ORIGINAL RESEARCH

Coronary Artery Calcium as a Synergistic Tool for the Age- and Sex-Specific Risk of Cardiovascular and Cancer Mortality: The Coronary Artery Calcium Consortium

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BACKGROUND: Coronary artery calcium (CAC) is a predictor for the development of cardiovascular disease (CVD) and to a lesser extent cancer. The age- and sex-specific relationship of CAC with CVD and cancer mortality is unknown.

METHODS AND RESULTS: Asymptomatic patients aged 40 to 75 years old without known CVD were included from the CAC Consortium. We calculated sex-specific mortality rates per 1000 person-years' follow-up. Using parametric survival regression modeling, we determined the age- and sex-specific CAC score at which the risk of death from CVD and cancer were equal. Among the 59 502 patients included in this analysis, the mean age was 54.9 (±8.5) years, 34% were women, and 89% were white. There were 671 deaths attributable to CVD and 954 deaths attributable to cancer over a mean follow-up of 12±3 years. Among patients with CAC=0, cancer was the leading cause of death, the total mortality rate was low (women, 1.8; men, 1.5), and the CVD mortality rate was exceedingly low for women (0.3) and men (0.3). The age-specific CAC score at which the risk of CVD and cancer mortality were equal had a U-shaped relationship for women, while the relationship was exponential for men.

CONCLUSIONS: The age- and sex-specific relationship of CAC with CVD and cancer mortality differed significantly for women and men. Our age- and sex-specific CAC score provides a more precise estimate and further facilitates the use of CAC as a synergistic tool in strategies for the prediction and prevention of CVD and cancer mortality.

Key Words: aging ■ cardiovascular disease ■ competing risk ■ coronary artery calcium ■ sex differences

Cardiovascular disease (CVD) and cancer are the 2 leading causes of death in the developed Western world and account for nearly half of all deaths in the United States.[1,2] While CVD remains the leading cause of death, CVD-associated mortality has declined over the past decades and some projections estimate that cancer may replace CVD as the leading cause of death by as early as 2020.[3] Indeed, in the United States, cancer is already the leading cause of death among women aged 35 to 74 years old and men aged 55 to 74 years old.[4,5]

CVD and cancer are typically thought of as unrelated disease entities. However, they both share numerous underlying risk factors such as age, obesity, tobacco use, unhealthy diet, low physical activity, and diabetes mellitus.[4–9] In this context, the measurement of coronary artery calcium (CAC) can serve as a valuable risk-stratification tool for both CVD and cancer, as it integrates

CLINICAL PERSPECTIVE

What Is New?

- The age- and sex-specific relationship of coronary artery calcium with cardiovascular disease and cancer mortality differed significantly for women and men.
- This more comprehensive understanding for the relationship of coronary artery calcium with cardiovascular disease and cancer mortality improves the utility of coronary artery calcium scoring as a synergistic tool for risk prediction and prevention strategies of both cardiovascular disease and cancer.

What Are the Clinical Implications?

- These results provide a more personalized estimate of an individual's cardiovascular disease versus cancer mortality risk, which allows for a focus on prevention strategies that are most likely to extend life and reduce mortality.

Nonstandard Abbreviations and Acronyms

CAC	coronary artery calcium
CHD	coronary heart disease
CVD	cardiovascular disease
ICD-9	*International Classification of Diseases, Ninth Revision*
ICD-10	*International Classification of Diseases, Tenth Revision*

an individual's lifetime exposure to shared risk factors and also serves as a marker of an individual's overall health status.[10–12] Indeed, previous studies have shown that CAC is not only associated with an increased CVD risk but also with an increased risk for incident cancer.[13]

However, there are important sex-specific differences in the epidemiology of CVD and cancer. For instance, women generally develop CVD ≈10 years later in life than men[14] and cancer subtypes differ considerably between women and men. In addition, women have an ≈2-fold higher risk for CVD mortality compared with men with the same CAC burden. Therefore, we sought to determine the age- and sex-specific relationship of CAC with CVD and cancer mortality.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We used the CAC Consortium, which is composed of individuals without known CVD who underwent a physician-ordered CAC scan for clinical CVD risk stratification between 1991 and 2010 for this analysis.[15] Details on the study population and design of the CAC Consortium have been described elsewhere.[15] In brief, the CAC Consortium enrolled asymptomatic patients aged 18 years or older, without known coronary heart disease (CHD) at the time of the CAC scan, who were referred for CVD risk stratification. Four participating sites were included in the CAC Consortium: Cedars-Sinai Medical Center, Los Angeles, California (n=13 972); PrevaHealth Wellness Diagnostic Center, Columbus, Ohio (n=7042); Harbor-UCLA Medical Center, Torrance, California (n=25 563); and Minneapolis Heart Institute, Minneapolis, Minnesota (n=20 059). In keeping with the 2019 American Heart Association/American College of Cardiology Primary Prevention guideline, we excluded individuals <40 years old (n=4855) and ≥75 years of age (n=2279), for a total of 59 502 asymptomatic patients aged 40 to 75 years old.[16] Consent was obtained from all study participants at individual centers at the time of CAC scanning, and Institutional Review Board approval for coordinating center activities was obtained at the Johns Hopkins Hospital.

Measurement of Coronary Artery Calcium Scores

Cardiac gated, noncontrast computed tomography scans were performed using standardized protocols. The majority of scans were performed using electron beam tomography, which delivers equivalent CAC scoring compared with multidetector computed tomography imaging.[15,17] CAC scores in this study were categorized as 0, 1 to 99, 100 to 399, or ≥400 Agatston units.

Risk Factors

Each site obtained patient demographics and cardiovascular risk factors from referral visit information or by means of a semistructured interview at the time of the CAC scan. Categorical CVD risk factors were documented as hypertension, dyslipidemia, diabetes mellitus, and current smoking. A family history of CHD was recorded by 3 of the study facilities if a first-degree relative had CHD and at 1 facility (Columbus, OH) if there was a family history of premature CHD (<55 for men and <65 for women). Ten-year atherosclerotic CVD risk was calculated using the Pooled Cohort Equations.[15] Missing values for systolic blood pressure or lipid levels were imputed on the basis of

the participants' other available CVD risk factors. Our method of imputation has been described in detail elsewhere.

Cause-Specific Mortality Ascertainment and Follow-Up

We have previously described the algorithms used to perform death matching in detail.[18] In brief, the algorithm, which is based on the National Death Index search criteria, uses unique patient identifiers (eg, name, date of birth, and Social Security number) in a semiflexible hierarchical matching process. The following 3 dependent outcome variables were measured: nondeaths; cause-specific deaths (main outcome), for example, CVD or cancer mortality; or competing risk deaths (all other deaths besides main outcome). Death was considered to be present (1) if there was a match on Social Security number and 1 additional patient identifier, or (2) in instances where Social Security number was not available, a death match required a complete match on all other patient identifiers. The Social Security Administration Death Master File was searched through June 2014 to determine patient mortality. Using these data, death certificates were obtained from the National Death Index, and on the basis of *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes, causes of death were classified into common groups such as CVD, CHD, and cancer. The time to event was defined as the time from baseline (CAC Scan Date) until date of death or June 1, 2014 (if alive). Notably, the proportion of cancer- and CVD-associated deaths in the CAC Consortium are similar to recent mortality data from the US Centers for Disease Control and Prevention and the American Cancer Society.[3,19]

Statistical Analysis

Overall and cause-specific mortality with risk factor adjustment

Within each CAC and age group, we calculated the overall and cause-specific mortality per 1000 person-years' follow-up.

Cause- and age-specific mortality risk associated with CAC

Cox proportional hazard models tend to overestimate risk relationships.[20–23] Therefore, to accurately account for competing risks of CVD and cancer mortality, Fine and Gray subdistribution hazard modeling was performed, which takes these competing risks into account.[24] Statistical models were adjusted for age, sex, hyperlipidemia, hypertension, diabetes mellitus, smoking, and family history.

Age- and sex-specific CAC score at which the risk of CVD and cancer mortality is equal

Using parametric survival regression methods, we modeled the rate of incident CVD and cancer as a function of ln(CAC+1) by age for women and men. In order to allow for age-dependent changes in the relationship, we added a binary interaction term for age 65 and ln(CAC+1) for women. We did not add a binary interaction term for men because we did not observe an age-dependent change in the relationship. To derive the CAC score at which the risk of CVD mortality is equal to the risk of cancer mortality, we solved the equations for ln(CAC+1). This resulted in the following age- and sex-specific functions, which we have also graphically displayed:

Women:

$$\mathrm{Ln}(\mathrm{CAC}+1) = [(X1-\beta1)\times\mathrm{Age}+(X3-\beta3)\times\mathrm{Age}65$$
$$+(X4-\beta4)\times\mathrm{Age}\times\mathrm{Age}65$$
$$+(X0-\beta0)]/(\beta2-X2)+(\beta6-X6)\times\mathrm{Age}65$$

Men:

$$\mathrm{Ln}(\mathrm{CAC}+1) = [(X1-\beta1)\times\mathrm{Age}+(X0-\beta0)]/(\beta2-X2)$$

For a more detailed explanation of what the individual terms in these equations represent, please refer to Data S1.

RESULTS

Overall, the mean age of participants was 54.9 (±8.5) years, 34% were women, 89% were white, and the mean 10-year atherosclerotic CVD risk was 6.8% (±6.8). The distribution of risk factors between both sexes was similar, although women were slightly older and had a lower 10-year atherosclerotic CVD risk (Table 1). Overall, the median CAC score was lower for women (interquartile range, 0–21) compared with men (interquartile range, 0–153), and the difference in median CAC score increased with age (Figure S1). Over a mean 12±3 years of follow-up, there were 671 deaths attributable to CVD and 954 deaths attributable to cancer.

Among individuals aged 40 to 55 years old, the total mortality rate was low. For women, there were 21 deaths attributable to CVD (0.23%) and 70 deaths attributable to cancer (0.77%), while for men there were 115 deaths attributable to CVD (0.52%) and 114 deaths attributable to cancer (0.52%). Overall, cancer was the leading cause of death among women regardless of age, while CVD overtook cancer as the leading cause of death among men aged 70 to 75 years old (Figure S2).

Among the group of patients with CAC=0, cancer was the leading cause of death in both sexes, although

Table 1. Participant Characteristics

	Total Cohort (n=59 502)	Women (n=19 964)	Men (n=39 538)	*P* Value
Age, y	54.9±8.5	56.2±8.3	54.3±8.5	<0.001
White	89.4	89.0	89.6	0.06
Hypertension	31.1	31.8	30.8	0.01
Hyperlipidemia	54.7	52.6	55.7	<0.001
Diabetes mellitus	6.8	6.4	6.9	0.02
Current smoking	9.6	9.1	9.8	0.006
Family history of CHD	45.8	53.2	42.1	<0.001
10-y atherosclerotic CVD risk	6.8±6.8	4.5±4.9	8.0±7.2	<0.001
Atherosclerotic CVD risk category				<0.001
<7.5%	68.8	83.0	61.6	
7.5%-20%	26.0	15.1	31.5	
≥20%	5.3	1.9%	7.0	
CAC >0	56.7	39.0	65.7	<0.001
CAC score*	4 (0–96)	0 (0–21)	15 (0–153.3)	<0.001

Value reported as mean (SD) or percent unless otherwise noted. CAC indicates coronary artery calcium; and CVD, atherosclerotic cardiovascular disease.
*Median (interquartile range).

the total mortality rate was low (Figure 1). CVD and CHD mortality rates were low as well for both women and men, at 0.3 and 0.1 per 1000 person-years, respectively (Table 2). For women and men the proportion of deaths attributable to CVD increased with higher CAC scores, and the relative proportion of deaths attributable to cancer decreased (Figure 2). For both women and men the rate of CVD and cancer mortality increased with higher CAC scores, and CVD overtook cancer as the leading cause of death in individuals with a CAC ≥400. Among the group with CAC ≥400, women had a higher rate of both cancer and CVD compared with men.

The subdistribution hazard of CVD increased significantly, with higher CAC scores for both men and women, but there was no statistically significant sex-specific relationship between CAC and cancer (Table 3).

Using the functions described in the methods section, we derived the following age- and sex-specific equations for the CAC score at which the risk of CVD and cancer mortality are equal:

Women:

$$Ln(CAC+1) = (-0.01944 \times Age) + (-3.5496 \times Age65) + (0.04937 \times Age \times Age65) + (2.6655)/0.2601 + (-0.03157 \times Age65)$$

Men:

$$Ln(CAC+1) = [0.02914(Age) - 0.62748]/0.20711$$
$$= Ln(CAC+1)$$
$$= (0.1407 \times Age) - 3.0297$$

We observed a U-shaped relationship between CAC and the risk for CVD versus cancer mortality among women, while the relationship was exponential for men (Figure 3). At age 55 CVD overtook cancer as the leading cause of death at a CAC score of 462 for women and a CAC score of 110 for men, while at age 65 CVD overtook cancer as the leading cause of death at a CAC score of 218 for women and 452 for men.

CAC=0   **CAC≥400**

Women

21.3% 39.5% 60.5% 78.7%

Men

32.1% 44.9% 55.1% 67.9%

■ Cancer Death
■ CVD Death
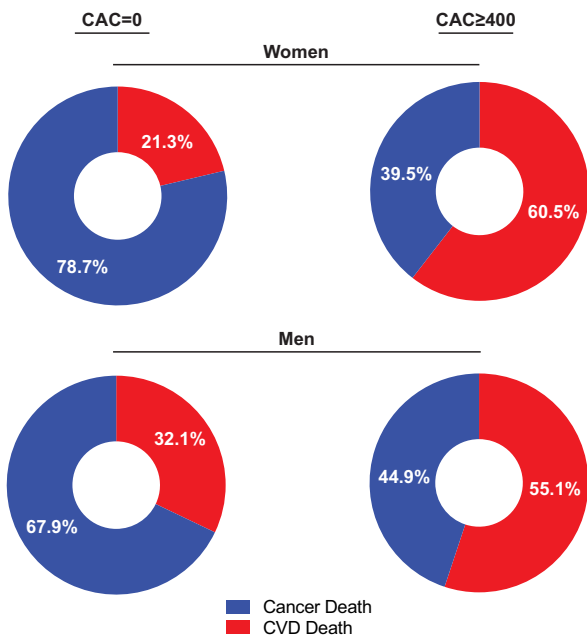
Figure 1. Proportion of cardiovascular and cancer deaths by CAC group and sex.
CAC indicates coronary artery calcium; CVD, cardiovascular disease.

Table 2. **Cause-Specific Mortality Rate per 1000 Person-Years' Follow-Up, Stratified by CAC and Sex**

	Total Population	CAC=0	CAC 1–99	CAC 100–399	CAC ≥400
Total mortality					
Women	3.1	1.8	3.7	6.2	13.6
Men	3.4	1.5	2.5	4.8	9.0
Cardiovascular disease					
Women	0.7	0.3	0.7	2.0	5.2
Men	1.0	0.3	0.6	1.4	3.3
Coronary heart disease					
Women	0.3	0.1	0.2	1.0	2.1
Men	0.6	0.1	0.3	0.8	2.2
Cancer					
Women	1.4	1.0	1.8	2.2	3.4
Men	1.3	0.7	1.0	1.8	2.7

CAC indicates coronary artery calcium.

DISCUSSION

In this study, we describe the age and sex-specific relationship of CAC with CVD and cancer mortality. While CVD and cancer mortality increase with higher CAC scores for both sexes, the age-specific CAC threshold score at which CVD overtakes cancer as the leading cause of death was considerably different between women and men. Our age- and sex-specific CAC equations provide a more precise estimate for an individual's competing risk of CVD and cancer mortality, which further improves the utility of CAC as a synergistic tool for CVD and cancer risk prediction and prevention strategies.

With the decline of CVD mortality, cancer has been projected to overtake CVD as the leading cause of death by as early as 2020.[3] In this new context of shifting mortality risks, individual risk estimation and selection of appropriate primary prevention strategies can be challenging. Currently, there are no guideline-based recommendations for combined CVD- and cancer-risk prediction, and in clinical practice, risk estimates for both disease entities are commonly performed in isolation. The estimation of competing mortality risks is especially difficult because age-dependent CVD and cancer mortality rates differ considerably between men and women,[25] and distinct sex disparities in cancer incidence and mortality are known to exist.[26] With a lack of clinical studies providing clear guidance in this respect, global sex- and age-specific CVD and cancer risk stratification as well as appropriate selection of primary prevention strategies is likely to be suboptimal in the typical daily clinical routine.

We have previously investigated sex-specific CVD mortality based on CAC scores and showed that women have a higher CVD risk when compared with men with comparable CAC burden.[27] Our study adds further detail to this body of knowledge by showing that the CAC score at which CVD mortality overtakes cancer varies considerably by not only age but also by sex. We show that younger men with even mildly elevated CAC scores are more likely to die from CVD than cancer, while for younger women aged 40 to 65 years, elevated CAC scores are less strongly associated with CVD mortality and more strongly associated with cancer mortality. In contrast, for older individuals aged >65 years, our results show that while men with even relatively high CAC scores are less likely to die from CVD rather than cancer, women with only moderate CAC scores are more likely to suffer a fatal CVD event.

Proposed reasons for differences in CVD susceptibility are variations in sex-specific plaque composition and plaque erosion patterns[28,29] as well as differences in inflammation and endothelial function.[30,31] Moreover, studies have shown that naturally higher estrogen levels in women are likely to exert a protective effect against CVD,[32–34] which is at least one well established explanation for why especially younger women aged 40 to 55 have a lower CVD risk than men. Women also generally develop CAC and CVD ≈10 years later in life than men.[14] Accordingly, coronary dissection is the predominant cause of CHD among young women (rather than plaque rupture). In addition, the prevalence of heart failure with preserved ejection fraction is much higher among women compared with men.[35] Therefore, these sex-specific differences in nonatherosclerotic cardiovascular disease may also contribute to the observed sex-specific differences for the relationship of CAC with CVD and cancer.

Indeed, our results suggest that at higher CAC scores women have a higher mortality rate of both CVD
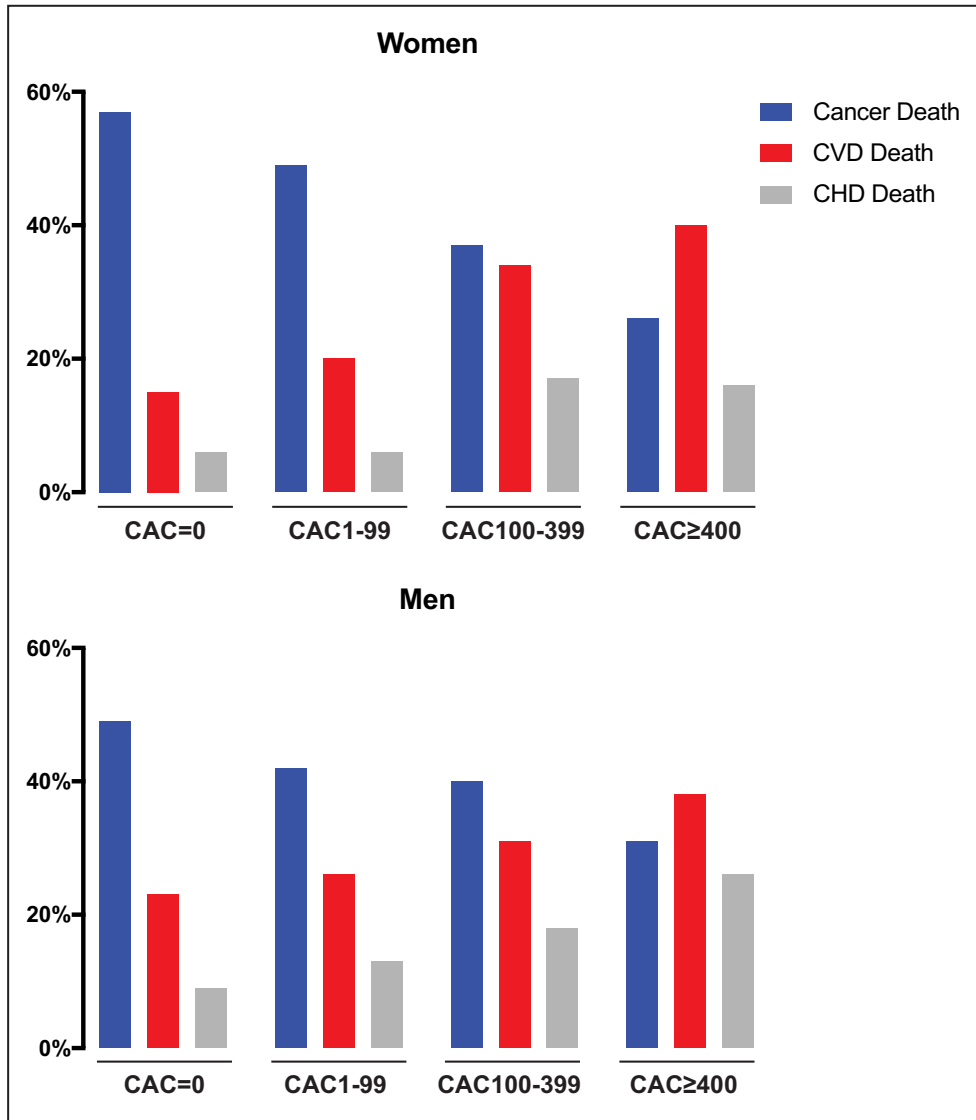
Figure 2. Proportion of deaths attributable to cancer, CVD, and CHD stratified by sex.
CAC indicates coronary artery calcium; CHD, coronary heart disease; and CVD, cardiovascular disease.

and cancer compared with men with the same CAC burden. In addition, while higher estrogen levels are protective against CVD, they are thought to increase the incidence of hormone-sensitive cancers, for example, breast and ovarian cancer.[36–40] This suggests that distinctive CAC- and age-dependent mortality risks of

Table 3. Fine and Gray Subdistribution Hazard of Cause-Specific Mortality, by CAC Score and Sex

	CAC=0	CAC 1–99	CAC 100–399	CAC ≥400	*P* for Trend
Cardiovascular disease					
Women	Reference	1.71 (1.11–2.64)	3.29 (2.08–5.22)	6.33 (3.92–10.22)	<0.001
Men	Reference	1.27 (0.92–1.76)	2.11 (1.51–2.94)	3.62 (2.59–5.06)	<0.001
Coronary heart disease					
Women	Reference	1.29 (0.61–2.74)	3.87 (1.95–7.68)	5.98 (2.79–12.80)	<0.001
Men	Reference	1.62 (0.99–2.65)	3.11 (1.89–5.12)	6.13 (3.73–10.09)	<0.001
Cancer					
Women	Reference	1.25 (0.97–1.62)	1.17 (0.81–1.69)	1.51 (0.99–2.29)	0.059
Men	Reference	0.91 (0.72–1.15)	1.09 (0.84–1.41)	1.18 (0.91–1.53)	0.083

Adjusted for age, sex, hypertension, hyperlipidemia, smoking, diabetes mellitus, family history of coronary heart disease. CAC indicates coronary artery calcium.
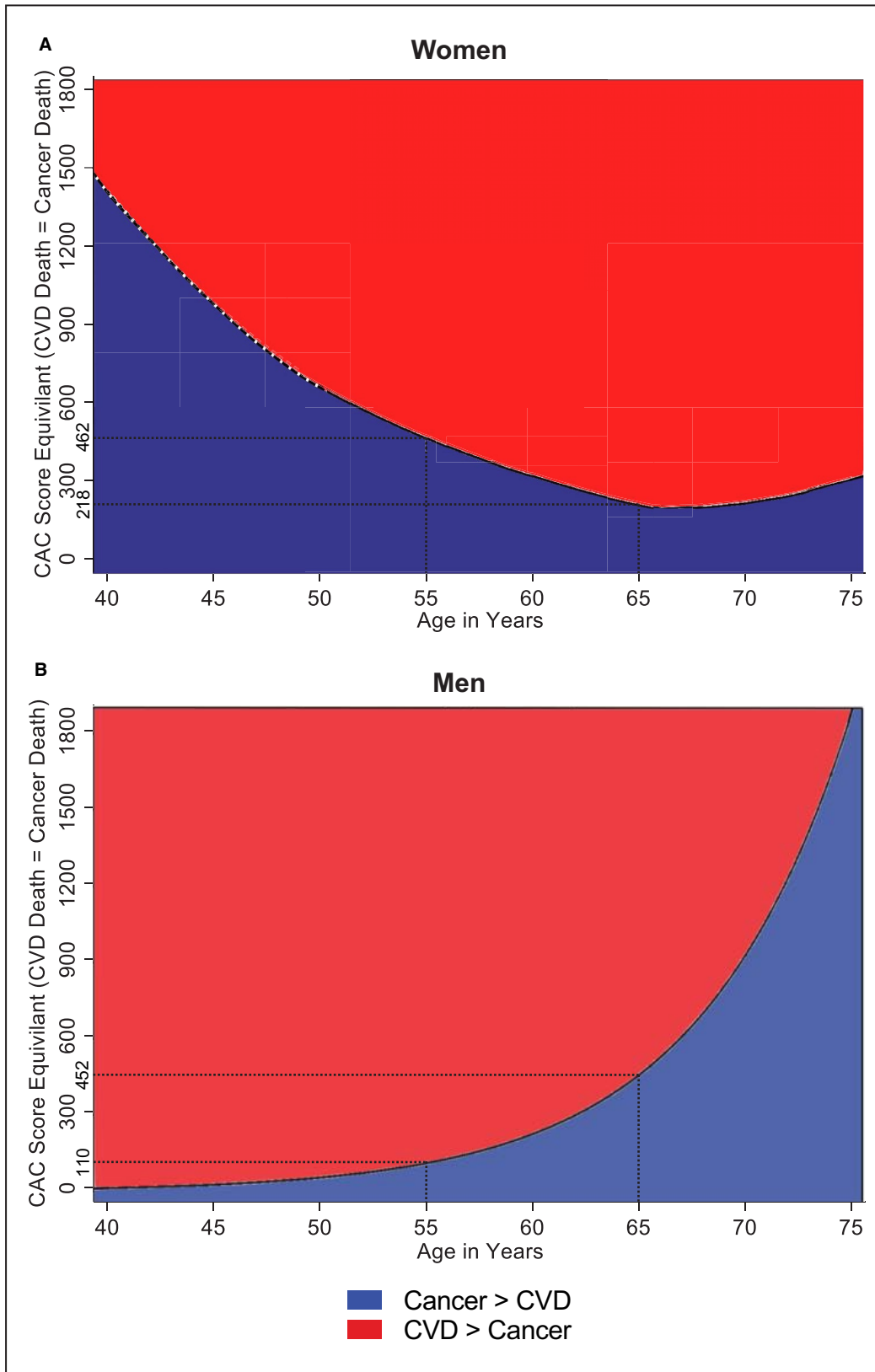
Figure 3.   CAC score at which the rate of CVD and cancer mortality are equal for women (A) and men (B).
Dotted line for women aged 40 to 50 represents a low number of CVD events and a reduced precision for the estimate of where the rate of CVD and cancer mortality are equal for women. CAC indicates coronary artery calcium; and CVD, cardiovascular disease.

women observed in our study could at least in part be attributed to differing CVD and cancer effects of estrogen.

The findings of this study have a number of significant clinical implications. Both men and women with low CAC or CAC=0 had a higher risk of dying from cancer than from CVD irrespective of age, which underlines the importance of age-appropriate cancer screening in individuals with low CAC. Identification of these individuals, who are generally healthy but nonetheless have a higher risk of dying from cancer than CVD, can be helpful in the physician–patient discussion by providing a more concrete, individualized risk estimate, which in turn may motivate increased participation in cancer prevention programs. This is especially important as participation in cancer prevention programs in the United States is still well below (65% participation) the national targets as defined by the Healthy People 2020 Initiative.[41] These individuals with low CAC may also represent a target group for future screenings such as genetic cancer risk scores, especially if they have a family history of certain cancers.

For individuals with elevated CAC scores, the results of our study demonstrate that younger men with even mildly elevated CAC scores are more likely to experience death from CVD than cancer, while for younger women aged 40 to 65 years, elevated CAC scores are less strongly associated with CVD mortality and more strongly associated with cancer mortality. In contrast, for older individuals aged >65 years, our results show that while even men with relatively high CAC scores are less likely to die from CVD, women with only moderate CAC scores are more likely to suffer a fatal CVD event. Accordingly, maximal CVD prevention treatment strategies have a much higher likelihood for extending life and reducing CVD mortality among people with elevated CAC scores. Conversely, among individuals with CAC=0, CVD preventive therapies are unlikely to reduce CVD mortality, and less strict CVD risk factor treatment goals can be considered in a shared decision-making process.

The results presented in this study should be considered with the following limitations: First, most of the participants in the CAC Consortium are white, and we were therefore not able to examine whether there are ethnicity-based differences in the observed relationship. Second, we did not have information on the prevalence of cancer at the time of CAC scan, although it is unlikely that many patients with cancer had a clinically ordered CAC scan for CVD risk stratification. Third, limitations exist in the ascertainment of cause of death by relying on the documentation provided by death certificates only. However, the death certificate data used in this analysis are also used by the Centers for Disease Control and Prevention to monitor mortality trends in the United States. Fourth, we do not have information on downstream procedures and CVD medications and among individuals with a higher CAC score could bias the results presented in this study, although it would make our results more conservative.

CONCLUSIONS

For both women and men with CAC=0, cancer was the leading cause of death, while the total mortality rate was low and the CVD mortality rate was exceedingly low. Among individuals with CAC ≥1, the relationship for CVD versus cancer mortality was U-shaped for women and exponential for men, which reflects underlying age- and sex-specific differences in CVD and cancer mortality. These findings provide a more precise understanding for the relationship of CAC with CVD and cancer mortality and thereby improve the utility of CAC as a synergistic tool for risk prediction and prevention strategies of both CVD and cancer. Therefore, these results can provide a more personalized estimate of an individual's CVD versus cancer mortality risk, which allows for a focus on prevention strategies that are most likely to extend life and reduce mortality.

Affiliations

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Disclosures

None.

Supplementary Materials

Data S1
Figures S1 and S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Methods to derive the equation to estimate the CAC score at which the risk of CVD mortality is equal to the risk of cancer mortality.

Common statistical notations were used in both formulas. The terms used are as follows:

Ln (CAC+1): ln of total CAC score +1
Age: Age in years
Age65: Binary term for age < & ≥ 65yrs old
Age X Age65: Interaction term for Age and Age 65
Ln (CAC+1) X Age 65: Interaction term for Ln(CAC+1) and Age 65
X: Coefficient for Cancer Death model
β: Coefficient for CVD Death model

For easy reference here, the equations from the manuscript with comments on which part of the equation correlate with "CDV Death Risk" and "Cancer Death Risk" for both women and men:

Women:
Ln (CAC+1) = [(X1- β1)* Age + (X3- β3)* Age65 + (X4- β4)* Age X Age65 + (X0- β0)] / (β2-X2)+ (β6-X6)*Age65

CVD Death Risk = β1*Age + β2*Ln (CAC+1) + β3*Age65 + β4*AgeXAge65 + β6 * Ln (CAC+1)X Age65 + β0
Cancer Death Risk = X1*Age + X2*Ln (CAC+1) + X3*Age65 + X4*AgeXAge65 + X6 * Ln (CAC+1)X Age65 + X0

Men:
Ln (CAC+1) = [(X1- β1)* Age + (X0- β0)] / (β2-X2)"

CVD Death Risk = β1* Age + β2* Ln (CAC+1) + β0
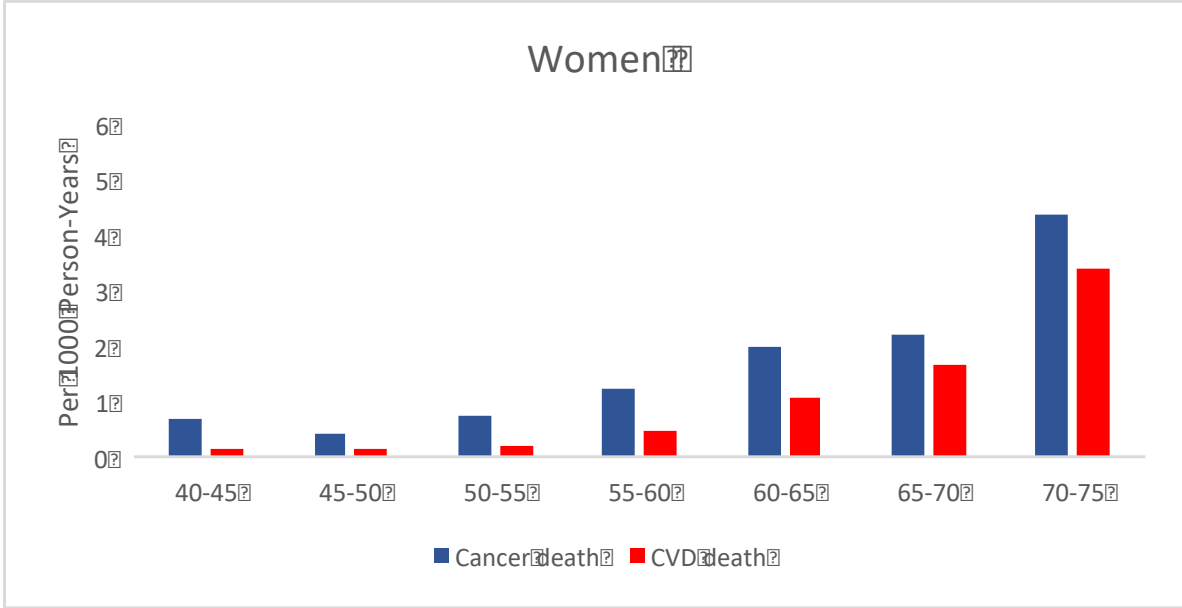**Cancer Death Risk** = X1* Age +X2* Ln (CAC+1) + X0

Figure S1. Median total CAC score for women and men stratified by age, among those with CAC≥1.
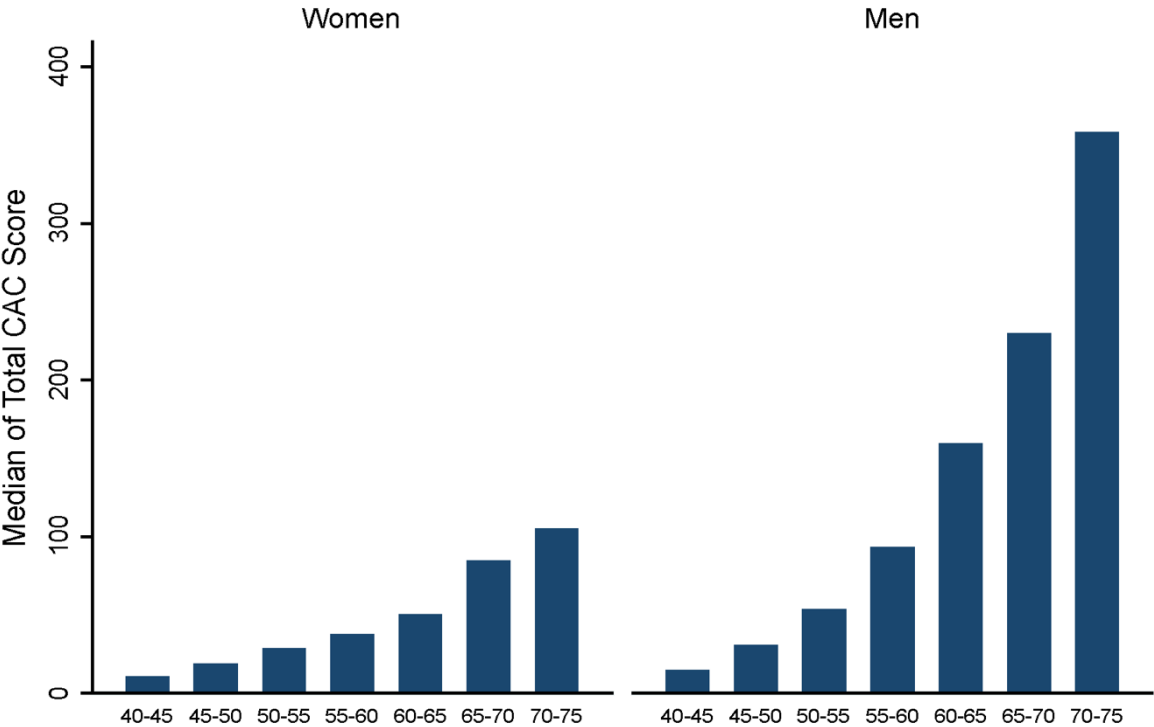
Figure S2. Cancer and CVD mortality rate for women (A) and men (B) stratified by age per 5 year intervals.

A

B