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Publication Date

2020-12-01

DOI

10.1016/j.ajpc.2020.100119

Peer reviewed

Original Research

Association between coronary artery calcium and cardiovascular disease as a supporting cause in cancer: The CAC consortium

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ARTICLE INFO

ABSTRACT

Background: Identifying cancer patients at high risk of CVD is important for targeting CVD prevention strategies and evaluating chemotherapy options in the context of cardiotoxicity. Coronary artery calcium (CAC), a strong marker of coronary atherosclerosis, is used clinically to enhance risk assessment, yet the value of CAC for assessing risk of CVD complications in cancer is poorly understood.

Objective: In cases of cancer mortality, to determine the value of CAC for predicting risk of CVD as a supporting cause of death.

Methods: The CAC Consortium is a multi-center cohort of 66,636 asymptomatic adults without CVD who underwent CAC scanning. During a follow-up of 12.5 years, 1129 patients died of cancer and were included in this analysis. The primary outcome was presence of CVD listed as a supporting cause of cancer mortality on official death certificates obtained from the National Death Index. Logistic regression models were used to assess the odds of CVD being listed as a supporting cause of death by CAC.

Results: CVD was listed as a supporting cause of death in 306 (27%) cancer mortality cases. Baseline CAC was significantly higher in individuals with CVD-supported mortality. Odds ratios of having CVD-supported death increased by ASCVD risk score category [1.15 (0.81, 1.65) for 5–20% 10-year risk and 1.97 (1.36, 2.89) for ≥20% risk, in reference to <5% 10-year ASCVD risk] and CAC category [1.07 (0.73, 1.57) for CAC 1–99, 1.29 (0.87, 1.93) for CAC 100–399, and 2.14 (1.48, 3.09) for CAC ≥400 relative to CAC 0]. In the CAC ≥400 group, these associations remained significantly elevated after adjustment for traditional CVD risk factors [1.66 (1.08, 2.55)]. A sensitivity analysis using a more specific ASCVD-supported mortality outcome, defined as coronary heart disease, stroke, and peripheral artery disease, demonstrated that adjusted odds of ASCVD-supported cancer mortality were significantly elevated in the CAC ≥400 group relative to CAC 0 [3.09 (1.39, 7.38)].

Conclusions: In cancer mortality cases, high antecedent CAC predicted risk of having CVD as a supporting cause of death on official death certificates, independently of ASCVD risk score and CVD risk factors. CAC may be useful for identifying cancer patients at high CVD risk who might benefit from more intense preventive cardiovascular therapies.

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1. Introduction

Heart disease is the most common cause of non-cancer death among cancer patients [1]. Even in cases where cancer is the primary cause of death, cardiovascular disease (CVD) complications often play a profound role in cancer morbidly and mortality [2]. For example, cardiovascular complications from cardiotoxic cancer treatments can negatively influence the health of cancer patients and are more common in those with pre-existing diagnosed or subclinical CVD [2]. Thus, an understanding of CVD risk in cancer patients is imperative for weighting concerns regarding cardiotoxicity of treatment options and helping guide chemotherapy decisions, especially in patients at high risk of CVD complications. Additionally, for patients with high risk of cardiovascular complications from chemotherapy, early initiation of targeted preventive measures to manage modifiable CVD risk factors and close monitoring of cardiotoxic effects from cancer therapy can minimize the burden of cardiovascular complications in cancer patients [2,3].

Coronary artery calcium (CAC), an imaging marker, is one of the strongest predictors of atherosclerotic cardiovascular disease and has demonstrated value for assessing cardiovascular risk in the general population [4,5]. CAC is currently recommended in clinical guidelines for refining CVD risk assessment [6]. Due to its role as an integrator of lifetime cardiovascular risk factor exposure and a marker of cumulative subclinical vascular injury, CAC is not only a strong predictor of cardiovascular outcomes but also has been found to be predictive of non-CVD conditions, including cancer [7–9]. However, little is understood about the value of CAC in predicting CVD complications in the context of cancer cases. To fill this knowledge gap, we aimed to quantify the value of CAC, beyond traditional cardiovascular risk factors, in evaluating risk of CVD-supported death in cancer mortality cases.

2. Methods

2.1. Study population

The CAC Consortium is a multicenter database of 66,636 asymptomatic patients without history of coronary heart disease who were clinically- or self-referred for CAC scanning between 1991 and 2010. The current analysis included only patients who experienced cancer mortality during follow-up identified through National Death Index (NDI) linkage, further described below (Supplemental Fig. 1). Informed consent was collected at each respective medical center at the time of CAC scanning and approval for coordinating center activities was obtained from the Johns Hopkins Hospital Institutional Review Board.

2.2. Coronary artery calcium assessment

CAC scanning was performed during baseline using standardized non-contrast cardiac-gated computed tomography (CT) at each site and quantified using the Agatston method [10]. CAC score was categorized into clinical cutoffs of 0 (no coronary calcium), 1–99 (mild), 100–399 (moderate), and ≥400 (extensive).

2.3. Collection of baseline characteristics

Cardiac risk factors and demographic variables were obtained at baseline through questionnaires and/or interviews with medical staff. Diabetes mellitus was defined as having a prior clinical diagnosis of diabetes or use of insulin or other diabetes medication. Dyslipidemia was defined as having a previous diagnosis for dyslipidemia, treatment with lipid-lowering drugs, a low density lipoprotein cholesterol (LDL-C) level ≥160 mg/dL, a high density lipoprotein cholesterol (HDL-C) level <40 mg/dL for males, or <50 mg/dL for females, or a fasting triglyceride ≥150 mg/dL. Family history of premature coronary heart disease was defined as having a primary relative diagnosed with coronary artery disease or a cardiac event prior to age 55 and 65 for males and females,

respectively. Smoking was determined as self-reported current smoking status at the time of clinical visit. Hypertension was defined as having a previous diagnosis of hypertension or receiving anti-hypertensive therapy. The American Heart Association/American College of Cardiology (AHA/ACC) Pooled Cohort Equation was used to determine 10-year risk of atherosclerotic CVD (ASCVD) [11].

2.4. Outcome ascertainment

Mortality through June 2014 was ascertained by linkage with the Social Security Administration Death Master File (DMF), yielding a median follow-up of 12.5 years [IQR 10.6, 14.1]. Cause of death was collected via coded death certificates from the NDI (Fig. 1) [12]. Primary cause of mortality was derived from the underlying cause of death listed in death certificates [13]. Only CAC Consortium participants with cancer listed as the primary cause of mortality were included in this study. Supporting causes of mortality were derived from contributing causes of death listed in the same death certificate form [13]. These supporting causes of mortality were factors that directly contributed to death, independent of the primary cause of mortality. Presence of CVD listed as a supporting cause of mortality was the outcome used in this study.

These primary and supporting causes of mortality from the NDI's death certificates are listed as International Classification of Diseases (ICD)-9 and ICD-10 codes. Thus, we categorized these ICD-9 and ICD-10 codes to identify cancer mortality cases and CVD supporting causes of death. Cancer mortality was defined as death with the primary cause listed as cancer [ICD-9: 140–239, ICD-10: C00-D48]. CVD as a supporting cause of death included coronary heart disease, stroke, heart failure, and other arterial diseases [ICD-9: 390–459, ICD-10: I00–I99]. Additional information on methods for outcome ascertainment are further outlined in the CAC Consortium design publication [14].

2.5. Statistical analyses

Participant characteristics were stratified by absence or presence of CVD listed as a supporting cause of mortality. Continuous participant characteristics were presented as averages if they were normally distributed (age) or otherwise as medians (CAC, 10-year ASCVD risk) then compared using Welch's t-tests or Wilcoxon-Mann-Whitney tests, respectively. Categorical variables were expressed as counts and proportions then compared using Pearson's chi-square tests. Cochran-Armitage tests were used to assess trends in presence of CVD as a supporting cause of mortality by increasing CAC score and ASCVD risk categories.

Univariable and multivariable logistic regressions were used to estimate progressively adjusted odds ratios of having CVD as a supporting cause for mortality by CAC category (vs. CAC = 0 reference) or continuous ln(CAC + 1). A restricted cubic spline graph was used to depict the association between continuous CAC score and the fully adjusted odds ratios. Analyses were repeated in sex, age (<65 and ≥ 65), and lung cancer-related versus non-lung cancer-related mortality subgroups. As a secondary analysis, we also examined the association between CAC and ASCVD (stroke, CHD, peripheral artery disease [PAD]) versus non-ASCVD supporting causes of mortality. As a sensitivity analysis, multivariable logistic regression was used to create a cubic spline graph to evaluate if odds of having CVD listed as a supporting cause changed over follow-up time to cancer mortality. All analyses were performed using Stata version 14.2 and R version 3.4.4.

3. Results

In a population of 66,636 CVD-free patients who underwent CAC scanning, 1129 patients experienced cancer mortality a median of 6.1 [IQR: 3.1, 9.1] years after baseline assessment. Of these patients, the average age was 64, with 65% males and 27% having a CVD-supported cause of mortality (Table 1). The most common cancer type was lung

Fig. 1. United States Standard Death Certificate Form: Primary and Supporting Causes of Death. This figure provides an example of relevant sections of death certificates that were used to evaluate cancer mortality and the exposure of interest, cardiovascular disease as a supporting cause of mortality. Adapted from a figure in the Center for Disease Control (CDC) website [13].

*Primary cause of death (eg. cancer in this study).

†Supporting cause of death (eg. cardiovascular disease in this study).

followed by pancreatic and colorectal. Those with CVD listed as a supporting cause of mortality tended to be older and more likely hypertensive. There was a greater proportion of individuals with diabetes in those who had CVD listed as a supporting cause of mortality; however, the difference was not statistically significant. The prevalences of hyperlipidemia and family history of heart disease were similar between the two groups. The median CAC score for the study population was 75 [IQR: 0, 403] with 25.5% of participants with CAC = 0. CAC was significantly higher in those with CVD-supported cancer mortality (Table 1).

Fig. 2 presents the proportion of individuals with CVD-supported cancer mortality across CAC and ASCVD risk categories. There was a distinct increase in proportion of patients with CVD-supported mortality in higher CAC categories (p < 0.001). In those with CAC ≥400, 38% had

a CVD-supported mortality. Likewise, in higher ASCVD risk categories, the proportion of CVD-supported cancer mortality cases increased accordingly (p < 0.001).

The odds ratios of having a CVD-supported mortality increased incrementally in higher CAC categories (Fig. 3). Even after adjustment for ASCVD risk (**Model 2**) and traditional cardiac risk factors (**Model 3**), CAC ≥400 remained a significant predictor of CVD-supported mortality in cancer death. On a continuous scale, adjusted odds of having a CVD supporting cause of mortality increased with higher CAC score.

In subgroup analyses, CAC remained a significant predictor of CVD-supported mortality within sex and age (<65 and ≥ 65) strata (p < 0.001). Secondary analysis also showed similar results when separately considering lung cancer-related mortality and non-lung cancer-related

Table 1
Participant characteristics by presence of cardiovascular disease supporting cause in cancer mortality.

	Overall	No CVD Supporting Cause of Mortality	CVD Supporting Cause of Mortality	P
	(n = 1129)	(n = 823)	(n = 306)	
Age, years	64.3 (10.1)	63.6 (9.7)	66.0 (10.8)	0.001
Male (%)	731 (64.7%)	524 (63.7%)	207 (67.6%)	0.241
Diabetes (%)	137 (12.1%)	90 (10.9%)	47 (15.4%)	0.055
Current Smoker (%)	148 (13.1%)	103 (12.5%)	45 (14.7%)	0.384
Hypertension (%)	464 (41.1%)	318 (38.6%)	146 (47.7%)	0.007
Hyperlipidemia (%)	631 (55.9%)	468 (56.9%)	163 (53.3%)	0.310
CHD Family History (%)	455 (40.3%)	334 (40.6%)	121 (39.5%)	0.804
CAC, median [IQR]	75 [0, 403]	55 [0, 330]	154 [11, 743]	<0.001
CAC Category (%)				<0.001
0	288 (25.5%)	225 (27.3%)	63 (20.6%)	
1–99	317 (28.1%)	244 (29.6%)	73 (23.9%)	
100–399	241 (21.3%)	177 (21.5%)	64 (20.9%)	
>400	283 (25.1%)	177 (21.5%)	106 (34.6%)	
10- Year ASCVD Risk, median (IQR)	11.7 [5.7, 21.1]	10.6 [5.2, 19.6]	14.8 [7.1, 25.0]	<0.001
ASCVD Risk Category (%)				<0.001
0–5%	254 (22.5%)	198 (24.1%)	56 (22.5%)	
5–20%	565 (50.0%)	426 (51.8%)	139 (45.4%)	
≥20%	310 (27.5%)	199 (24.2%)	111 (36.3%)	
Cancer Type (%)				0.025
Lung	235 (20.8%)	163 (19.8%)	72 (23.5%)	
Pancreas	119 (10.5%)	93 (11.3%)	26 (8.5%)	
Colorectal	66 (5.8%)	57 (6.9%)	9 (2.9%)	
Prostate	63 (5.6%)	45 (5.5%)	18 (5.9%)	
Brain	56 (5.0%)	36 (4.4%)	20 (6.5%)	
Breast	45 (4.0%)	33 (4.0%)	12 (3.9%)	
Ovarian	37 (3.3%)	33 (4.0%)	4 (1.3%)	
Lymphoma	43 (3.8%)	28 (3.4%)	15 (4.9%)	
Melanoma	28 (2.5%)	24 (2.9%)	4 (1.3%)	
Kidney	28 (2.5%)	22 (2.7%)	6 (2.0%)	
Bladder	27 (2.4%)	17 (2.1%)	10 (3.3%)	
Multiple myeloma/plasma cell dyscrasia	22 (1.9%)	16 (1.9%)	6 (2.0%)	
Liver	16 (1.4%)	15 (1.8%)	1 (0.3%)	
Uterine	11 (1.0%)	9 (1.1%)	2 (0.7%)	
Non-melanoma skin cancer	10 (0.9%)	9 (1.1%)	1 (0.3%)	
Thyroid	5 (0.4%)	3 (0.4%)	2 (0.7%)	
Cervical	3 (0.3%)	3 (0.4%)	0 (0.0%)	
Other GI cancer	92 (8.1%)	65 (7.9%)	27 (8.8%)	
Other cancer	223 (19.8%)	152 (18.5%)	71 (23.2%)	

Values are mean (standard deviation) or n (%) unless otherwise noted.

ASCVD = Atherosclerotic cardiovascular disease; CAC = Coronary artery calcium; CHD = Coronary heart disease; CVD = Cardiovascular disease; IQR= Interquartile range.
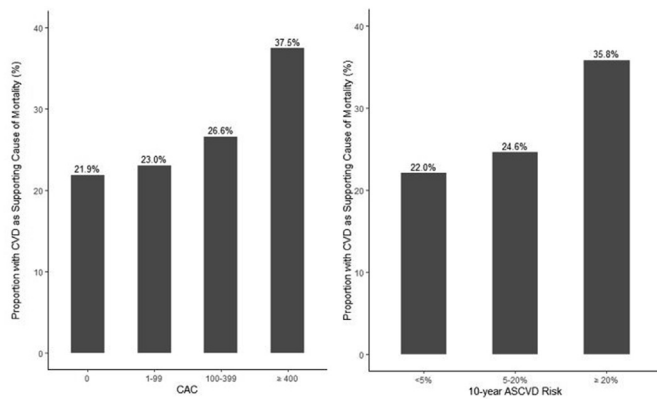
Fig. 2. Proportion of cancer mortality with cardiovascular disease supporting cause by CAC score (left) and ASCVD risk category (right). This bar chart depicts that, as CAC and ASCVD risk increase, the proportion of individuals who had CVD listed as a supporting cause of cancer mortality increased, suggesting CAC and ASCVD risk both may have value in evaluating incidence of cardiovascular complications in cancer cases.
ASCVD = Atherosclerotic cardiovascular disease; CAC = Coronary artery calcium; CVD = Cardiovascular disease.

mortality cases. Additionally, although there was limited statistical power, the association between CAC and CVD-supported mortality appeared to be driven by ASCVD (stroke, CHD, PAD). Adjusted odds of having an ASCVD-supported cancer mortality was elevated in the CAC ≥400 category relative to CAC 0 [odds ratio: 3.09 (1.39, 7.38)]. Furthermore, the odds of CVD as a supporting cause of cancer mortality did not change over follow-up time from baseline CAC scanning (i.e. time to cancer mortality was not a confounder in our study, Supplemental Fig. 2).

4. Discussion

To our knowledge, this is the first study to demonstrate that, in patients free of coronary heart disease, baseline CAC measured over 6 years prior to cancer mortality is a predictor of CVD as a supporting mortality cause at the time of cancer death. In these cancer mortality cases, over a quarter had CVD listed as a supporting cause of mortality. CAC was found to be an independent predictor of CVD-supported mortality, where individuals with higher CAC were at elevated risk of having CVD contribute to their death, an association that persisted within age and sex subgroups.

Cancer patients have greater burden of CVD risk factors and are at higher risk of CVD compared to the general population, suggesting that CVD risk reduction is important for reducing mortality and morbidity in this population [15–17]. Underdiagnosis and undertreatment of CVD is often an issue in cancer patients who suffer from both diseases, as often cancer treatment is prioritized. Due to earlier cancer diagnosis and better survival with modern therapy, cancer patients are now just as likely to die from other comorbid conditions, such as CVD, as from cancer [18]. Thus, a combined approach to cancer treatment and CVD prevention, especially for individuals at elevated CVD risk, may be instrumental for lowering mortality of both diseases. From the findings of this study, CAC may be instrumental for helping assess CVD risk in the cancer population, beyond traditional cardiovascular risk factors, and identifying cancer patients at high risk of cardiovascular complications.

In light of stronger recommendations for routine CAC in clinical guidelines, CAC testing for assessment of CVD risk is becoming more common [6,19]. Additionally, incidental CAC is often detected through non-gated chest CT during routine cancer imaging. However, these CAC findings are rarely reported and used in the clinical management of cancer patients [20]. Extending prior work showing that CAC predicts cardiovascular events in participants of lung cancer screening trials (many of whom did not end up having cancer) [21] and cancer mortality
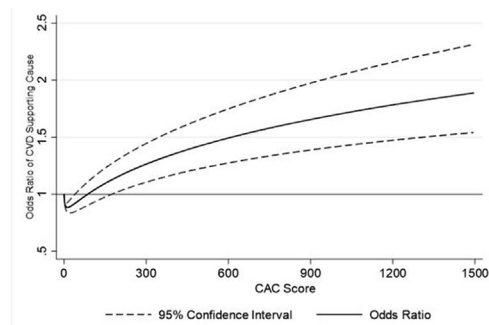
	CAC Category	n	Unadjusted	Model 1	Model 2	Model 3
Cancer Mortality (n=1,129)	0	288	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	1-99	317	1.07 (0.73, 1.57)	0.99 (0.67, 1.46)	0.99 (0.67, 1.46)	0.97 (0.65, 1.44)
	100-399	241	1.29 (0.87, 1.93)	1.12 (0.73, 1.71)	1.09 (0.72, 1.65)	1.04 (0.67, 1.60)
	≥400	283	2.14 (1.48, 3.09)	1.78 (1.17, 2.69)	1.66 (1.11, 2.49)	1.66 (1.08, 2.55)
	LN(CAC+1)	1129	1.12 (1.07, 1.18)	1.10 (1.04, 1.16)	1.08 (1.03, 1.14)	1.08 (1.02, 1.15)

Fig. 3. Odds ratios of CVD as supporting cause of cancer mortality by CAC score. Using logistic regression models, odds of having a cardiovascular disease supported cancer mortality were modeled by continuous and categorical CAC score. After adjustments for cardiovascular risk factors, as CAC score increased, odds of cardiovascular contributions to cancer mortality increased. In the CAC≥400 group, risk of CVD listed as a supporting cause of mortality was significantly higher, suggesting that high CAC may be an important, independent factor that can be used to assess risk of cardiovascular complications in the context of cancer.
*Model 1: Adjusted for age and gender; Model 2: Adjusted for ASCVD Risk, Model 3: Adjusted for age, gender, diabetes, smoking, hypertension, hyperlipidemia, family history of CVD. Figure based on fully-adjusted Model 3.
ASCVD = Atherosclerotic cardiovascular disease; CAC = Coronary artery calcium; CVD = Cardiovascular disease.

[22], the results of our study suggest that CAC may be valuable for identifying cancer patients at high CVD risk. CAC information, especially from pre-existing scans or incidental CT findings, may be leveraged to assess risk of cardiotoxicity for decision-making in chemotherapy treatment and minimize the burden of cardiovascular comorbidities in cancer patients. Additional studies are necessary to further understand whether CAC can be used to inform risk of chemotherapy-related CVD complications and help guide cancer therapy choices.

A limitation of this study was the inability to re-adjudicate causes of mortality and supporting causes beyond the data available from the NDI such as by using medical records, especially since the accuracy of supporting causes in death certificates is not well understood and difficult to evaluate. Additionally, a broad outcome of CVD-supported mortality was used which included not only coronary heart disease, but also other CVD mortality causes (such as hypertensive heart disease and heart failure). This broad definition may partly explain cases with antecedent CAC 0 that later experienced a CVD-supported cause of mortality. However, notably, in secondary analyses, our results appeared stronger when restricting to a narrow ASCVD definition. Similarly, although CVD risk may vary by cancer subtypes [17], we did not have adequate statistical power to further stratify these analyses by individual cancer types. In addition, our analysis was conducted on a cohort of patients who were referred for CAC, potentially due to suspected subclinical CVD, which may introduce selection bias of a study population possibly at higher CVD risk than the general asymptomatic adult population with no history of coronary heart disease; however, these results likely reflect the current *asymptomatic, coronary heart disease-free* population with CAC imaging results in the clinical setting. Due to the study design, another limitation is that CAC score may have influenced whether CVD was coded as a supporting cause of mortality; however, our supplemental analysis showed that the association between CAC and CVD-supported mortality did not decrease over time, suggesting that antecedent CAC results likely did not strongly influence death certificate coding. Also, since the follow-up from CAC scan to observed mortality was substantial (median

6 years), and, in that interim, patients developed cancer and likely received an array of tests and treatments, we believe the CAC score is not likely to have a substantial influence on death certificate coding (which commonly occurs in the hospital or by coroners with limited knowledge of outpatient testing from many years prior). Lastly, since cancer treatment data was not available in the current analysis, further research is necessary to examine the utility of CAC for evaluating cardiovascular disease risk in the context of chemotherapy and potential treatment cardiotoxicity.

In conclusion, this is one of the first studies assessing the role of antecedent CAC testing in evaluating risk of cardiovascular influences on cancer death. In a population of patients who were free of coronary heart disease at baseline, we found that higher CAC burden was associated with later having CVD as a supporting cause of cancer death. Further studies should continue to examine the value of CAC for understanding CVD risk in the context of cancer and guiding targeted preventive therapies for those at high CVD risk to potentially reduce the large burden of cardiovascular comorbidities in the cancer population.

Funding

Disclosures

Authors declare no conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: None.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajpc.2020.100119.

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