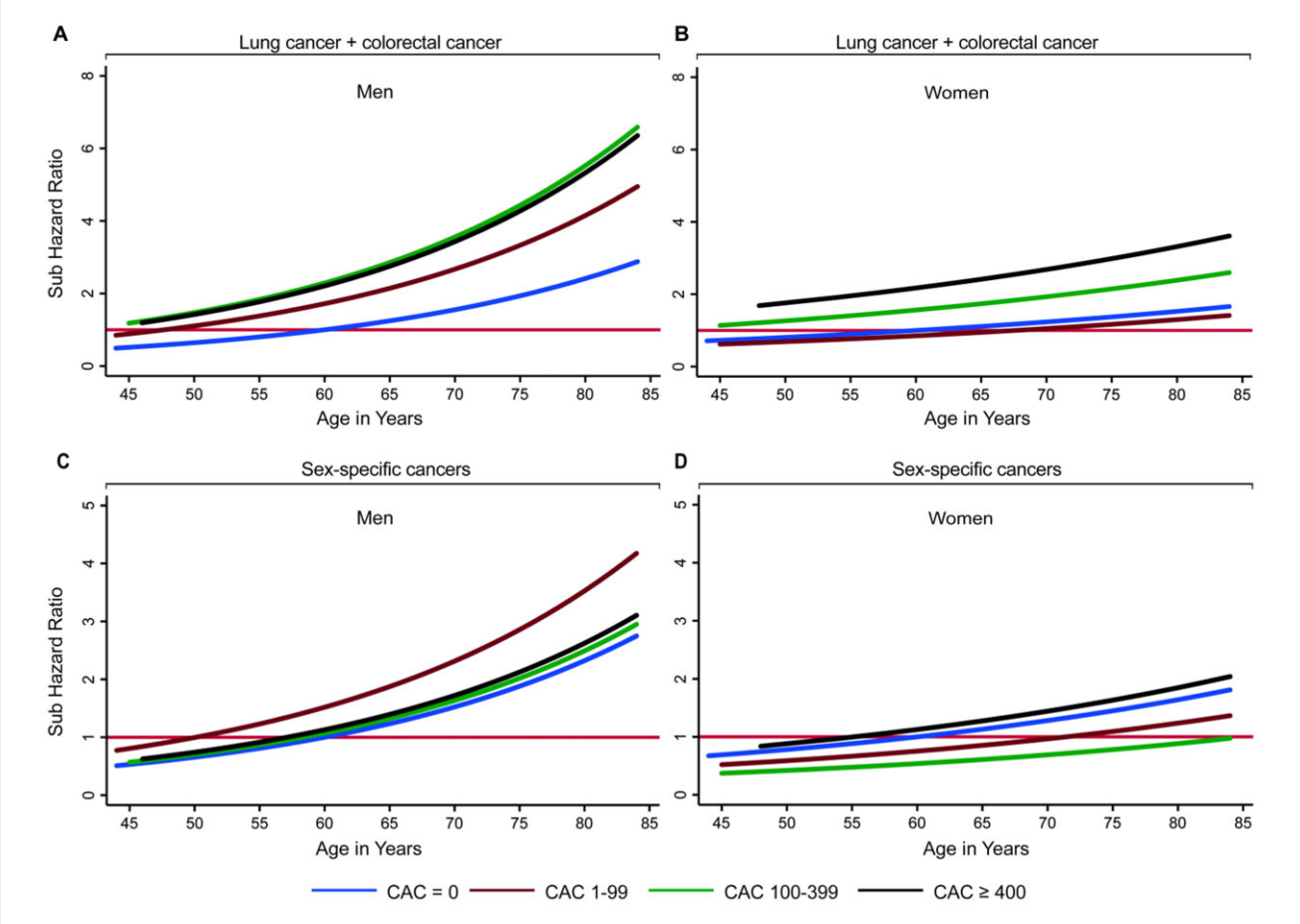


Figure 3 Subdistribution hazard ratio for lung and colorectal cancer, and sex-specific cancers as a function of age by CAC score group and sex. Graphed subdistribution hazard ratios (SHRs) as a function of age. SHR were adjusted for conventional risk factors (age, sex, race, body mass index, physical activity, income >40K, completed high school, health insurance, pack-years of smoking, healthy diet) for lung and colorectal cancer (*A* and *B*) and sex-specific (*C* and *D*) cancers. Sex-specific cancers = prostate (men); ovarian, endometrial, and breast cancer (women). SHR are stratified by CAC score group and refer to the CAC = 0 group at age 60 years. With increasing age and CAC score, cancer risk continues to increase exponentially for lung and colorectal cancer, but not for sex-specific cancers. CAC, coronary artery calcium score.

the USA.[11,27,28] As colorectal and lung cancer are strongly linked to these modifiable risk factors that have a relevant overlap with the risk factor profile of CVD and as well account for a substantial proportion of cancer deaths, we grouped these entities accordingly.[11,14,16] Islami *et al.*[11] recently showed that these two specific cancer entities attributable to modifiable and thus preventable risk factors account for the largest proportion of overall cancer cases and deaths. Conversely, sex-specific cancers that are generally related to hormonal processes have a less clear lifestyle-dependent risk factor profile. Higher oestrogen levels exert a protective effect against CVD for instance in ovarian and breast cancer.[29,30]

Additionally, there is a growing body of literature pointing to chronic inflammation and related cellular processes, that are similarly found in cancer, including increased cellular proliferation, inhibition of cell death, and cell cycle progression, among the driving mechanisms for CVD progression.[31,32] These overlapping mechanisms might further improve risk prediction models for both diseases and could eventually translate into combined therapeutic considerations.[32]

As reported previously, CAC may be predictive for incident cancer outcome because of (i) shared risk factors of CVD and cancer; (ii) CAC representing a marker of tissue vulnerability (or resilience) to risk factor-related injury.[10,33–35] General associations of CAC with cancer incidence and mortality have been shown for the MESA as well as for the CAC Consortium.[35,36] Indeed, while development of CAC has been shown to be associated with a diagnosis of cancer,[10,37] absence of CAC is also predictive for a lower risk of cancer and other non-cardiovascular events; this indicates that CAC might be considered as a measure of vulnerability (or resilience) to risk factor-mediated organ damage.[37] Given the shared risk factor profiles for both CVD and cancer, particularly smoking and adverse dietary patterns are of relevance for the development of lung and colorectal cancer.[12,15] As such, CAC can be considered as indicative of an individual's lifestyle, risk factor exposure, and overall health status and an increased CAC reflects cumulative exposure to key shared risk factors that then exerts a predictive value for both cancer and CVD risk. Thus, CAC reflects the risk factor-related damage on multiple organs

that manifests as CVD and/or cancer. Although we observed an association for CAC with lung and colorectal cancer incidence (strongest for CAC ≥ 400), CAC represents a measure of biologic age and can be therapeutically influenced via attention to the underlying shared risk factors (although an exception is that statins decrease CVD and possibly risk but increase CAC scores).[38,39] Additionally, radiation exposure due to CAC scanning for the MESA cohort has been previously reported to be comparable to mammography and thus less likely to substantially increase cancer incidence,[40,41] while, however, patient-specific radiation doses for downstream cardiovascular and non-cardiovascular imaging procedures were not systematically collected. However, in the MESA study, limited reporting of CAC results was not accompanied by any routine referral for additional testing.

Our study contributes to a more comprehensive understanding of these associations by showing that CAC scores are particularly associated with cancer entities attributable to modifiable risk factors. We further show that risks of these cancers increased with CAC in both sexes and age, while sex-specific cancers with relation to hormonal processes appeared to have only limited CAC association.

For sex-specific cancers, the dependence on modifiable risk factors and overall risk factor-related organ damage is less strong.[11] This likely explains the absence of an independent association with CAC. Additionally, some have pointed to the involved complex hormonal processes that might have favourable effects on the cardiovascular system that even lower CAC burden,[42,43] although further research is needed in this field.

Based on the shared risk factor profiles and the pathophysiological overlap between CVD and specific cancer subtypes translating into increased CAC, CAC measurement could thus be helpful for synergistic risk assessment for distinct cancer entities and CVD.[34,44,45] While at very low CAC scores or even CAC = 0 individuals had the lowest mortality risk (though with a larger proportion of deaths from cancer rather than from CVD), those with higher CAC scores had a generally higher mortality for both CVD and cancer.[35,37] For very high CAC scores ≥1000, all-cause mortality including cancer-related mortality in the CAC Consortium population was significantly increased compared to CAC ≥400 underscoring the dose-dependent relationship of CAC and cancer outcome.[7,46] Moreover, these risks substantially overlap with those for CVD and thus might offer future possibilities for synergistic risk assessment and potential combined preventive approaches.[33–35]

Study limitations

There are some relevant limitations to this study. First, the diagnosis of cancer and distinct cancer entities during the study follow-up is based on ICD-9 codes from hospitalizations or inpatient procedures. Therefore, participants who received care exclusively in the outpatient setting may not be fully captured. Second, while we have adjusted for pack-years or smoking and a healthy dietary pattern, these are complex exposures, and our analysis does not allow to exclude smoking and diet-related residual confounding. Third, we did not have any information on the histological subtype, cancer-related treatment, and whether radiation or surgery were also part of the treatment procedure. Fourth, it is possible that a few participants might have had undetected cancer at the time of the baseline MESA exam. To address this aspect, we excluded those participants with self-reported history of cancer at baseline, and furthermore, we performed additional analyses excluding participants by defining potential indicators of undiagnosed cancer at baseline. Finally, to address any concern that the baseline exam itself (which included CAC amongst many other lab and imaging tests) might have led to cancer ascertainment, we excluded those with a cancer diagnosis within 180 days after baseline. Despite these limitations, the MESA cohort represents one of the only settings to study the association of CAC with incident cancer in a comprehensively phenotyped community-based study cohort with ethnical diversity and detailed information on risk factors.

Conclusions

Our results demonstrate an association of CAC with increased risk of cancers attributable to modifiable risk factors. With respect to overlapping risk factors that are accessible to aggressive preventive action, we provide evidence that CAC score assessment might play a potential role for combined cancer and CVD risk evaluation. Future prospective studies investigating CAC and cancer risks are warranted.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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