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ORIGINAL ARTICLE



Predicting the risk of cardiovascular comorbidities in adult cancer survivors

A.Y. Tashakkor MD, A. Moghaddamjou,* L. Chen,* and W.Y. Cheung MD MPH*†*

ABSTRACT

Objectives

Data on how to identify cancer survivors (CSS) at the greatest risk for cardiovascular conditions are limited. We aimed to characterize the clinical factors associated with ischemic heart disease (IHD) and congestive heart failure (CHF) in CSS and to develop a stratification schema for predicting the risk of cardiovascular comorbidities in CSS.

Methods

Cancer survivors and non-cancer controls (NCCS) were identified from the U.S. National Health and Nutrition Examination Survey. Independent factors associated with increased relative risk (RR) for cardiovascular conditions were determined. A risk stratification schema was devised that correlated risk score with the prevalence of cardiovascular comorbidities in CS.

Results

Baseline characteristics were similar for the 1869 CSS and 24,337 NCCS included in the study. Compared with NCCS, CSS were more likely to report IHD (13.7% vs. 5.2%), CHF (7.9% vs. 2.1%), or both (4.2% vs. 1.2%; all $p < 0.01$). Based on multivariate analyses, risk factors for cardiovascular problems included ages 40–60 years (RR: 3.66; 95% CI: 1.87 to 7.17), 60–80 years (RR: 14.18; 95% CI: 7.65 to 26.30), and 80 years or older (RR: 25.34; 95% CI: 13.16 to 48.78); male sex (RR: 2.25; 95% CI: 1.72 to 2.94); U.S. citizenship (RR: 2.10; 95% CI: 1.08 to 4.08); annual incomes of $20,000–$45,000 (RR: 1.81; 95% CI: 1.21 to 2.70) and less than $20,000 (RR: 3.05; 95% CI: 1.81 to 5.14); comorbid diabetes mellitus (RR: 2.97; 95% CI: 2.05 to 4.32); and physical inactivity (RR: 1.98; 95% CI: 1.41 to 2.79).

CONCLUSIONS

Independent risk factors for IHD and CHF in CSS were identified. The risk stratification schema presented here may be helpful in developing a risk-based approach to preventive cardiovascular strategies for CSS.

KEY WORDS

Cardiovascular, comorbidities, survivors

1. INTRODUCTION

The incidence of cancer increases with advancing age. For example, more than 60% of patients are more than 65 years of age at the time of their initial cancer diagnosis[1]. Recent diagnostic and therapeutic advances in oncology, coupled with the increased life expectancy of the general population, indicate that the number of elderly cancer survivors (CSS) will continue to grow[2,3]. Importantly, the comorbidity burden in this aging group of survivors is high, which can pose significant challenges to treatment. Cancer survivors are more likely to develop second malignancies and other medical conditions such as cardiovascular disease (CVD) and diabetes mellitus[2–4], partly because of their age, but also because of late effects from prior cancer therapies. These associations are concerning, because comorbidities can worsen long-term outcomes in CSS, independent of the stage of their primary disease and the type of prior treatment[5].

Cardiovascular disease is a particularly important cause of morbidity and mortality in the elderly population. Because of similarities in risk factors for CVD and some cancers, the same individual may harbour both conditions, either concurrently or sequentially. Anticancer therapies can result in significant heart problems, and CVD may exacerbate cancer symptoms, limit the available diagnostic and therapeutic options for cancer, and worsen overall

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prognosis. The use of cardiovascular medications in cancer patients who are undergoing active anticancer therapies (for example, hormonal treatment) can also lead to polypharmacy, which can increase the risk of nonadherence, the cost of treatment, and the potential for drug interactions[6,7].

Cardiovascular risk factors have been reported to be highly prevalent among breast[8], testicular[9], and prostate[10] cancer patients. Yet, despite those observations, few guidelines are available on how to best manage CSS with significant cardiovascular morbidities. Data on ways to identify CSS who are at the greatest risk and who may benefit most from preventive measures are also limited[11]. Expert panels have highlighted the need for research aimed at identifying CSS at risk for CVD and have underscored the importance of optimizing screening and treatment strategies in this vulnerable population[11]. The goals of the present study were therefore to characterize the clinical risk factors associated with ischemic heart disease (IHD) and congestive heart failure (CHF) in CSS, and to develop a simple stratification schema for predicting the risk of cardiovascular morbidities in CSS.

3. METHODS

3.1 Description of the Data Source

Our study used the U.S. National Health and Nutrition Examination Survey (NHANES 2002–2008) to examine the prevalence of CVD among CSS. A cross-sectional nationally representative survey, the NHANES is conducted biennially in the homes of participants in conjunction with well-equipped mobile medical centres designed to assess the health and nutrition status of adults in the United States. The survey consists of an in-person interview component that collects self-reported demographics, general health, and socioeconomic and dietary status, and a clinical component that collects medical, physiologic, and laboratory measurements taken by trained professionals. The NHANES has been approved by the National Center for Health Statistics, with informed consent from all participants. The cohort was limited to participants 18–85 years of age at the time of the study.

3.2 Identification of CSs and Non-Cancer Control Subjects

Respondents who reported ever having cancer (excluding non-melanoma skin cancer) in the questionnaire were classified as CSS. They were compared with non-cancer control subjects (NCCS) who denied any history of a prior or current cancer diagnosis. The CSS were further categorized by duration of survivorship—5 years or less (short-term survivors) or more than 5 years (long-term survivors)—based on the interval between their age at the time of survey completion and their age at the time of diagnosis. For individuals with a history of multiple malignancies, age at first cancer diagnosis was used. Cancers were grouped into broad categories based on anatomic site.

3.3 Definition of CVD

The NHANES participants are specifically asked if they have ever been informed by a physician or a health professional that they have certain medical conditions such as heart disease. Respondents who indicated having any one or more of CHF, coronary artery disease (CAD), heart attack, or angina at any point in the past were considered to have CVD for purposes of the present study. In particular, those who reported angina, heart attack, or CAD were further defined as having IHD and were subsequently compared with the subjects having CHF.

3.4 Description of Covariates

All available demographic features, socioeconomic characteristics, and health statuses used to describe the CSS at the time of the survey were compared with those of the NCCS. Specifically, participant demographics included age, sex, place of birth, citizenship, race, and marital status. Age was grouped into four categories (<40, 40–60, 60–80, and >80 years). Race was grouped into white and non-white, and marital status was categorized into four groups (married or living with partner, divorced or separated, never married, and widowed). Socioeconomic status was estimated by self-reported levels of education (less than high school, high school, and postsecondary) and household income (categorized as <$20,000, $20,000–$45,000, $45,000–$75,000, and >$75,000).

To estimate the health status of the CSS, we used physical activity, body mass index (BMI), and presence of diabetes mellitus. Self-reported history of diabetes was included because this condition correlates with cardiac health and represents a long-term morbidity. Participants who reported being told by a health care professional to increase their physical activity were identified to be physically inactive. Body mass index was categorized into four groups: underweight (≤18.5), normal weight (18.5–25), overweight (25–29), and obese (≥30).

3.5 Statistical Considerations

All statistical analyses were performed using the Stata software application (version 11.0: StataCorp LP, College Station, TX, U.S.A.). For the results to accurately reflect the non-institutionalized American population, appropriate survey weighting algorithms provided by NHANES were applied to all univariate and multivariate regression models to account for sampling errors, nonresponses, and the overall complex survey design. Trends and risk factors reported in

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this study are therefore statistically representative of the U.S. population.

Characteristics are reported as weighted proportions for categorical variables and as weighted means for continuous variables. The chi-square test was used as a determiner of significance in univariate analyses. Univariate and multivariate regression models were constructed using odds ratios (ORs) and 95% confidence intervals (CIs) to identify characteristics of CSS associated with an elevated relative risk for CVD, IHD, and CHF. All estimates are adjusted for CSS compared with NCCS, meaning that all of the reported relative risks (RRS) take into account the case and control groups. A p value of 0.05 was used in all comparisons to evaluate for statistical significance. The Wald test was used in the regression models to derive global p values.

3.6 Development of the Risk Stratification Schema

A simple risk stratification schema was devised to estimate the prevalence of CVD, IHD, and CHF. Based on the multivariate logistic regression models, we identified demographic characteristics and clinical parameters that were independently correlated with an elevated RR for each of the cardiovascular outcomes. Based on the weight of the RR, points were assigned to every significant risk factor identified. Factors with RRS of 1–2, 2–3, and more than 3 were assigned point values of 1, 2, and 3 respectively (Table I). People in our study cohort were then assigned a composite risk score by summing the points from their clinical profile. We subsequently tabulated the relationships between the various composite scores and the prevalences of CVD, IHD, and CHF among CSS and NCCS.

4. RESULTS

4.1 Cohort Characteristics

Of the 26,206 total participants, 1869 were CSS (761 identified as being ≤5 years from diagnosis, 1090 identified as being >5 years from diagnosis), and 24,337 were NCCS. In the overall cohort, mean age was 45.0 ± 17.4 years, and 48.1% were men. As outlined in Table II, both groups of CSS contained a greater proportion of women, white people, and U.S. citizens than did the group of NCCS. In addition, the CSS tended to be more highly educated, to have lower incomes, and to be less physically active. Furthermore, both CS groups were more likely to report all comorbidities, including IHD, CHF, and diabetes mellitus.

TABLE I Risk score categories

Relative risk	*Risk category*
1–2	1
2–3	2
>3	3

Table III summarizes the prevalence of CVD, IHD, and CHF stratified by cancer type. The CSS most likely to have CVD or IHD were those with gastrointestinal (28.4% and 22.9% respectively), genitourinary (22.7% and 19.6%), and lung (21.8% and 20.8%) malignancies. Among the CSS with CHF, the most prevalent cancer types were gastrointestinal (15.2%), hematologic (9.7%), and genitourinary (8.8%) malignancies.

4.2 Cardiovascular Risk Factors

The univariate models presented in Table IV demonstrate an increased RR for CVD, IHD, and CHF in both CS groups compared with the NCC group. Once adjustments were made for strongly significant variables in the multivariate regressions (Table V), any effect of cancer survivorship on cardiac outcomes dissipated.

Identified IHD risk factors from the multivariable regression models include ages 40–60 years (RR: 3.89), 60–80 years (RR: 14.60), and 80 years or older (RR: 22.92); male sex (RR: 2.57); U.S. citizenship (RR: 2.16); less than a high school education (RR: 1.25); annual incomes of $20,000–$45,000 (RR: 1.58) and less than $20,000 (RR: 2.89); comorbid diabetes mellitus (RR: 2.40); and being physically inactive (RR: 2.23). Identified CHF risk factors included ages 60–80 years (RR: 11.73) and 80 years or older (RR: 19.60); male sex (RR: 1.74); annual incomes of $45,000–$75,000 (RR: 2.54), $20,000–$45,000 (RR: 3.73), and less than $20,000 (RR: 4.08); and comorbid diabetes mellitus (RR: 3.40). Risk factors for CVD included ages 40–60 years (RR: 3.66), 60–80 years (RR: 14.18), and 80 years or older (RR: 25.34); male sex (RR: 2.25); U.S. citizenship (RR: 2.10); annual incomes of $20,000–$45,000 (RR: 1.81) and less than $20,000 (RR: 3.05); comorbid diabetes mellitus (RR: 2.97); and being physically inactive (RR: 1.98).

4.3 Risk Stratification

Table VI tabulates the frequency of CVD, IHD, and CHF among CSS and NCCS based on their various risk scores. The prevalence of CVD, IHD, and CHF was consistently higher in both CS groups than in the NCC group, except for short-term CSS with the highest risk scores (9 or more). For instance, CSS with risk scores of 6 or less, 7–8, and 9 or more had, respectively, an 8.0%, 23.8%, and 35.0% chance of reporting CVD compared with a 2.6%, 15.6%, and 31.4% chance for NCCS (Figure 1). In general, IHD and CHF followed a similar trend, but the absolute prevalence of CHF was lower than that for IHD in both CSS and NCCS. The risk of IHD (6.3%, 20.7%, and 28.3% for risk scores of ≤6, 7–8, and ≥9 respectively) and CHF (2.8%, 10.1%, and 17.0% for risk scores of ≤6, 7–8, and ≥9 respectively) were significantly higher for CSS than for NCCS. When

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TABLE II Characteristics of the population groups

Characteristic	*Population group [*n *(weighted %[a])]*		
	Cancer survivors		*Non-cancer control subjects*
	≤5 Years	*≥5 Years*	
Population	761	1,090	24,337
Mean age (years)	59.4	61.9	45.1
Sex			
Men	382 (42)	436 (31)	11,682 (49)
Women	379 (58)	654 (69)	12,655 (51)
Ethnicity			
White	492 (85)	787 (89)	11,707 (75)
Black	137 (9)	158 (7)	4,958 (12)
Hispanic	111 (7)	120 (4)	6,693 (13)
Education			
Less than high school	206 (24)	271 (22)	6,410 (20)
High school	167 (28)	232 (29)	4,681 (26)
More than high school	259 (47)	397 (49)	8,527 (54)
Income			
0–$20,000	194 (23)	303 (23)	5,455 (17)
$20,000–$45,000	246 (32)	337 (32)	7,158 (29)
$45,000–$75,000	109 (21)	185 (22)	4,638 (24)
$75,000+	119 (24)	166 (22)	4,670 (29)
Marital status			
Married	455 (67)	629 (63)	14,482 (64)
Widowed	148 (14)	233 (17)	2,303 (6)
Divorced or separated	100 (13)	158 (15)	2,993 (12)
Never married	49 (57)	52 (5)	4,020 (18)
Citizenship status			
U.S. citizen	723 (97)	1,061 (99)	20,760 (91)
Other	38 (3)	28 (1)	3,517 (9)
Mean BMI	27.68	28.31	28.30
Physical activity			
Yes	625 (83)	906 (83)	21,139 (88)
No	136 (17)	284 (17)	3,198 (12)
Congestive heart failure			
Yes	70 (7)	91 (7)	778 (2)
No	682 (93)	992 (93)	23,469 (98)
Coronary artery disease			
Yes	78 (8)	102 (7)	976 (3)
No	678 (92)	974 (93)	23,229 (97)
Angina			
Yes	60 (7)	91 (6)	757 (2)
No	696 (93)	989 (94)	23,487 (98)
Heart attack			
Yes	84 (9)	113 (8)	1,048 (3)
No	674 (91)	972 (92)	23,224 (97)
Cardiovascular disease			
Yes	164 (17)	223 (16)	2,123 (7)
No	596 (83)	866 (84)	2,209 (93)
Ischemic heart disease			
Yes	136 (15)	181 (13)	1,707 (5)
No	615 (85)	883 (87)	22,405 (95)
Diabetes			
Yes	111 (11)	192 (14)	2,487 (7)
No	632 (89)	877 (86)	21,486 (93)

[a] Survey weighting adjustments provided by NHANES were used to accurately reflect the American population.

the CS group was categorized into short- and long-term survivors, the prevalences of CVD, IHD, and CHF for risk scores of 6 or less and of 7–8 were higher for short-term than for long-term CSS; however, compared with NCCS, both CS groups had higher prevalences. At the highest risk scores (9 or more), short-term CSS had a lower prevalence of CVD, IHD and CHF than did long-term CSS and NCCS. For example, short-term CSS with risk scores of 6 or less, 7–8, and 9 or more had, respectively, a 9.2%, 26.3%, and 29.5% chance of reporting CVD, which compared with 7.1%, 22.1%, and 38.7% for long-term CSS and with 2.6%, 15.6%, and 31.4% for NCCS in the same risk categories.

5. DISCUSSION AND CONCLUSIONS

With the number of CSS increasing and the prognosis of many types of cancers improving, the screening, prevention, and treatment of CVD in CSS has become an essential component of comprehensive cancer care. Our results indicate that, across risk score categories, the prevalence of CVD is generally higher in both short- and long-term CSS than in NCCS.

Several aspects of survivorship may account for our observations. Foremost, the cardiotoxic and antiangiogenic effects of commonly used systemic therapies and radiation schedules can contribute to new CVD and exacerbate cardiac symptoms in patients with a pre-existing history of CVD[1,11–13]. In CSS, CVD mortality has been shown to increase by a factor of 8 compared with that seen in NCCS, even 25 years after completion of anticancer treatment[12]. Our results further identified advanced age, male sex, physical inactivity, comorbid diabetes mellitus, low socioeconomic status, and U.S. citizenship as significant independent risk factors for CVD in CSS (Table V). Many of those variables are consistent with well-established risk factors for CVD in NCCS[14–17].

As in the present study, Fiscella *et al.*[14] also observed that low socioeconomic status was a risk factor for CVD, reporting a relative risk of 1.5 for subjects with an education level of grade 12 or less. Lack of awareness and knowledge about cardiac health, suboptimal access to preventive care, and prohibitive

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TABLE III Prevalence of cardiovascular disease, by cancer site

Site	*Cardiovascular disease [n (weighted %[a])]*		*Ischemic heart disease [n (weighted %[a])]*		*Congestive heart failure [n (weighted %[a])]*	
	No	*Yes*	*No*	*Yes*	*No*	*Yes*
Breast	261 (85.2)	62 (14.8)	271 (88.4)	43 (11.6)	293 (95.1)	27 (4.9)
Lung	38 (78.2)	12 (21.8)	39 (79.2)	11 (20.8)	46 (93.0)	4 (7.0)
Melanoma	93 (84.8)	23 (15.2)	95 (86.2)	20 (13.8)	106 (95.9)	7 (4.1)
Skin	381 (80.6)	124 (19.4)	393 (83.3)	103 (16.7)	460 (92.3)	45 (7.7)
Gastrointestinal	127 (71.6)	52 (28.4)	135 (77.1)	41 (22.9)	150 (84.8)	26 (15.2)
Genitourinary	315 (77.3)	105 (22.7)	323 (80.4)	89 (19.6)	379 (91.2)	38 (8.8)
Gynecologic	260 (90.9)	38 (9.1)	261 (93.2)	30 (6.8)	283 (96.2)	15 (3.8)
Hematologic	48 (86.6)	10 (13.4)	47 (89.1)	9 (10.9)	50 (90.3)	6 (9.7)
Head-and-neck	47 (87.5)	11 (12.5)	48 (89.5)	10 (10.6)	52 (93.4)	6 (6.6)
Other	90 (85.8)	21 (14.2)	93 (89.4)	18 (10.6)	98 (89.8)	13 (10.2)
Multiple	184 (80.6)	55 (19.4)	186 (82.6)	47 (17.4)	217 (93.1)	21 (6.9)
TOTAL	1,844 (82.8)	513 (17.3)	1,891 (85.5)	421 (14.5)	2,134 (92.9)	208 (7.1)

[a] Survey weighting adjustments provided by NHANES were used to accurately reflect the American population.

diagnostic and treatment-related costs may explain the increased prevalence in this subset of the population. Notably, subgroup analyses in clinical trials indicate that, compared with their high socioeconomic status counterparts, subjects with low socioeconomic status benefit equally from interventional and possibly from preventive measures[14], underscoring the need to offer adequate management to this group of CSS for whom non-cancer follow-up may be particularly poor[18–20]. Our results also suggest that U.S. citizenship is associated with a doubling of the risk for IHD (2.16) and CVD (2.10). That observation is noteworthy and might potentially be explained by the Western diet and sedentary lifestyle, which have contributed to a dramatic increase in obesity rates in the United States[15].

The prevalence of CVD increased for both short- and long-term CSS as well as for NCCS with increasing risk scores (Table VI), albeit more prominently for CSS. Interestingly, at the highest risk score, a higher prevalence of CVD was seen for NCCS than for short-term CSS. A possible explanation is that, in very high-risk individuals, a cancer diagnosis and potential toxicities from anticancer treatments may prove insignificant when the baseline risk profile for CVD is already quite substantial. In addition, although citizenship and physical activity were risk factors for CVD and IHD, they were not identified to be risk factors for CHF. Because CHF affected only a small number of the CSS in our cohort, the study may have been underpowered to detect additional risk factors for this particular cardiac outcome. Furthermore, our definition for IHD was more inclusive (encompassing, for example, CAD, heart attack, and angina) than that for CHF, which may have preferentially enhanced the study's sensitivity to identify more risk factors for IHD.

An interesting finding is that, in some instances, the prevalence of CVD among long-term CSS appears lower than that among short-term CSS. That observation might be a result of selection bias among the survey respondents, whereby CSS who lived beyond 5 years were invariably healthier (for example, they had better lifestyle behaviours), which in and of itself might have contributed to their long survival. In contrast, CSS who lived for fewer years might have been less healthy. Specifically, some of these individuals might have had significant comorbidities—such as CVD—that would have contributed to their shorter survival and inability to complete the survey more than 5 years after their cancer diagnosis.

In contrast to earlier studies that explored CVD in CSS from smaller populations or single institutions, the large sample size in this study allows our results to be representative of the U.S. population. Enright *et al.*[21] reported a related study on the control of cardiovascular risk factors in adult CSS. They concluded that, despite the comparable frequencies of CVD risk factors among CSS and NCCS, the overall CVD prevalence was suboptimal in both groups. A distinguishing feature of the present study is that we internally validated our proposed risk factors by developing a stratification schema that showed a positive correlation between CVD and risk scores. We also included non-modifiable risk factors, whereas Enright *et al.*[21] explored only modifiable risk factors that were previously established for the general population by the American Heart Association and American College of Cardiology[22]. Even though variables such as age, sex, socioeconomic status, and citizenship cannot be modified *per se,* their identification as risk factors for CVD in CSS can prompt physicians to select patient subgroups for whom preventive measures should be emphasized.

There are several limitations to this study. First, although we analyzed surveys across several calendar years, each questionnaire was cross-sectional and

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TABLE IV Univariate relative risk (RR) for cardiovascular disease, ischemic heart disease and congestive heart failure

Variable	*Cardiovascular disease*				*Ischemic heart disease*				*Congestive heart failure*			
	RR	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	Total p	*RR*	*95% CI*	p *Value*	*Total* p
Cancer				<0.001				<0.001				<0.001
No cancer	Reference				Reference				Reference			
Short-term survivor[a]	3.46	2.38 to 4.21	<0.001		3.58	2.91 to 4.41	<0.001		4.11	3.12 to 5.43	<0.001	
Long-term survivor[a]	3.11	2.61 to 3.70	<0.001		3.04	2.54 to 3.64	<0.001		3.59	2.80 to 4.60	<0.001	
Age				<0.001				<0.001				<0.001
<40 Years	Reference				Reference				Reference			
40 to 60 Years	7.61	5.50 to 10.54	<0.001		8.21	5.68 to 11.89	<0.001		6.28	0.92 to 7.75	<0.001	
60 to 80 Years	31.98	23.48 to 43.55	<0.001		34.37	24.15 to 48.92	<0.001		26.76	3.39 to 40.56	<0.001	
≥80 Years	58.26	42.16 to 80.50	<0.001		55.34	38.76 to 78.99	<0.001		52.48	31.23 to 88.19	<0.001	
Sex				<0.001				<0.001				0.036
Women	Reference				Reference				Reference			
Men	1.36	1.21 to 1.54	<0.001		1.50	1.30 to 1.72	<0.001		1.20	1.01 to 1.43	0.036	
Place of birth				<0.001				< 0.001				<0.001
United States	Reference				Reference				Reference			
Outside United States	0.51	0.43 to 0.61	<0.001		0.51	0.42 to 0.62	<0.001		0.49	0.37 to 0.65	<0.001	
Citizenship				<0.001				<0.001				<0.001
Other	Reference				Reference				Reference			
U.S. citizen	3.08	2.31 to 4.10	<0.001		3.13	2.24 to 4.37	<0.001		3.02	2.02 to 4.51	<0.001	
Education				<0.001				<0.001				<0.001
More than high school	Reference				Reference				Reference			
Less than high school	2.34	2.06 to 2.66	<0.001		2.07	1.81 to 2.37	<0.001		3.52	2.78 to 4.46	<0.001	
High school	1.51	1.29 to 1.78	<0.001		3.50	2.92 to 4.20	<0.001		1.69	1.28 to 2.22	<0.001	
Marital status				<0.001				<0.001				<0.001
Never married	Reference				Reference				Reference			
Divorced or separated	3.75	2.89 to 4.90	0.215		4.06	2.99 to 5.51	0.639		3.25	2.23 to 4.75	<0.001	
Married or partnered	3.40	2.61 to 4.40	<0.001		3.89	2.88 to 5.26	<0.001		2.16	1.52 to 3.07	<0.001	
Widowed	14.50	11.07 to 18.99	<0.001		14.20	10.42 to 19.36	<0.001		12.16	8.38 to 17.64	<0.001	

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TABLE IV Continued

Variable	*Cardiovascular disease*				*Ischemic heart disease*				*Congestive heart failure*			
	RR	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p
Income				<0.001				<0.001			<0.001	
$75,000+	Reference				Reference				Reference			
$45,000 to $75,000	1.41	1.10 to 1.81	0.008		1.36	1.06 to 1.75	0.017		1.82	1.30 to 2.55	0.001	
$20,000 to $45,000	2.17	1.78 to 2.65	<0.001		1.98	1.60 to 2.45	<0.001		4.00	2.93 to 5.45	<0.001	
0 to $20,000	3.63	2.98 to 4.43	<0.001		3.12	2.56 to 3.81	<0.001		6.20	4.48 to 8.60	<0.001	
Race				<0.001				<0.001			0.032	
White	Reference				Reference				Reference			
Non-white	0.63	0.56 to 0.70	<0.001		0.57	0.50 to 0.64	<0.001		0.84	0.71 to 0.98	0.032	
Diabetes mellitus				<0.001				<0.001				<0.001
No	Reference				Reference				Reference			
Yes	5.80	5.16 to 6.522	<0.001		5.10	4.42 to 5.90	<0.001		7.42	6.36 to 8.66	<0.001	
Body mass index				<0.001				<0.001				<0.001
Normal weight (18.5 to 25)	Reference				Reference				Reference			
Underweight (<18.5)	1.04	0.59 to 1.83	0.901		1.03	0.55 to 1.94	0.928		0.71	0.32 to 1.58	0.392	
Overweight (25 to 30)	1.62	1.44 to 1.83	<0.001		1.60	1.40 to 1.84	<0.001		1.36	1.33 to 2.20	<0.001	
Obese (≥30)	1.95	1.72 to 2.22	<0.001		1.91	1.69 to 2.17	<0.001		1.27	1.87 to 2.96	<0.001	
Physical activity				<0.001				<0.001				<0.001
Normal activity	Reference				Reference				Reference			
Physically inactive	2.51	2.22 to 2.85	<0.001		2.51	2.15 to 2.93	<0.001		3.12	2.40 to 4.07	<0.001	

[a] Short-term: 5 years or less; long-term: more than 5 years.

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TABLE V Multivariate relative risk (RR) for cardiovascular disease, ischemic heart disease, and congestive heart failure

Variable	*Cardiovascular disease*				*Ischemic heart disease*				*Congestive heart failure*			
	RR	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p
Cancer				0.464				0.402				0.425
No cancer		Reference				Reference				Reference		
Short-term survivor[a]	1.43	0.76 to 2.69	0.252		1.52	0.82 to 2.82	0.171		1.88	0.72 to 4.95	0.184	
Long-term survivor[a]	1.25	0.73 to 2.14	0.388		1.11	0.66 to 1.85	0.686		1.18	0.50 to 2.75	0.690	
Age				<0.001				<0.001				<0.001
<40 Years		Reference				Reference				Reference		
40 to 60 Years	3.66	1.87 to 7.17	0.001		3.89	1.85 to 8.19	0.001		2.67	0.92 to 7.75	0.069	
60 to 80 Years	14.18	7.65 to 26.30	<0.001		14.60	7.63 to 27.96	<0.001		11.73	3.39 to 40.56	0.001	
≥80 Years	25.34	13.16 to 48.78	<0.001		22.92	11.79 to 44.57	<0.001		19.60	6.21 to 61.86	0.000	
Sex				<0.001				<0.001				0.015
Women		Reference				Reference				Reference		
Men	2.25	1.72 to 2.94	<0.001		2.57	1.87 to 3.53	<0.001		1.74	1.13 to 2.68	0.015	
Place of birth				0.706				0.337				0.732
United States		Reference				Reference				Reference		
Outside United States	1.11	0.63 to 1.93	0.706		1.36	0.70 to 2.62	0.337		0.82	0.25 to 2.68	0.732	
Citizenship				0.031				0.0311				0.261
Other		Reference				Reference				Reference		
U.S. citizen	2.10	1.08 to 4.08	0.031		2.16	1.08 to 4.30	0.031		2.66	0.45 to 15.69	0.261	
Education				0.295				0.139				0.689
More than high school		Reference				Reference				Reference		
Less than high school	1.19	0.90 to 1.59	0.209		1.25	1.01 to 1.55	0.043		1.17	0.72 to 1.19	0.503	
High school	0.96	0.70 to 1.31	0.776		1.09	0.73 to 1.64	0.645		0.97	0.65 to 1.45	0.864	
Marital status				0.314				0.609				0.225
Never married		Reference				Reference				Reference		
Divorced or separated	1.01	0.49 to 2.10	0.977		1.21	0.53 to 2.73	0.631		0.744	0.24 to 2.30	0.586	
Married or partnered	1.40	0.68 to 2.87	0.340		1.26	0.66 to 3.51	0.305		0.88	0.36 to 2.13	0.767	
Widowed	1.54	0.70 to 3.38	0.260		1.27	0.69 to 3.40	0.270		1.35	0.50 to 3.71	0.535	

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TABLE V Continued

Variable	*Cardiovascular disease*				*Ischemic heart disease*				*Congestive heart failure*			
	RR	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p	*RR*	*95% CI*	p *Value*	*Total* p
Income				0.004				0.003				0.117
$75,000+		Reference				Reference				Reference		
$45,000 to $75,000	1.46	0.94 to 2.25	0.088		1.26	0.79 to 1.99	0.309		2.54	1.01 to 6.36	0.048	
$20,000 to $45,000	1.81	1.21 to 2.70	0.006		1.58	1.01 to 2.48	0.047		3.73	1.26 to 11.04	0.020	
0 to $20,000	3.05	1.81 to 5.14	<0.001		2.89	1.73 to 4.82	<0.001		4.08	1.33 to 12.50	0.017	
Race				0.959				0.539				0.109
White		Reference				Reference				Reference		
Non-white	1.01	0.66 to 1.54	0.959		0.85	0.49 to 1.48	0.539		1.66	0.88 to 3.14	0.109	
Diabetes mellitus				<0.001				<0.001				<0.001
No		Reference				Reference				Reference		
Yes	2.97	2.05 to 4.32	<0.001		2.40	1.65 to 3.48	<0.001		3.40	2.02 to 5.71	0.000	
Body mass index				0.875				0.962				0.707
Normal weight (18.5 to 25)		Reference				Reference				Reference		
Underweight (<18.5)	1.42	0.38 to 5.34	0.582		0.92	0.26 to 3.25	0.894		1.73	0.36 to 8.32	0.467	
Overweight (25 to 30)	1.04	0.74 to 1.48	0.803		0.93	0.64 to 1.37	0.707		1.36	0.72 to 2.59	0.322	
Obese (≥30)	1.11	0.74 to 1.67	0.579		1.02	0.66 to 1.57	0.930		1.27	0.75 to 2.13	0.348	
Physical activity				<0.001				<0.001				0.061
Normal activity		Reference				Reference				Reference		
Physically inactive	1.98	1.41 to 2.79	0.001		2.23	1.54 to 3.22	<0.001		1.81	0.97 to 3.38	0.061	

[a] Short-term: 5 years or less; long-term: more than 5 years.

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TABLE VI Prevalence of cardiovascular disease, ischemic heart disease, and congestive heart failure based on risk score

Variable		*Risk score*			p *Value*
		≤6	*7–8*	*≥9*	
Cancer survivors [*n* (%)]					
Overall	Cardiovascular disease	86 (8.0)	187 (23.8)	118 (35.0)	<0.001
	Ischemic heart disease	65 (6.3)	159 (20.7)	95 (28.3)	<0.001
	Congestive heart failure	33 (2.8)	75 (10.1)	57 (17.0)	<0.001
Short-term[a]	Cardiovascular disease	38 (9.2)	85 (26.3)	41 (29.5)	<0.001
	Ischemic heart disease	31 (8.0)	72 (22.5)	33 (24.5)	<0.001
	Congestive heart failure	14 (2.9)	37 (11.9)	19 (13.0)	<0.001
Long-term[a]	Cardiovascular disease	46 (7.1)	102 (22.1)	75 (38.7)	<0.001
	Ischemic heart disease	34 (5.3)	87 (19.5)	60 (30.6)	<0.001
	Congestive heart failure	17 (2.6)	38 (8.9)	36 (19.3)	<0.001
Non-cancer control subjects	Cardiovascular disease	517 (2.6)	945 (15.6)	661 (31.4)	<0.001
	Ischemic heart disease	427 (2.2)	760 (12.9)	520 (25.8)	<0.001
	Congestive heart failure	163 (0.7)	329 (5.2)	286 (13.2)	<0.001

[a] Short-term: 5 years or less; long-term: more than 5 years.

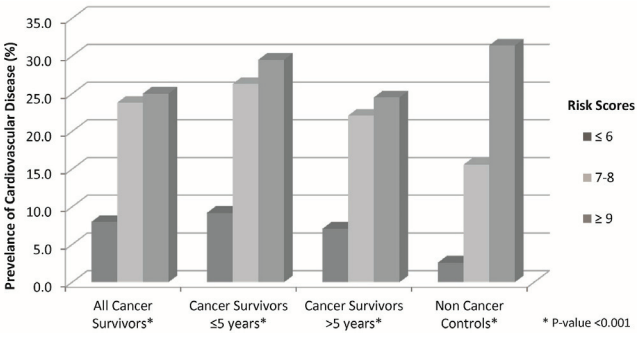


FIGURE 1 Prevalence of cardiovascular disease in cancer survivors and non-cancer control subjects, by risk score.

sampled a different respondent. We were therefore unable to characterize the longitudinal patterns of cardiac risk for individual subjects. Second, although we captured CSS with a variety of cancer diagnoses, the absolute number of respondents with specific cancers was small. We were therefore unable to analyze cardiac risk factors based on the anatomic site of the cancer. Third, considering that the NHANES was designed for the general U.S. population, detailed cancer-specific data were lacking—for example, information concerning the type and dose of chemotherapy and radiation treatment received, which can certainly modify cardiac risks. Fourth, as in other retrospective analyses of cross-sectional survey data, our report may have been partially subject to confounding factors. Specifically, the difference in RR for CVD observed in univariate analysis between CSS and NCCS may be partly attributable to incidental diagnoses of concurrent CVD in patients seeking medical attention for cancer, or vice versa. Finally, our analyses were subject to the recall bias and misclassification error that are common to most survey studies.

Despite the foregoing limitations, the risk-factor stratification schema of this preliminary study can potentially lead to a useful clinical tool for identifying CSS at high risk for CVD, allowing primary physicians, cardiologists, and oncologists to streamline preventive efforts. However, before the risk stratification model can be used clinically, it needs to be prospectively validated. Specifically, additional confirmatory studies are required to ensure that the prevalence reported by our model is accurate ("calibration") and that our stratification schema can reliably discern CSS at low and high risk of CVD ("discrimination")[23]. Similar attempts to design a prediction algorithm akin to our simple risk stratification schema have been made in the past. Among the most recognized is an investigation by Wilson *et al.*[24] that used data from the Framingham heart study to devise an algorithm predicting the risk of CAD. That algorithm has been shown to adequately discriminate short-term risk for CAD in men and women, but it was unable to identify subjects with low short-term and high lifetime risk for CAD[25]. Moreover, it was not designed for use among CSS.

Studies investigating the frequency of CVD in CSS provide valuable insight into some of the long-term medical issues facing CSS, thus ensuring that gains from recent cancer advances are not lost because of poor non-cancer care. Our findings highlight the need for more aggressive screening and preventive measures for CVD among CSS, especially those with higher risk scores. Our results further suggest the need for closer collaboration between cardiologists and oncologists to devise guidelines for managing the cardiac health of CSS. The close rapport that frequently develops between patients and cancer specialists during and after cancer treatments may provide a valuable opportunity for optimizing the

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screening and prevention of CVD and allow for the early involvement of cardiologists in the care of CSS.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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Correspondence to: Winson Y. Cheung, BC Cancer Agency–Vancouver Clinic, 600 W. 10th Avenue, Vancouver, British Columbia V5Z 4E6.
E-mail: wcheung@bccancer.bc.ca

* University of British Columbia, Vancouver, BC.
† Division of Medical Oncology, BC Cancer Agency, Vancouver, BC.

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