

TITLE: Impact of Health Behaviors and Health Perceptions on Subsequent Mortality in Childhood Cancer Survivors

WORKING GROUP: Epidemiology/Biostatistics

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A. SPECIFIC AIM

To date, the primary focus in mortality studies of childhood cancer survivors has been on diagnosis, treatment, and late effects as the primary contributors to early mortality. A recent exploratory analysis suggests that CCSS participants' self-reported baseline health behaviors and health perceptions may contribute significantly and independently to mortality. We therefore propose to examine the potential impact of health promoting behaviors, health risk behaviors, screening behaviors, and health perceptions as influences on the occurrence of mortality in this vulnerable population. This study will use the resources of participants within the Childhood Cancer Survivor Study (CCSS) cohort who were alive at recruitment and age ≥ 18 years when they provided self-report baseline data. Within this defined subset of the CCSS cohort the following specific aim will be addressed:

Study Aim: Assess associations between overall and cause-specific mortality of CCSS survivors with health promotion behaviors (testicular self-exam, breast self-exam, physical activity); health risk behaviors (smoking, alcohol use); health screening behaviors (general physical exam recency, dental care recency, Pap Smear recency, professional breast exam recency, mammogram recency) and health perceptions (health status, future health risks, risk of developing cancer, risk of cancer recurrence).

Hypotheses:

- 1) CCSS participants who are still alive by January 1, 2008 will be more likely to have self-reported positive health promotion/screening behaviors and more positive health perceptions at baseline than those who have died.
- 2) CCSS participants who died before January 1, 2008 will be more likely to have self-reported health-risk behaviors and more negative health perceptions at baseline than those who are still alive.

B. BACKGROUND AND SIGNIFICANCE:

Although 5-year survival of cancer in those under the age of 20 has been estimated to be 80% [1], long-term survivors of childhood cancer are at increased risk of mortality from life-threatening late effects of their cancer and treatment including second malignancies, cardiac and vascular abnormalities, and pulmonary complications [2-14]. A limited number of investigations of childhood cancer survivors [4, 5, 7, 10, 11, 14-17] have shown excesses in long-term mortality and have defined high-risk groups by era of treatment [5, 7, 10, 11, 14, 15, 18, 19], treatment [8], diagnosis [4, 5, 7, 8, 10, 11, 14, 15, 19], and demographic characteristics [8, 19]. Recurrence of the original cancer accounts for 57% to 75% of deaths in survivors [4, 5, 8, 10, 11, 14-17], especially if it occurs within 5-9 years after diagnosis [4, 5, 7, 8, 10, 11, 14-17].

Health Risk Behaviors: In the US, the leading behavioral contributors to mortality are tobacco use, level of exercise, and excessive alcohol use [20-27]. No studies to date, however, have investigated mortality as a

function of these behaviors in childhood cancer survivors. In children receiving treatment for acute myeloid leukemia, overweight patients were less likely to survive (HR, 1.88; 95% CI, 1.25-2.83; P=.002) and more likely to have treatment-related mortality (HR, 3.49; 95% CI, 1.99-6.10; P<.001) than normal-weight patients [28].

Health Screening Behaviors: In the general population, mammography and Papanicolaou (Pap) tests are essential components of early detection and treatment for cancer [29], and mortality rates are substantially decreased when breast and cervical cancers are detected and treated at an early stage [30-34]. Because mammography is limited in its ability to evaluate the pre-menopausal breast, the Children's Oncology Group (COG) recommends a breast cancer surveillance program that includes monthly BSE beginning at puberty for patients at high risk of breast cancer concurrent with biannual clinician breast exams and annual mammography [35]. There is evidence that breast self-examination one time per year or greater compared to less than once per year or not at all is associated with a decreased risk of mortality in older women [26].

Although poor oral health affects a large number of people around the world and contributes to increased morbidity and mortality [36], no studies to date have examined the association between recency of dental exams and mortality. Relationships between some aspects of oral health and mortality have been investigated, but investigators did not adequately control for important confounding factors that may be related to oral health and which are also independent risk factors for mortality [37-44]. The relationship of these screening evaluations to mortality in childhood cancer survivors has not been explored.

Health Seeking Behavior: Infrequent physician visits and high frequency utilization are associated with increased risk of mortality [45] in the general population. Use of care for general checkups measures, in part, patient-initiated care that is unrelated to medical problems [46]. A trial of multiphasic health checkups in patients enrolled in a health maintenance organization found that mortality was inversely related to the number of checkups received, an effect that was independent of specific preventive services [47]. An analysis of a nationally representative sample from the first National Health and Nutrition Examination Survey (NHANES) that included adults 25-64 years old found that, after adjusting for all other baseline variables, not obtaining a general checkup was associated with higher mortality in women (hazard ratio=1.64; 95% CI=1.16,2.32), but not in men (hazard ratio=1.07; 95% CI=0.80,1.42) [46].

In patients with medical conditions, seeking care from a specialist was associated with reduced mortality. In elderly patients who had experienced a myocardial infarction, those who saw a cardiologist had a lower two-year mortality rate than matched patients who saw only an internist or a family practitioner (14.6% vs. 18.3%, P<0.001) [48]. Similarly, patients with chronic renal insufficiency who had earlier consultation with a nephrologist and more frequent specialist encounters had lower mortality rates in the first year of dialysis compared to those who were not referred early and saw a specialist less frequently [49]. The association between mortality and source of medical care was also evaluated among males with hemophilia [50]. Persons who received care at hemophilia treatment centers during the study period were 40% less likely (RR=0.6; 95% CI, 0.5-0.8; P=.002) to die than those who had received their care elsewhere. The associations between health seeking behavior, specialist care and mortality have not been explored in childhood cancer survivors.

Health Care Resources: Even after accounting for social, demographic, and health status factors and behaviors, uninsured individuals are at a 25% greater risk of premature death [51, 52]. In analyses of cancer survival for all cancer sites combined, patients who were uninsured and those who were Medicaid-insured at the time of diagnosis were 1.6 times as likely to die in 5 years as those with private insurance [53]. In childhood cancer survivors, rates of coverage of health insurance, especially public insurance, were higher in all diagnostic groups than in the general population [54], though recent studies have shown a continued disparity of insurance access for most subgroups of survivors [55-58]. Lack of health insurance is associated with a lower likelihood of having a usual source of care, and lack of access to health care can adversely affect cancer incidence and mortality throughout the continuum from cancer prevention and early detection to treatment, survivorship, and palliative care [53].

While the ability to obtain life insurance does not directly predict increased mortality, per se, there is an association between mortality risk and obtaining life insurance. Mortality risk is the risk people that people will live shorter than anticipated due to higher than expected mortality rates [59]. Subsequently, deterioration in life expectancy has a negative impact on life insurance companies, since death benefits must be paid out sooner

than anticipated. Because of this, people with medical conditions that increase their mortality risk may not be able to obtain life insurance or the rates may be so high that they cannot afford life insurance. Therefore, it is not that the inability to obtain life insurance predicts increased mortality. Rather, it is the pre-existing conditions that make them ineligible for life insurance that also predicts their mortality risk.

Health Perceptions: Self evaluations of health status have been shown to predict mortality [60-64], above and beyond the contribution to prediction made by indices based on the presence of health problems, physical disability, and biological or lifestyle risk factors [65]. Investigators have found that men who assessed their health as bad or poor were 6.75 times as likely to die as men who assessed their health as excellent [65]. Women in the extreme poor health category were 3.12 times as likely to die as women who rated their health as excellent [65]. Even when self-reports of chronic and acute illnesses, sex, age, income, education, health practices, and social networks were controlled, adults who assessed their health as poor had increased relative risks of mortality of approximately 1.95 compared to those who said they were in excellent health [63].

Preliminary Exploratory Analyses:

We recently completed a very cursory exploratory time to event analysis (Cox Proportional Hazard Model) with and without selected covariates in an effort to determine whether or not the project was feasible. The association between survival time (person-time from baseline to death/censoring) and reported health behaviors was studied among those that participated in baseline and a number of the targeted variables emerged as significant parameters associated with mortality including having ever smoked (HR1.27; 95% CI 1.08-1.49) and lower frequency of exercise (HR of none vs. 4 days/week 0.46; 95% CI 0.37-0.81).

C. METHODS

Sample Source and Eligibility: The study sample will include participants in the CCSS who:

Entry Criteria:

- 1) Were ≥ 18 years of age at CCSS baseline study;
- 2) Provided self-report data to the CCSS baseline questionnaire (alive at baseline);

Study Design: The study will be a matched case-control design.

Case Definition: Subjects who died after baseline and prior to January 1, 2008, with cause of death other than recurrence/progression of initial cancer or an external cause. All deaths since baseline through December 31, 2007 will be evaluated through the NDI and associated documentation. This work effort is anticipated to be completed in October, 2010.

Control Definition: Controls will be utilized from the risk set of each case. The risk set of a case includes everyone who was alive and at risk of death at the time of the case's death, including those who died after the case's death. Cases will be matched to controls on (a) initial cancer diagnosis; (b) age at completion of baseline questionnaire (+/- 12 months); (c) time from initial cancer diagnosis to completion of baseline questionnaire (+/- 6 months). All potential matches from a case's risk set will be included in the analysis. In the unlikely event that a case has no eligible matched controls, they will be excluded from the analysis.

Sample Size: Currently there approximately 400 deaths documented among CCSS participants meeting our case definition. The documentation of deaths since 2002 and before January 1, 2008 is anticipated to provide an additional 200+ cases.

CCSS Data Required: Table 1 identifies the CCSS data required to complete the analyses. Variable names and baseline identification numbers of the variables are provided.

Analyses:

Only deaths with known causes not due to recurrence/progression of the original cancer or external causes will be included in cause-specific analyses for the following: secondary or subsequent cancer (ICD 140-239), cardiac causes (ICD 390-398), 402, 404, 410-429), pulmonary causes (ICD 460-519), external causes

(accidents, suicides, poisonings, ICD 800-999), and other causes (all other ICD codes). For cause-specific analyses, the matched controls for only the relevant cause-specific cases will be included in each analysis.

Associations between mortality and health risk behavior, health promotion behaviors, health screening behaviors and health perceptions will be studied by comparing cases and controls utilizing conditional logistic regression to calculate odds ratios and corresponding 95% confidence limits. One model will be developed for each of the following categories of health behaviors: health seeking behavior, risk behavior, beliefs/concerns and perception. Potential confounding factors we will include in the model are those characteristics that may be associated with health behaviors/perception and/or are risk factors for death. Candidates include race, sex, marital status, education, insurance status, household/personal income, chronic disease status (CTCAE v4) at baseline and treatment exposures. Candidate confounding factors will be screened in univariable analyses and any with $p < 0.1$ will be evaluated in the multivariable model. Factors will be retained if they are significant at $\alpha < 0.05$ or if their exclusion modifies the associations of other key factors with case/control status by more than 10%.

Because of the case-control study design, we will not be able to evaluate probabilities of survival for subjects with different characteristics.

Proposed tables:

Descriptive statistics [n (%) or mean \pm s.d.] and crude associations [OR (95% CI) and p value]

	Alive/Censored (n =)	Died (n =)	OR (95% CI)	P value
Age at baseline (mean \pm s.d.)*				
Male				
Race				
White				
Black				
Hispanic				
Other				
Unknown				
Education				
< HS grad				
HS grad				
> HS grad				
Marital status				
Never married				
Married				
Living as married				
Widowed				
Divorced				
Separated				
Health insurance – Yes				
Total household income				
Less than \$9,999				
\$10,000 - \$19,999				
\$20,000 - \$39,999				
\$40,000 - \$59,999				
Over \$60,000				
Total personal income				
Less than \$9,999				
\$10,000 - \$19,999				
\$20,000 - \$39,999				
\$40,000 - \$59,999				

	Alive/Censored (n =)	Died (n =)	OR (95% CI)	P value
Over \$60,000				
Diagnosis				
Hematologic cancer				
CNS				
Other solid tumor				
Age at diagnosis (mean ± s.d.)				
Years since diagnosis (mean ± s.d.)*				
Treatment				
Chemotherapy - Yes				
Anthracycline(s)				
Alkylating agent(s)				
Both				
Neither				
Radiation - Yes				
CRT				
Chest				
Other				
None				
Amputation - Yes				

*Matched factors

Health-seeking behaviors:

	Alive/Censored (n =)	Died (n =)	OR (95% CI)	P value
Health care received – Yes				
Where health care received				
Physician				
Nurse				
Chiropractor				
Physical therapist				
Other				
# MD visits				
0 times				
1 – 2 times				
3 – 4 times				
5 – 6 times				
7 – 10 times				
11 – 20 times				
More than 20 times				
# CA-related visits				
0 times				
1 – 2 times				
3 – 4 times				
5 – 6 times				
7 – 10 times				
11 – 20 times				
More than 20 times				
# times telephoned MD				
0 times				
1 – 2 times				
3 – 4 times				
5 – 6 times				
7 – 10 times				
11 – 20 times				
More than 20 times				
General PE				
Less than 1 year ago				
1 – 2 years ago				
3 – 4 years ago				
5 or more years ago				
Never				
Dental care recency				
Less than 1 year ago				
1 – 2 years ago				
3 – 4 years ago				
5 or more years ago				
Never				
Pap Smear recency				
Less than 1 year ago				

-
- 1 – 2 years ago
 - 3 – 4 years ago
 - 5 or more years ago
 - Never

Professional breast exam

- Less than 1 year ago
- 1 – 2 years ago
- 3 – 4 years ago
- 5 or more years ago
- Never

Mammogram

- Less than 1 year ago
 - 1 – 2 years ago
 - 3 – 4 years ago
 - 5 or more years ago
 - Never
-

Health behaviors:

	Alive/Censored (n =)	Died (n =)	OR (95% CI)	P value
Smoking				
Never				
Past				
Current				
On average, how many cigarettes a day do/did you smoke?				
How many years, in total, have you smoked?				
Have you ever used any of the tobacco products listed below?				
Chewing tobacco				
Snuff tobacco				
Pipes				
Cigars				
Never used				
Yes, no longer use				
Yes, occasionally use				
Yes, regularly use				
Alcohol use				
In your entire life, have you ever had at least 2 drinks of any kind of alcoholic beverage?				
Yes				
No				
During the past 2 years, on the average, how many times per month did you drink the following (Wine, beer, mixed drink)				
On the days that you drink, on average, how many drinks do you have?				
0-past 2 years				
1 drink/day				
2				
3				
4				
5				
6 or more drinks/day				
Physical activity				
0 days				
1 day				
2 days				
3 days				
4 days				
5 days				
6 days				
7 days				
Testicular SE				

Regularly (once a month)

Occasionally

Rarely or never

Breast SE

Regularly (once a month)

Occasionally

Rarely or never

BMI

Obese – Yes

Health beliefs/concerns:

	Alive/Censored (n =)	Died (n =)	OR (95% CI)	P value
Future health				
Very concerned				
Somewhat concerned				
Concerned				
Not very concerned				
Not at all concerned				
Ability to have children				
Very concerned				
Somewhat concerned				
Concerned				
Not very concerned				
Not at all concerned				
Developing cancer				
Very concerned				
Somewhat concerned				
Concerned				
Not very concerned				
Not at all concerned				
Ability to get health insurance				
Very concerned				
Somewhat concerned				
Concerned				
Not very concerned				
Not at all concerned				
Ability to get life insurance				
Very concerned				
Somewhat concerned				
Concerned				
Not very concerned				
Not at all concerned				

Table 1: Baseline Data Variables to be Included in Mortality Study

Demographic(to examine as covariates, strata, adjustments in analytical models):

Race [A4; A4a]
Age at death (derived from a combination of CCSS data, NDI, death certificates, parent report)
Sex [A2]
Marital Status [L1-L3]
Highest level of schooling completed [O1]
Health insurance [Q2]
Total household income [Q8]
Total personal income [Q9]

Health-Seeking Behaviors:

Health care received [B1]
Where health care received [B2]
MD visits [B3]
CA-related visits [B4]
times telephoned MD [B5]
General PE [N16]
Dental care recency [N17]
Pap Smear recency [N20]
Professional breast exam [N21]
Mammogram [N22]

Health Behaviors:

Smoking [N1-N2]
Alcohol use [N3-N8]
Physical activity [N9]
Testicular SE [N18]
Breast SE [N19]
BMI

Health Beliefs/Concerns:

Concerns [R1-R6]
Future health
Ability to have children
Developing cancer
Ability to get health insurance
Ability to get life insurance
Other

Health Perceptions:

Health status [N15]

Chronic Illness:

CTCAE v4

Provider Contact:

Health care providers seen [B1]
Where received health care [B2]
Times saw a physician [B3]
Times had cancer-related visit [B4]
Times telephone doctors' office [B5]
Times admitted to any hospital [B6]

Medical Record Data:

1. Diagnosis
2. Year of Diagnosis
3. Treatment Exposures
4. Date of death (from MR if known, otherwise from supporting data)
5. Second malignancy

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