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Non-cancer Related Mortality Risks in Adult Survivors of Pediatric Malignancies: The Childhood Cancer Survivor Study

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Abstract

Purpose—We sought to identify factors, other than cancer-related treatment and presence/severity of chronic health conditions, which may be associated with late mortality risk among adult survivors of pediatric malignancies.

Methods—Using the Childhood Cancer Survivor Study cohort and a case-control design, 445 participants who died from causes other than cancer recurrence/progression or non-health related events were compared with 7162 surviving participants matched for primary diagnosis, age at baseline questionnaire, time from diagnosis to baseline questionnaire, and time at-risk. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for overall/cause-specific mortality. Independent measures included number/severity of chronic conditions, medical care, health-related behaviors, and health perceptions/concerns.

Results—Adjusting for education, income, chemotherapy/radiation exposures, and number/severity of chronic health conditions, an increased risk for all-cause mortality was associated with exercising fewer than 3 days/week (OR=1.72, CI:1.27 – 2.34), being underweight (OR=2.58, CI: 1.55 – 4.28), increased medical-care utilization ($p<0.001$), and self-reported fair to poor health ($p<0.001$). Physical activity was associated with a higher risk of death among males (OR=3.26, CI: 1.90 – 5.61) reporting no exercise compared to those who exercised 3 times per week. Ever consuming alcohol was associated with a reduced risk of all-cause (OR=0.61, CI: 0.41–0.89) and

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other non-external causes of death (OR=0.40, CI: 0.20–0.79). Concerns/worries about future health (OR=1.54, CI: 1.10–2.71) were associated with increased all-cause mortality.

Conclusions—Factors independent of cancer treatment and chronic health conditions modify the risk of death among adult survivors of pediatric cancer.

Implications for Cancer Survivors—Continued cohort observation may inform interventions to reduce mortality.

Keywords

mortality risk; childhood cancer; surveillance; cancer survivorship

INTRODUCTION

Childhood cancer survivors are at increased late mortality risk because of the late effects of their cancer and treatment; survivors' life expectancy is reduced by as much as 28% [1–8]. Mortality risk has been modified by era of treatment [9–10], type of treatment [5,9], diagnosis [3,5,11], and demographic characteristics [5,10]. Although risk of mortality from recurrence or progression of primary disease decreases with length of follow-up, survivors demonstrate excess late mortality including a 15-fold increased risk of death attributable to subsequent neoplasms, 7-fold increase in risk of cardiac deaths, and 9-fold increase in risk of pulmonary deaths [11]. Health-related behavior, self-perceived health status, and health concerns are independent predictors of mortality in the general population, but they have not been assessed in association with mortality in adult survivors of childhood cancer. We hypothesized that these factors would be associated with late mortality risk due to physical causes (excludes mental health) among these survivors; additionally we explored the possibility that these risks would likely occur at an earlier age than in the general population.

METHODS

Study Sample

The CCSS is a retrospective cohort of 20,691 eligible 5+-year childhood cancer survivors diagnosed between January 1, 1970 and December 31, 1986 at 27 institutions in the United States and Canada [12–13]. The study protocol was approved by the institutional review boards at all participating sites. Participants provided informed consent, release of medical records, completed baseline and follow-up questionnaires. Questionnaires used to collect all patient-reported data for the current analysis are available at <http://ccss.stjude.org>.

Design

This study used a matched case-control design. We selected this design in contrast to a person-time approach because subjects had varying lengths of follow-up from the time of cohort entry (5 years post-diagnosis) to the baseline questionnaire time point, at which the behavioral characteristics were ascertained. We restricted the sample to CCSS participants from the United States (Figure 1). Participants residing outside the US were excluded from the study; their deaths may not be recorded by the National Death Index (NDI). Cases included CCSS participants alive at recruitment and at completion of the baseline

questionnaire that subsequently died of causes other than recurrence/progression of their initial cancer or of a non-health related cause. In 2010–2012, deceased cases were identified through a search of the NDI for deaths occurring in the U.S. before January 1, 2008. Primary and underlying causes of death were used to exclude individuals who died of recurrence/progression of their initial cancer or of non-health-related causes (i.e., external causes, accidents and suicide). All available controls (age 18 years or older at baseline completion) were selected from the risk set of each case, which consisted of all participants who were alive and at risk of death for at least the same length of time as that between cancer diagnosis and the case's death, including those subjects who subsequently died. Controls were matched to cases' initial cancer diagnosis, age at baseline questionnaire (± 12 months), and time from initial cancer diagnosis to baseline questionnaire (± 6 months).

Analysis

Descriptive statistics were generated for all demographic and clinical variables (Table 1). The associations between all-cause and cause-specific mortality and self-reported lifestyle/surveillance behaviors, health status, medical-care utilization, and health concerns were tested using conditional logistic regression to estimate ORs and corresponding CIs. Models were developed for each of the following risk categories: (1) Medical Care; (2) Lifestyle and Self-Care Behaviors; and (3) Health Concerns (Table 2). Models were adjusted for potential confounding factors: race/ethnicity, sex, and baseline measures of marital status, education, health-insurance status, household/personal income, number/severity of chronic-health conditions (NCI's Common Terminology Criteria for Adverse Events, version 4), and cancer-treatment exposures (chemotherapeutic agents and sites of radiation therapy). Model factors were retained if inclusion modified the association of the primary variables with case/control status by more than 10%. Due to the exploratory nature of this study, we chose not to adjust for multiple comparisons so that all possible risk factors were identified to be explored in future studies. Including an interaction term between sex and each of the variables of interest addressed the possible modification by sex. An additional analysis included the examination of all previously-determined significant variables stratified by time to death to evaluate whether the associations varied with length of time from covariate assessment. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). Two-sided *P*-values are reported, and *P*=0.05 is the critical alpha value.

RESULTS

Characteristics of the 445 cases and 7162 matched controls are provided in Table 1. There were a variable number of controls per case: Mean=16.1, MD=14, Mode=11, Min=1, Max=106. Cases were slightly older, more often of black race, less likely to have a post-high school education or to be married, more likely to have household incomes below \$20,000, and have an existing grade 3 or 4 (serious/life threatening/disabling) chronic health condition. Common causes of death among cases were malignant neoplasm (42%), cardiac (20%) and pulmonary (7%). The mean age at death for the cases was 37.6 years (SD=7.3, MD=38, range 19–55).

Medical Care Utilization

Regression models including all subjects, adjusting for socio-demographics, cancer therapy and severity of chronic health conditions showed that ever having received health care and having had five or more physician visits in the year prior to completing the baseline questionnaire were associated with late mortality. As anticipated, there was a positive association between the severity of chronic conditions and number of physician visits ($X^2 = 935.0$, $df = 24$, $p = 0.001$). Recency of general physical exam or dental care was not associated with risk of late mortality. Among females, there was no significant association between risk of mortality and history/recency of cervical or breast screening.

Lifestyle and Self-Care Behaviors

A history of engaging in no exercise in the previous seven days was associated with a nearly 2-fold risk of death when compared to exercising 3 or more days per week, while exercising 1–2 days per week was associated with a 1.6-fold risk of death. Survivors who were underweight ($BMI < 18 \text{ kg/m}^2$) had a more than 2-fold increase in the risk of death compared to normal weight survivors. Smoking history was not associated with mortality. Consumption of alcohol was found to be associated with a lower risk of all-cause death. Self-care activities consisting of breast self-examination and testicular self-examination were not significantly associated with a reduction in risk of late all-cause mortality.

Sex modified the association between physical activity and mortality ($P = 0.005$ for interaction). Males reporting no exercise were more than three times as likely to die, and those reporting 1 to 2 days of exercise weekly were more than twice as likely to die, compared to those who reported exercising 3 or more days/week.

Self-reported Health Status and Health Concerns

After adjusting for socio-demographics, treatment, and serious/life-threatening/disabling chronic health conditions, a self-reported “fair to poor” health status was associated with higher mortality risk as compared to those who rated their health “good to excellent”. Survivors with at least some concern about their future health or ability to obtain life insurance were more likely than others to subsequently die (Table 2).

Time to Death

Follow-up strata were defined based upon tertiles (<5.7 , $5.7 - 8.9$, >8.9 years) for the cases (Table 3); the matched controls were included in the same stratum. Health care received was not significant within the first time stratum, but remained significantly associated with death in later time strata. While not always achieving statistical significance, the observed patterns of increased risk of death with increasing number of doctor visits per year, lower physical activity frequency, being underweight, self-report of fair or poor current health status, concern about future health, and presence of a serious chronic health condition was present within all three time strata (T1–T3). Alcohol consumption was protective in all 3 time strata, but the effect diminished progressively in tertiles 2 and 3 (T1, $OR=0.48[0.24-0.96]$; T2, $OR=0.56[0.29-1.10]$; T3, $OR=0.69[0.36-1.30]$).

Cause-Specific Mortality

Analyses of factors associated with medical access (Table 4) found risk of death due to a second malignant neoplasm to be significantly associated with having received health care and five or more annual physician visits. Risk of cardiac/pulmonary death or death from other non-external causes (e.g., benign neoplasm, diabetes, ulcers, cirrhosis, nephritis, AIDS) was significantly increased with increasing number of physician visits/years (7–10 visits per year through >20 visits per year). Women who had a Pap smear within two years prior to completing their baseline questionnaire had lower risk estimates only in death from non-external causes.

Relative to lifestyle and self-care factors (Table 4), death due to cardiac/pulmonary or other non-external causes was associated with less physical activity. Being underweight was associated with a greater than 2-fold increase in the risk of death due to SMN or other non-external causes and a greater than 3-fold increase in the risk of death due to cardiac/pulmonary causes, while being overweight was associated with a significantly higher risk of death due to cardiac causes. There was an increased risk of cardiac/pulmonary death among men who rarely or never performed self-testicular examination. History of smoking (current or past) did not significantly increase risk of death from second malignancy, cardiac, or other non-external causes. Ever having consumed alcohol decreased significantly the risk of death only due to other non-external causes.

A self-reported health status of “fair to poor” was associated with a greater than 3-fold increase in mortality due to other-related causes. Being concerned/very concerned about the ability to obtain health insurance was associated with increased risk of death from other non-external causes (Table 4).

DISCUSSION

Aging of the CCSS cohort enabled an initial detailed assessment of the role of non-treatment related factors in determining risk of late-mortality. Their mean age at death was 37.6 and more than two-thirds of the sample died within 8.9 years (Table 3). The number of deaths in our sample was unavoidably small; we excluded those resulting from progression of the original cancer or other non-health related causes. However, the data were sufficient to reveal novel predictors of mortality in this population not associated with primary disease, treatment, or late effects.

As in the general population [14–15], the risk of death among survivors was associated with black race, absence of a spouse/partner, <high school education, and annual household income <\$20,000. We observed for the first time that mortality risk increases with the annual frequency of physician visits; the greater the severity of chronic conditions, the greater the frequency of physician visits. These findings are not surprising, as the number of physician visits and providers increases during the last 2 years of life in the general population [16]. Among survivors who died of a second malignancy, only 5–6 visits or >20 visits were weakly associated with mortality, probably reflecting the small sample sizes in the other categories.

Female survivors had a lower risk of death due to non-external other causes if they had a Pap smear or professional breast examination within the 2 years prior to the baseline questionnaire. Occasional breast self-examination was associated with significantly lower risk than regular breast self-examination, perhaps partly reflecting risk-based counseling for survivors treated with chest radiation [17]. Female survivors in the CCSS who performed regular breast self-examination were almost twice as likely to have undergone chest irradiation as those who performed less frequent self-examination (OR = 1.79; 95% CI: 1.54–2.09). These results suggest that frequency of breast self-examination is not an independent predictor of death.

Male survivors reporting rarely or never performing testicular self-examination had an increased risk of cardiac/pulmonary death. Men who do not engage in this self-care behavior may well neglect other important health promotion/risk reduction behaviors. While there is an established link between treatment for testicular cancer and cardiac mortality [18] the wide confidence interval indicates that our analysis lacks precision; additional data are needed to explore this finding. Regardless of cancer survivorship status, however, men should be reminded to perform this self-exam regularly.

Mirroring the general population [19–20] a low BMI was associated with both early and late all-cause mortality and was significant for each of the mortality causes. Survivors with a low BMI do not have the reserve to battle the acute/chronic health problems that may surface. Being overweight was associated only with death related to cardiac/pulmonary causes, consistent with findings in the general population [2]. Ever having used alcohol was associated with a lower risk of mortality in the overall study group and in those who died of other non-external causes, consistent with findings in the general population. Alcohol use in this sample is well within reasonable limits and consistent with what the current literature considers to be protective in the general population [22–23]. Without sufficient numbers in the upper categories of alcohol use, we are underpowered to study the point at which alcohol use may be deleterious. The smoking association with mortality is null and not even suggestive at this point. Given the short observation time, it could be that smoking does not have an independent effect over and above the treatment variables. Other considerations include the younger age of the participants in that either there hasn't been sufficient induction time for the effects of smoking to manifest, or they haven't yet been exposed to sufficient smoke to demonstrate an association between smoking and death. Only with continued observation, will we be able to examine the independent effects of smoking. No exercise or exercising only 1–2 days per week was associated with a greater risk of mortality [24]. Decreased physical activity could also be explained by illness.

Worry/concerns that cause chronic stress may increase an individual's risk of illness and premature death. A meta-analysis of 20 studies of incident cardiac disease found an increased risk for cardiac death in individuals reporting substantial health-related worry, independent of demographic variables, biological risk factors, and health behaviors [25]. However, a tendency toward optimism (rather than worry) has been associated with a lower risk of all-cause and cardiovascular mortality [26]. Not surprisingly, some excess worry can benefit health by increasing an individual's sensitivity to potential threats or vigilance in lifestyle and surveillance behaviors [27–28]. Health worries and concerns have not

previously been assessed in association with mortality in survivors of childhood cancer. We found that greater concern about future health at baseline and about the ability to obtain life insurance were associated with a greater risk of mortality in all subjects; concern about the ability to obtain health insurance was associated with a greater risk of mortality in those who died of other non-external causes. Worry and anxiety can affect health, and ultimately mortality, indirectly through behavior (e.g., smoking, poor nutrition, inactivity) and directly through CNS, immune, endocrine and cardiovascular changes [28].

In the general population self-rated health has been shown to predict mortality independently of health problems, physical disability and biological or lifestyle risk factors [29–30]. A meta-analysis of 22 community-based cohort studies found that the risk of death in individuals reporting poor health was twice that in individuals reporting excellent health after adjustment for self-reported or objectively measured disease [29]. Moreover, longitudinal changes in self-rated health are a more sensitive predictor than baseline/recent assessment, and the metric appears to be more predictive of mortality in chronic than in acute illness [30]. Mortality increased as self-rated health declined from “very good” to “poor” among all subjects and among those who died of non-external causes. Self-assessment of health status summarizes objective health states and incorporates personal (possibly unconscious) expectations of longevity, reflecting the individual’s awareness of risk factors (e.g., unhealthy or risk-taking behaviors) [31]. Self-reported health could be used in clinical practice to obtain important prognostic information not identified by clinical and laboratory assessment [32]. If survivors’ self-reported health status is only “good” to “fair”, or shows a downward trend on repeated visits, the clinician should consider a more detailed consultation and intensified support.

Limitations

Potential inaccuracy of information obtained from death certificates can result in misclassification of cause of death. For misclassification to be differential and cause substantial bias, the misclassification of death would have to be associated with health concerns, lifestyle and health behavior factors. This is unlikely; therefore any bias due to misclassification of death is likely non-differential. The number of statistical tests performed at $\alpha=0.05$ may result in significant findings by chance. Due to the exploratory nature of this study, we chose not to adjust for multiple comparisons so that all possible risk factors were identified to be explored in future studies. The number of cases likely impacts the statistical power, particularly for cause-specific analyses. There may have been changes in the covariates since baseline; however, the associations remained largely consistent even when stratified by time. We feel that bias was eliminated by matching on the age at baseline and time from diagnosis to baseline, but generalizability may be impacted. The relatively young age of the sample and corresponding short length of observation may not be sufficient to identify associations that may emerge later in life (e.g., longer duration of tobacco use). Continued follow-up will evaluate these factors. Our sample was limited to participants in the CCSS, reflecting a historical cohort of patients diagnosed/treated 1970–86; our findings may not be generalizable to more recently treated patients.

CONCLUSIONS

We have demonstrated that behavior, self-reported health status, worries/concerns, and medical-care utilization are associated with mortality in 5⁺-year survivors of childhood cancer. We observed clear trends between mortality and surveillance/lifestyle behaviors that are predictive in the general population and will emerge as predictive in this cohort as observation continues. While these factors are established predictors of mortality in non-clinical populations, we demonstrated that they independently contributed to mortality in survivors who were, on average, less than 40 years of age.

Implications for Adult Childhood Cancer Survivors

Even at this preliminary stage, our findings can inform provider strategies to reduce the risk of premature mortality: (1) recognizing treatment-associated risks requiring more intensive follow-up; (2) sensitivity to diminished/declining self-reported health status; (3) targeting at-risk survivor groups (e.g., African-Americans, males) with more vigilant monitoring; and (4) increasing survivors' awareness of recommended medical surveillance. Clinician and survivor awareness of mortality risk status has the potential to enhance health/longevity in this high risk group. With continued observation, we will be better able to begin to quantify the respective contributions of these factors in combination with the long-term impact of disease and treatment factors. Risk profiles will ultimately be better informed and interventions can be more effectively targeted.

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Figure 1.
Consort Diagram for Study Sample

Table 1

Characteristics of the study population and associated odds ratios for mortality among cases and controls

	Controls-Alive (n = 7162)	Cases-Deceased (n = 445)	OR (95% CI)*	P value
Age at baseline (mean ± SD)	28.8 ± 6.4	30.5 ± 6.6	1.06 (0.93, 1.21)	†
Male sex, n (%)	3670 (51%)	220 (49%)	1.19(0.98–1.45)	0.09
Race, n (%)				
White	6394 (89%)	383 (86%)	1.00	
Black	260 (4%)	27 (6%)	1.62 (1.06–2.47)	0.03
Hispanic	326 (5%)	25 (6%)	1.31 (0.85–2.02)	0.22
Other	166 (2%)	9 (2%)	1.08 (0.52–2.13)	0.84
Education, n (%)‡				
< High School graduate	491 (7%)	42 (10%)	1.11 (0.76–1.64)	0.59
High School graduate	1328 (20%)	105 (26%)	1.00	
> High School graduate	4956 (73%)	257 (64%)	0.61 (0.48–0.78)	<0.001
Marital status, n (%)				
Never married	2967 (42%)	180 (41%)	1.00	
Married	2874 (41%)	166 (38%)	0.70 (0.54–0.91)	0.007
Living as married	510 (7%)	30 (7%)	0.77 (0.51–1.16)	0.22
Widowed	10 (<1%)	2 (1%)	2.22 (0.46–10.72)	0.32
Divorced	322 (5%)	28 (6%)	0.96 (0.61–1.49)	0.84
Separated	334 (5%)	28 (6%)	1.12 (0.73–1.73)	0.61
Health insurance				
Yes	6019 (85%)	376 (86%)	1.01 (0.76–1.35)	0.94
No	1051 (15%)	59 (14%)	1.00	
Total household income, n (%)‡				
Less than \$9,999	461 (6%)	52 (12%)	2.83 (1.93–4.15)	<0.001
\$10,000 – \$19,999	736 (10%)	71 (16%)	2.21 (1.57–3.12)	<0.001
\$20,000 – \$39,999	1965 (27%)	111 (25%)	1.26 (0.93–1.72)	0.13
\$40,000 – \$59,999	1514 (21%)	74 (17%)	1.13 (0.81–1.57)	0.47
Over \$60,000	1694 (24%)	77 (17%)	1.00	
Unknown	792 (11%)	60 (14%)	2.02 (1.40–2.90)	<0.001
Chronic conditions (CTAE)§				
< Grade 3	5265 (74%)	230 (52%)	1.00	
Grade 3 or 4	1897 (26%)	215 (48%)	2.39 (1.95–2.93)	<0.001
Cause of death, n (%)				
SMN		187 (42%)		
Cardiac causes		88 (20%)		
Pulmonary causes		33 (7%)		
Other¶		137 (31%)		
Diagnosis, n (%)				†
Hematologic cancer	5213 (73%)	272 (61%)		

	Controls-Alive (n = 7162)	Cases-Deceased (n = 445)	OR (95% CI)*	P value
CNS	814 (11%)	74 (17%)		
Other solid tumor	1135 (16%)	99 (22%)		
Age at diagnosis, n (%)				
0 to 4	1639 (23%)	61 (14%)	1.00	
5 to 9	1131 (16%)	73 (16%)	1.75 (0.72–4.25)	0.22
10 to 14	2095 (29%)	140 (31%)	3.22 (1.04–9.99)	0.04
15 to 19	2031 (28%)	142 (32%)	4.35 (1.27–14.83)	0.02
20+	266 (4%)	29 (7%)	6.62 (1.73–25.31)	0.006
Years since diagnosis (mean ± SD)	17.5 ± 4.2	18.1 ± 4.6	1.26 (0.98–1.61)	0.07
Chemotherapy, n (%)				
None	1581 (25%)	107 (28%)	1.00	
Any	4655 (75%)	275 (72%)	1.28 (0.97–1.69)	0.09
Specific agent, n (%)				
Anthracycline(s)	445 (10%)	22 (8%)	1.69 (0.92–3.12)	0.09
Alkylating agent(s)	1782 (38%)	121 (44%)	1.59 (0.97–2.63)	0.07
Both	1404 (30%)	100 (36%)	2.25 (1.36–3.72)	0.002
Other	1024 (22%)	32 (12%)	1.00	
Radiation, n (%)				
None	1295 (21%)	50 (13%)	1.00	
Any	4947 (79%)	332 (87%)	2.38 (1.68–3.37)	<0.001
Radiation site, n (%)				
Cranium	1930 (31%)	112 (29%)	2.37 (1.50–3.73)	<0.001
Chest	2245 (36%)	170 (45%)	4.30 (2.66–6.94)	<0.001
Other	772 (12%)	50 (13%)	1.60 (1.02–2.50)	0.04
None	1295 (21%)	50 (13%)	1.00	
Amputation, n (%)				
No	6586 (95%)	397 (93%)	1.00	
Yes	335 (5%)	31 (7%)	1.21 (0.72–2.03)	0.48

* Adjusted for matched factors.

† Matched factor.

‡ Test for trend $p < 0.001$.

§ National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.

¶ Other causes of death include: External causes such as accidents/suicides, as well as medical conditions including, benign neoplasm, diabetes mellitus, cerebrovascular disease, rheumatic, hypertension without heart disease, ulcer of stomach and duodenum, cirrhosis of liver, nephritis and nephrosis and acquired immunodeficiency syndrome (AIDS).

Abbreviations: SMN, second malignant neoplasm; CNS, central nervous system; OR, Odds ratio; 95% CI, 95% confidence interval.

Table 2

Medical care, lifestyle/self-care behaviors, and health worry/concerns

	OR (95% CI)	P value
MEDICAL CARE[†]		
Health care received		
No	1.00	
Yes	1.99 (1.19–3.32)	0.008
No. doctor visits/year		
1 – 2	1.00	
3 – 4	1.09 (0.73–1.62)	0.68
5 – 6	2.07 (1.40–3.06)	<0.001
7 – 10	2.21 (1.44–3.40)	<0.001
11 – 20	2.26 (1.44–3.55)	<0.001
More than 20	3.87 (2.55–5.87)	<0.001
General physical examination		
Less than 1 year ago	1.00	
1 – 2 years ago	0.90 (0.66–1.24)	0.53
3 – 4 years ago	0.92 (0.60–1.42)	0.71
5 or more years ago	0.90 (0.61–1.34)	0.61
Never	1.22 (0.77–1.93)	0.41
Recency of dental care		
Less than 1 year ago	1.00	
1 year ago or more	0.91 (0.71–1.16)	0.43
Recency of Pap Smear		
Less than 1 year ago	1.00	
1 – 2 years ago	0.94 (0.60–1.45)	0.77
3 – 4 years ago	1.32 (0.66–2.63)	0.44
5 or more years ago	1.54 (0.64–3.70)	0.34
Never	1.16 (0.57–2.34)	0.68
Professional breast examination		
Less than 1 year ago	1.00	
1 – 2 years ago	0.60 (0.36–0.98)	0.04
3 – 4 years ago	0.84 (0.38–1.83)	0.66
5 or more years ago	0.66 (0.22–2.02)	0.47
Never	1.43 (0.65–3.12)	0.37
Mammography (ever)		
No	1.00	
Yes	1.32 (0.84–2.09)	0.23
LIFESTYLE AND SELF-CARE BEHAVIORS[†]		
Smoking		

	OR (95% CI)	P value
Never	1.00	
Past	0.95 (0.66–1.36)	0.79
Current	1.03 (0.74–1.44)	0.84
Alcohol consumption		
Never	1.00	
Ever	0.61 (0.41–0.89)	0.01
Drinks per month		
None	1.00	
1 to 4	0.83 (0.59–1.15)	0.26
5 +	0.75 (0.55–1.00)	0.05
Physical activity		
0 days per week	1.72 (1.27–2.34)	<0.001
1 – 2 days per week	1.65 (1.17–2.31)	0.004
3+ days per week	1.00	
Testicular self-examination		
Regularly (once a month)	1.00	
Occasionally	1.49 (0.76–2.94)	0.25
Rarely or never	1.32 (0.72–2.42)	0.36
Breast self-examination		
Regularly (once a month)	1.00	
Occasionally	0.68 (0.45–1.03)	0.07
Rarely or never	0.56 (0.35–0.91)	0.02
BMI		
Underweight	2.58 (1.55–4.28)	<0.001
Normal	1.00	
Overweight	1.12 (0.84–1.50)	0.43
Obese	1.03 (0.71–1.49)	0.88
HEALTH WORRY AND CONCERN*		
Current health status		
Good or excellent	1.00	
Fair or poor	1.98 (1.45–2.71)	<0.001
Future health		
Concerned/very concerned	1.54 (1.10–2.15)	0.01
Not very concerned/not concerned at all	1.00	
Ability to have children		
Concerned/very concerned	1.05 (0.81–1.36)	0.71
Not very concerned/not concerned at all	1.00	
Development/recurrence of cancer		
Concerned/very concerned	1.05 (0.82–1.36)	0.69
Not very concerned not concerned at all	1.00	
Ability to obtain health insurance		

	OR (95% CI)	P value
Concerned/very concerned	1.27 (0.99–1.62)	0.06
Not very concerned/not concerned at all	1.00	
Ability to obtain life insurance		
Concerned/very concerned	1.33 (1.03–1.71)	0.03
Not very concerned/not concerned at all	1.00	

Abbreviations: OR = Odds ratio; 95% CI = 95% confidence interval; SMN, second malignant neoplasm.

* Odds ratios are adjusted for matched factors and education, marital status, household income, chemotherapy type, radiation site, and any health condition grade 3 or 4.

† Odds ratios are adjusted for matched factors and education, ethnicity, marital status, household income, chemotherapy type, radiation site, and any health condition grade 3 or 4.

Table 3

Odds of death stratified by time from enrollment in CCSS to death

	Time from Enrollment to Death					
	Tertile 1 <5.7 years (Cases: n = 148; Controls: n = 2637)		Tertile 2 5.7–8.9 years (Cases: n = 148; Controls: n = 2373)		Tertile 3 >8.9 years (Cases: n = 149; Controls: n = 2152)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Health care received						
No	1.00		1.00		1.00	
Yes	1.34 (0.60, 2.97)	0.47	3.46 (1.32, 9.08)	0.01	3.17 (1.23, 8.15)	0.02
No. doctor visits/year						
1–2	1.00		1.00		1.00	
3–4	0.80 (0.36, 1.79)	0.59	1.23 (0.61, 2.48)	0.57	1.51 (0.81, 2.84)	0.20
5–6	1.05 (0.43, 2.51)	0.92	3.03 (1.55, 6.00)	0.001	2.72 (1.45, 5.06)	0.002
7–10	3.82 (1.82, 8.04)	<0.001	2.68 (1.28, 5.58)	0.009	2.00 (0.91, 4.42)	0.08
11–20	2.45 (1.12, 5.35)	0.02	4.29 (1.92, 9.58)	<0.001	2.08 (0.94, 4.47)	0.07
More than 20	5.64 (2.78, 11.43)	<0.001	5.52 (2.64, 11.54)	<0.001	4.88 (2.4, 9.93)	<0.001
Alcohol consumption						
Never	1.00					
Ever	0.48 (0.24, 0.96)	0.04	0.56 (0.29, 1.10)	0.09	0.69 (0.36, 1.30)	0.25
Physical activity						
0 days per week	2.06 (1.18, 3.61)	0.01	1.53 (0.90, 2.60)	0.12	2.13 (1.27, 3.56)	0.004
1–2 days per week	1.24 (0.62, 2.50)	0.55	2.61 (1.50, 4.53)	<0.001	1.43 (0.79, 2.57)	0.24
3+ days per week	1.00		1.00		1.00	
BMI						
Underweight	3.94 (1.48, 10.48)	0.006	2.40 (1.04, 5.54)	0.04	2.65 (1.15, 6.10)	0.02
Normal	1.00		1.00		1.00	
Overweight	1.02 (0.61, 1.72)	0.93	0.97 (0.58, 1.62)	0.90	1.12 (0.69, 1.81)	0.65
Obese	0.69 (0.33, 1.43)	0.32	1.09 (0.60, 1.98)	0.78	1.34 (0.72, 2.50)	0.35
Current health status						
Good or excellent	1.00		1.00		1.00	
Fair or poor	3.19 (1.86, 5.47)	<0.001	1.72 (0.99, 2.97)	0.05	2.28 (1.33, 3.90)	0.003

	Time from Enrollment to Death					
	Tertile 1 <5.7 years (Cases: n = 148; Controls: n = 2637)		Tertile 2 5.7–8.9 years (Cases: n = 148; Controls: n = 2373)		Tertile 3 >8.9 years (Cases: n = 149; Controls: n = 2152)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Future health						
Concerned to very concerned	1.88 (0.98, 3.59)	0.06	1.87 (1.03, 3.41)	0.04	1.40 (0.83, 2.38)	0.21
Not very concerned to not at all concerned	1.00		1.00		1.00	
Chronic Health Conditions						
0–2 vs. 3 or 4	3.55 (2.21, 5.69)	<0.001	1.99 (1.30, 3.06)	0.002	2.22 (1.44, 3.41)	<0.001
0–3 vs. 4	6.34 (3.65, 11.01)	<0.001	2.67 (1.51, 4.76)	<0.001	2.82 (1.56, 5.09)	<0.001

Odds ratios are adjusted for matched factors and education, marital status, household income, chemotherapy type, radiation site, and any health condition grade 3 or 4.

Table 4

Medical care, lifestyle/self-care behaviors, and health worry/concerns stratified by cause of death

	SMN (Cases: n = 187; Controls: n = 2975)		Cardiac/Pulmonary (Cases: n = 121; Controls: n = 2165)		Other (Cases: n = 137; Controls: n = 2165)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Health care received						
No	1.00		1.00		1.00	
Yes	3.85 (1.37–10.82)	0.01	2.11 (0.72–6.14)	0.17	1.37 (0.61–3.07)	0.44
No. doctor visits/year						
1–2	1.00		1.00		1.00	
3–4	1.08 (0.61–1.89)	0.80	0.85 (0.31–2.34)	0.75	1.34 (0.65–2.80)	0.43
5–6	1.83 (1.03–3.25)	0.04	2.14 (0.89–5.11)	0.09	2.03 (0.94–4.38)	0.07
7–10	1.40 (0.71–2.77)	0.33	3.16 (1.38–7.24)	0.007	3.19 (1.36–7.47)	0.008
11–20	1.60 (0.81–3.16)	0.18	3.11 (1.23–7.86)	0.02	2.72 (1.08–6.86)	0.03
More than 20	2.57 (1.37–4.80)	0.003	4.56 (1.81–11.47)	0.001	6.58 (2.98–14.54)	<0.001
General physical examination						
Less than 1 year ago	1.00		1.00		1.00	
1–2 years ago	0.90 (0.56–1.47)	0.68	0.80 (0.42–1.54)	0.51	1.04 (0.57–1.90)	0.90
3–4 years ago	1.27 (0.70–2.31)	0.43	0.67 (0.24–1.88)	0.45	0.68 (0.27–1.69)	0.40
5 or more years ago	0.93 (0.51–1.67)	0.80	0.61 (0.25–1.48)	0.27	1.08 (0.53–2.21)	0.83
Never	1.69 (0.87–3.31)	0.12	0.55 (0.19–1.61)	0.28	1.51 (0.61–3.73)	0.37
Recency of dental care						
Less than 1 year ago	1.00		1.00		1.00	
1 year ago or more	0.92 (0.63–1.33)	0.64	0.91 (0.53–1.55)	0.72	0.91 (0.57–1.45)	0.67
Recency of Pap Smear						
Less than 1 year ago	1.00		1.00		1.00	
1–2 years ago	1.05 (0.53–2.08)	0.89	1.97 (0.80–4.84)	0.14	0.26 (0.08–0.83)	0.02
3–4 years ago	2.34 (0.82–6.63)	0.11	1.78 (0.45–7.13)	0.41	0.39 (0.07–2.29)	0.30
5 or more years ago	2.02 (0.54–7.51)	0.29	1.95 (0.33–11.57)	0.46	1.34 (0.17–10.44)	0.78
Never	0.70 (0.16–3.09)	0.64	0.92 (0.19–4.30)	0.92	1.93 (0.58–6.36)	0.28
Professional breast examination						

SMN (Cases: n = 187; Controls: n = 2975)						Cardiac/Pulmonary (Cases: n = 121; Controls: n = 2022)						Other (Cases: n = 137; Controls: n = 2165)					
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
Less than 1 year ago	1.00				1.00				1.00				1.00				
1 – 2 years ago	0.66 (0.30–1.47)	0.31			0.47 (0.15–1.44)	0.19			0.46 (0.17–1.26)	0.13			0.46 (0.17–1.26)	0.13			
3 – 4 years ago	0.98 (0.32–2.97)	0.97			2.20 (0.54–9.03)	0.27			-				-				
5 or more years ago	1.38 (0.34–5.63)	0.65			0.60 (0.06–6.38)	0.67			-				-				
Never	2.26 (0.51–10.03)	0.28			0.98 (0.18–5.37)	0.98			1.44 (0.41–5.08)	0.57			1.44 (0.41–5.08)	0.57			
Mammography (ever)																	
No	1.00				1.00				1.00				1.00				
Yes	1.39 (0.68–2.62)	0.39			1.14 (0.41–3.22)	0.79			1.06 (0.40–2.85)	0.90			1.06 (0.40–2.85)	0.90			
LIFESTYLE AND SELF-CARE BEHAVIORS																	
Smoking																	
Never	1.00				1.00				1.00				1.00				
Past	0.89 (0.53–1.49)	0.65			1.41 (0.69–2.89)	0.35			0.95 (0.46–1.97)	0.90			0.95 (0.46–1.97)	0.90			
Current	1.15 (0.71–1.87)	0.58			0.94 (0.45–1.96)	0.86			1.19 (0.64–2.20)	0.58			1.19 (0.64–2.20)	0.58			
Alcohol consumption																	
Never	1.00				1.00				1.00				1.00				
Ever	1.04 (0.55–1.99)	0.90			0.55 (0.22–1.36)	0.20			0.40 (0.20–0.79)	0.008			0.40 (0.20–0.79)	0.008			
Drinks per month																	
None	1.00				1.00				1.00				1.00				
1 to 4	0.93 (0.56–1.53)	0.77			1.02 (0.51–2.06)	0.95			0.55 (0.28–1.08)	0.08			0.55 (0.28–1.08)	0.08			
5 +	0.84 (0.55–1.31)	0.44			0.87 (0.45–1.68)	0.68			0.50 (0.27–0.90)	0.02			0.50 (0.27–0.90)	0.02			
Physical activity																	
0 days per week	1.36 (0.88–2.09)	0.16			1.84 (0.92–3.68)	0.08			2.41 (1.29–4.52)	0.006			2.41 (1.29–4.52)	0.006			
1 – 2 days per week	1.13 (0.68–1.88)	0.64			2.07 (1.00–4.30)	0.05			2.37 (1.19–4.71)	0.01			2.37 (1.19–4.71)	0.01			
3+ days per week	1.00				1.00				1.00				1.00				
Testicular self-examination																	
Regularly (once a month)	1.00				1.00				1.00				1.00				
Occasionally	1.13 (0.40–3.16)	0.82			0.83 (0.06–11.04)	0.89			2.14 (0.54–8.51)	0.28			2.14 (0.54–8.51)	0.28			
Rarely or never	0.88 (0.33–2.32)	0.79			7.65 (1.36–42.95)	0.02			1.39 (0.39–4.94)	0.61			1.39 (0.39–4.94)	0.61			

SMN (Cases: n = 187; Controls: n = 2975)						Cardiac/Pulmonary (Cases: n = 121; Controls: n = 2022)						Other (Cases: n = 137; Controls: n = 2165)					
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		OR (95% CI)	P value	OR (95% CI)	P value		OR (95% CI)	P value	OR (95% CI)	P value	
Breast self-examination																	
Regularly (once a month)	1.00				1.00					1.00					1.00		
Occasionally	0.53 (0.28–0.99)	0.05			0.46 (0.19–1.02)	0.08				1.20 (0.47–3.06)	0.71						
Rarely or never	0.68 (0.34–1.34)	0.26			0.33 (0.10–1.11)	0.07				0.56 (0.19–1.65)	0.30						
BMI																	
Underweight	2.55 (1.10–5.90)	0.03			3.23 (1.08–9.57)	0.03				2.97 (1.23–7.18)	0.02						
Normal	1.00				1.00					1.00					1.00		
Overweight	0.90 (0.58–1.39)	0.63			2.44 (1.34–4.46)	0.004				0.80 (0.44–1.42)	0.43						
Obese	0.95 (0.53–1.70)	0.85			1.72 (0.78–3.75)	0.18				0.97 (0.48–1.93)	0.92						
HEALTH WORRY AND CONCERN																	
Current health status																	
Good or excellent	1.00				1.00					1.00					1.00		
Fair or poor	1.47 (0.88–2.46)	0.14			1.71 (0.87–3.33)	0.11				3.56 (2.05–6.18)	<0.001						
Future health																	
Concerned/very concerned	1.57 (0.96–2.58)	0.07			1.42 (0.68–2.98)	0.35				1.81 (0.92–3.53)	0.08						
Not very concerned/not concerned at all	1.00				1.00					1.00					1.00		
Ability to have children																	
Concerned/very concerned	0.97 (0.66–1.43)	0.88			0.85 (0.48–1.51)	0.58				1.35 (0.82–2.20)	0.24						
Not very concerned/not concerned at all	1.00				1.00					1.00					1.00		
Development/recurrence of cancer																	
Concerned/very concerned	1.23 (0.84–1.81)	0.29			0.88 (0.51–1.53)	0.65				0.92 (0.57–1.48)	0.73						
Not very concerned not concerned at all	1.00				1.00					1.00					1.00		
Ability to obtain health insurance																	
Concerned/very concerned	1.08 (0.74–1.56)	0.70			1.28 (0.75–2.19)	0.37				1.84 (1.14–2.96)	0.01						
Not very concerned/not concerned at all	1.00				1.00					1.00					1.00		
Ability to obtain life insurance																	
Concerned/very concerned	1.26 (0.86–1.85)	0.23			1.41 (0.82–2.43)	0.22				1.52 (0.93–2.48)	0.10						
Not very concerned/not concerned at all	1.00				1.00					1.00					1.00		

Abbreviations: OR = Odds ratio; 95% CI = 95% confidence interval; SMN, second malignant neoplasm. Odds ratios are adjusted for matched factors and education, marital status, household income, chemotherapy type, radiation site, and any health condition grade 3 or 4.