Study Title: Updated prevalence of long-term survivors of childhood cancer and estimated burden of morbidity using SEER and the Childhood Cancer Survivor Study

Working Group: Chronic Disease and Epidemiology/Biostatistics Working Groups

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Background and Rationale

Current estimates of the overall 5-year survival rates for childhood cancers have steadily increased since the 1970s and are estimated to be over 80%[1]. While increased survival rates are promising, the lack of specificity of curative treatments for childhood cancer often results in long-term and late effects due to their impact on normal healthy tissues [2]. As such, adult survivors of childhood cancer are often at an increased risk of adverse health-related and quality of life outcomes in comparison to individuals without a history of cancer [3]. Adverse outcomes include increased number and severity of chronic conditions [4, 5], health limitations [6, 7], hospitalizations [8, 9], risk of premature frailty [10], psychological distress [11], neurocognitive dysfunction [11, 12] and loss in productivity (i.e. inability to work or limitation in amount/kind or work) due to health problems [6]. In addition, adult survivors of childhood cancers report poorer overall health [6, 13] and physical health-related quality of life (HRQOL; [11]). Currently, the prevalence of the majority of these adverse outcomes are estimated,

individually from individual childhood cancer survivor cohort studies with little known about the overall specific burden of morbidity in childhood cancer survivors at the population level. As the number of survivors of childhood cancer is expected to continue to increase due to increased incidence[14] and advances in lifesaving treatments, it is becoming increasingly important to determine the overall burden of morbidity in this sub-group of cancer survivors at the population level. These data could have important practice and policy implications and be used to plan for healthcare needs, identify groups of childhood cancer survivors at particularly high risk for single and multiple morbidities and guide future research to explore intervention targets for preventing and/or reducing the burden of morbidity in this population.

Although there is not a U.S. population-based study, the Childhood Cancer Survivor Study (CCSS), provides rich, high-quality data on a wide range of potential adverse and late effects of cancer treatment [15]. CCSS is a large, geographically and socioeconomically diverse, multisite retrospectively established cohort study of individuals who survived 5 or more years post-treatment for cancer diagnosed during childhood or adolescence and have been prospectively followed for health and disease outcomes Data collected relevant to the development of morbidity in childhood cancer survivors include: self-reported chronic conditions, HRQOL, neurocognitive and physical functioning and psychological well-being. Using advanced statistical modeling techniques, it is possible to extrapolate data relevant to morbidity from the CSSS to population-level survivorship prevalence data from the Surveillance Epidemiology and End Results (SEER) program, a population-based registry of cancer incidence and survival in the United States (http://seer.cancer.gov). By combining CCSS and SEER data, it is possible to more accurately quantify the true population level burden of morbidity in childhood cancer survivors rather than relying on CCSS data alone. However, current published estimates of the prevalence of childhood cancer survivors from SEER only include prevalent cases through 2004[16]. Thus, in order to more accurately estimate the current burden of morbidity, data on the prevalence of survivors of childhood cancer need to be updated to include incidence and follow-up through 2010 [16]. Therefore, the purpose of present study is two-fold: 1) to update the prevalence of childhood cancer survivors in the U.S.

through 2010 using SEER and 2) to estimate the population-level burden of morbidity conceptualized as the prevalence of multiple indicators of morbidity, combining current prevalence estimates of childhood cancer survivors who are alive a minimum of 5 years post-treatment from SEER with estimates of adverse health outcome from the CCSS including chronic conditions (number and grade), second cancers, neurocognitive dysfunction, overall health status and HRQOL.

Findings from this study will update existing prevalence data for survivors of childhood cancer and provide the first quantification of the burden of morbidity in childhood cancer survivors at the population level. For the purposes of this study, burden of morbidity will be conceptualized as the prevalence of adverse health and quality of life related side effects of cancer and its treatment. These data may provide further insight into the true burden of morbidity in childhood cancer survivors and could provide insight into healthcare utilization, demographic and disease factors associated with greater morbidity burden, and potential interventions, programs and services that warrant further exploration to determine whether they may prevent, or reduce, the burden of morbidity in this population.

Specific Aims

The aims of the present study are as follows:

1. To use SEER data to update the prevalence statistics for long-term survivors of childhood cancer in the U.S. through January 1, 2010 from the most recently published manuscript (Mariotto et al., 2009) which contains data through 2005. In addition to overall prevalence counts, we will examine these data by:
    a. Current age (≤19, 20 to 29, 30 to 39, 40-49, 50+)
    b. Gender (male or female)
    c. Type of cancer (acute lymphoblastic leukemia, Acute myeloid leukemia, other leukemias, Hodgkin lymphoma, Non-Hodgkin lymphoma, Brain/central nervous system, Neuroblastoma, Renal tumors, bone tumors, Osteosarcoma, Ewing sarcoma, Soft tissue sarcoma, Germ cell tumors)

d. Time since diagnosis (<5 years, 5 to <10 years, 10 to <15 years, 15 to <20 years, ≥ 20 years)

2. Estimate and describe the burden of morbidity childhood cancer survivors who survive a minimum of 5 years post-treatment at the population level extrapolating data from CCSS to SEER. Specifically, we will estimate the following:

    a. Chronic conditions:

        i. Overall prevalence of the following conditions: none , Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening or disabling)

        ii. Prevalence of having any condition, a Grade 1-4 condition and/or Grade 3 or 4

        iii. Prevalence of multiple (≥ 2 and ≥ 3) chronic health conditions

    b. Overall prevalence of self-reported "high risk" for neurocognitive dysfunction as measured by a validated neuropsychological instrument.

    c. Overall prevalence of impaired health status conceptualized as impairment following domains: general health, mental health, functional impairment, activity limitations, pain as a result of cancer and/or its treatment and anxiety/fear as a result of cancer and/or its treatment.

    d. Overall prevalence of compromised HRQOL using the mental and physical health components of the 36-Item Short Form Health Survey (SF-36).

    e. Prevalence of all morbidity indicators will be examined as a function of time since diagnosis (5 to <10 years, 10 to <15 years, 15 to <20 years, ≥ 20 years) by demographic and disease characteristics including: current age (20-29, 30-39, 40+) or age at diagnosis; gender (male or female); Race (White, Black, Other); and cancer type (Leukemia, brain and central nervous system tumor, Hodgkin lymphomas, Non-Hodgkin lymphomas, renal tumors (VI), neuroblastoma, soft tissue, bone tumors)

Analysis Framework

Outcomes of Interest

Prevalence of childhood cancer survivors. SEER[17] data on incidence and follow-up from cancers diagnosed in individuals ≤ 19 years of age from 1975-2010 in 9 SEER registries including the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle/Puget Sound will be used to estimate prevalence. These registries represent ~ 10% of the U.S. population. The cancer sites to be considered include: leukemias (I), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (Ib), lymphomas (II), Hodgkin lymphomas (IIa), non–Hodgkin lymphomas including Burkitt lymphoma (IIb-c), brain and central nervous system tumors (III), neuroblastomas and sympathetic nervous system tumors (IV), retinoblastomas (V), renal tumors (VI), bone tumors (VIII), osteosarcomas (VIIIa), Ewing tumors (VIIIc), soft tissue tumors (IX), germ cell tumors (IX), and all cancer sites combined. Only malignant tumors will be considered, and all cancer sites combined will be modeled as a separate site. With the exception of ALL, all cancer sites will be coded using The International Classification for Childhood Cancer consistent with other publications using these data [16, 18]. ALL will be coded using the SEER site recode [19]. Justification for these choices are provided elsewhere [16]. Data from the Connecticut registry will be used to estimate cancer survival trends before 1975 using population estimates from the U.S. Census Bureau and all-cause mortality from the National Center for Health Statistics in the SEER*stat software [20].

Burden of morbidity. The prevalence of factors contributing to the burden of morbidity in survivors of childhood cancer ≥ 5 years of diagnosis will be estimated using the following data from the CCSS sample obtained via mailed questionnaire:

Chronic conditions and second cancers. Participants self-reported or a proxy reported on their behalf, if they were less than 18 years of age or deceased at the time of the questionnaire, on physical health conditions and age at onset of each condition via questionnaires completed at baseline (1994-1998) and during the 2000, 2003 and 2007 follow-up assessments. All second cancers ascertained from a

participant or physician report were verified by a review of a pathology report. Scoring of the severity of conditions is determined by the Common Terminology for Adverse Events (version4.03;[21]) consistent with the methodology used in Oeffinger et al. [4]. Briefly, the system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or disabling (grade 4). If a condition is not listed, it is categorized in the "other, specify" according to the organ system affected. If there is not enough information to distinguish between grades, the lower score was selected.

Self-reported neurocognitive functioning. Data on self-reported neurocognitive functioning were collected as part of the 2003 CCSS follow-up survey using the CCSS-Neurocognitive Questionnaire (CCSS-NCQ). This questionnaire has four factors: task efficiency, emotional regulation, organization and memory [22, 23] and has been shown to be reliable and valid for assessing neurocognitive functioning in the CCSS sample [12, 22]. The CCSS-NCQ asks participants to report the degree to which they experienced any of 25 problems over the past 6 months on a 3-point Likert scale ranging from 1 (*never a problem)* to 3 *(often a problem).* Items representing each of the 4 factors are summed and these values are converted to *T* scores, with higher scores indicating greater degree of impairment. Those individuals with scores falling below the 10^{th} percentile based on sibling groups norms (i.e. $\geq$ 63 on any of the 4 dimensions) will be classified as "impaired" as detailed in Kadan-Lottick et al[12].

Health-related quality of life. HRQOL data were collected during the 2003 follow-up assessment period using the SF-36, a widely-used, valid and reliable measure [24, 25]. The SF-36 assesses eight health-related dimensions: physical functioning, physical limitations, pain, behavior disturbances due to emotional problems, mental capacity, perceptions of health, social functioning, and feelings of energy/fatigue and yields psychometrically-based physical component summary (PCS) and mental component summary (MCS) measures. Scores range from 0-100 with higher scores indicative of better mental and physical health. Participants will be classified as having compromised PCS or MCS if they score $\leq$ 40 on either component summary measure.

Overall health status. Overall health status will be estimated using measures from 6 domains: general health, mental health, functional status, limitations of activity, pains as a result of the cancer or its treatment and anxiety/fears as a result of cancer and its treatment consistent with its conceptualization in a previous study in the CCSS [26].

General health was assessed at baseline and 2003 and 2007 follow-up, using the question, "In general, would you say that your health is excellent, very good, good, fair or poor?" Responses of fair or poor will be classified as having poor general health at each time period.

The 18-item Brief Symptom Inventory (BSI-18 [27]) was assessed at baseline and during the 2003 and 2007 follow-up assessments. The BSI-18 has 3 symptom-specific subscales (depression, somatization, and anxiety). Responses on the BSI-18 at each time point will be converted to *T* scores as described in Hudson et al.[26] with scores ≥ 63 being classified as "elevated" and those <63 considered "not elevated." These data will be used as an indicator of adverse mental health with participants classified as elevated on any of the 3 symptom specific subscales will be classified as having adverse mental health at that time point.

Functional status was assessed during 2007 follow-up by asking respondents' to indicate (*yes or no)* whether any impairment or health problems resulted in a) needing "help with personal care needs such as eating, bathing, dressing or getting around your home;" b) needing "help in handling routine needs, such as everyday household chores, doing necessary business, shopping or getting around for other purposes;" or c) "keeping you from holding a job or attending school." These data will be used as an indicator of functional impairment with survivors denoting a positive response on any of the 3 items being classified as having functional impairment.

Limitations in activity were assessed at baseline and 2007 follow-up using 3 questions which asked participants to indicate how long ($\geq$ 3months, $<$3 months or not all), over the last 2 years, their health was limited in: a) "the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling"; (b)"walking uphill or climbing a few flights of stairs" and c) "walking one block." These data will be used as an indicator to estimate activity limitations with participants who

reported they had been limited for ≥ 3 months being classified as having activity limitations at each time point at which it was reported.

Participants were asked "Do you currently have pain as a result of your cancer or its treatment?" at baseline and again in 2003 and "Do you currently have anxiety/fears as a result of your cancer or its treatment?" at baseline and 2007 follow-up. These questions will be dichotomized at each time point to represent presence (*yes or no)* of pain or anxiety/fear, respectively, as a result of the cancer or its treatment following the methods described by Hudson and colleagues [26].

Subject Population to be Included:

SEER prevalence update. All prevalent cases from SEER of incident childhood cancers diagnosed from 1975 through January 1, 2010 will be included in analyses to update estimates from Mariotto and colleagues [16].

Burden of morbidity. For modeling of these data by time since diagnosis, estimates from the CCSS sample for all outcomes of interest will be restricted to CCSS participants diagnosed with cancer between 0 to 19 years of age who are alive at that time period. These restrictions are consistent with the age range included in the SEER prevalence estimates. CCSS diagnosis data will be recoded using the International Classification for Childhood Cancer coding to ensure consistency with SEER data. Thus, SEER data will be limited to reflect the CCSS by including : a) only the cancer sites included in the CCSS (leukemia, central nervous system malignancy, Hodgkins disease, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer or bone cancer and b) only prevalent cases who had survived a minimum of 5 years as of January 1, 2010.

Exploratory Variables

Demographic and disease-specific data from SEER and CCSS may be used to stratify or explore prevalence of childhood cancer survivors and burden of morbidity data further. These variables include:

Age. SEER survivorship prevalence data and burden of morbidity data may be stratified based on age at diagnosis (obtained from SEER or CCSS) or current age (obtained from SEER or CCSS). In

addition, age at each chronic disease onset or questionnaire time point from the CCSS may be used to conduct time to event analyses or to censoring on age, follow-up time or death.

Gender. Gender (male or female) as indicated in SEER or CCSS.

Race. Data on Race obtained from SEER and/or CSSS will be corroborated from both studies to make it consistent.

Primary cancer diagnosis/type. Data on cancer diagnosis/type will be corroborated from SEER and CCSS to make coding consistent between the two datasets. These data may be used to stratify or explore survivor prevalence (using all cancer types) or burden of morbidity prevalence (restricted to cancer types in CCSS) data further.

Statistical Analyses

SEER Prevalence of Childhood Cancer Survivors in the U.S.

Analyses will mirror those conducted in Mariotto et al., 2009 to update prevalence through 2010. The number of people in the United States alive in 2010 and diagnosed with cancer between ages 0 and 19 years will be calculated in 3 steps. First, the proportion of survivors alive in the SEER-9 areas diagnosed with childhood cancer between years 1975-2010 and 2004 and ages 0 and 19 years by cancer site, sex, race (White, Black, other; where unknown race was grouped with White race) and age will be calculated using the SEER*Stat software [20] and the counting method [28]. To estimate complete U.S. childhood cancer survivor prevalence estimates for the United States, the site/sex/race/age specific SEER cancer prevalence proportions will be multiplied by the respective U.S. sex/race/age-specific populations. To obtain childhood cancer prevalence for all races combined, we will sum over all races. Third, complete prevalence of childhood cancer, which includes adults diagnosed with childhood cancer prior to 1975 (i.e. with 25 years or more from time of diagnosis), is calculated using the CHILDPREV method [29]. Briefly, long term childhood cancer survivors, diagnosed prior to 1975, were estimated using age and period parametric cancer site/sex specific incidence and survival models fitted to SEER data.

Population-level Estimates of the Burden of Morbidity

Data from SEER will be limited to include those who survive ≥5 years to be consistent with data obtained from CCSS participants. Chi-square tests will be conducted to determine whether the CCSS and SEER samples for each time point post-diagnosis vary significantly in terms of age at diagnosis, gender, race or cancer diagnosis.

Prevalence of all conditions will be calculated in the CCSS cohort at specific time points post cancer diagnosis when controlling for age at diagnosis. Prevalence will only be relevant among subjects alive at the time at which it is calculated, so denominators will be restricted to living CCSS survivors diagnosed before age 19 who are alive at the time point of interest. Chronic health conditions and second cancer prevalence estimates will represent the proportion of subjects who have experienced the outcome of interest in the post-diagnosis period specified. At discrete time points (e.g. 10, 15, 20, 25 …years since diagnosis), at risk subjects will be classified into prevalent cases vs non-cases by time since diagnosis, and associated covariates including current age, time since diagnosis, race, gender, and primary diagnosis will be paired with that binary outcome variable. A large data set will be constructed combining these outcome and covariate combinations for a full range of time points so that each individual contributes observations for any of the time points at which they were in follow-up for CCSS. The remainder of the health outcomes were evaluated cross-sectionally at one or more questionnaire time point and will necessarily be evaluated at the time points post-diagnosis at which they were assessed. Logistic regression models will be fit to each binary outcome, incorporating years post-diagnosis, as well as evaluating impact of sex, race, primary diagnosis factors, as needed, and predicted probabilities will be estimated. Since each individual likely contributes multiple outcome by covariate records to the analysis, either via the multiple time point scenario developed for the chronic condition outcomes, or where multiple assessments of a cross-sectional measure are made across different questionnaires, all observations will be incorporated into the model, utilizing generalized linear models with generalized estimating equations and robust sandwich variance estimates to account for intra-person correlation. Interactions between time variables and other factors will be included to allow for covariate level specific predictions of prevalence to change across time since diagnosis. Predicted probability estimates from the

full models will estimate prevalence of these conditions, along with associated confidence intervals and p-values for comparisons between groups.

Once final models are obtained for cancer prevalence and morbidity prevalence, combined estimates of burden of morbidity in the U.S. population will be obtained by multiplying the morbidity prevalence by the relevant number of cancer survivors within subgroups of the population deemed of interest and feasible for such calculations via the modeling process

Specific Tables and Figures

Table 1. U.S. Childhood Cancer Survivors as of 2010. Number of people previously diagnosed with cancer as children (ages 0-19) in the U.S. alive on January 1, 2010, by age group, time since diagnosis, sex and site.

Table 2. Characteristics of the CCSS sample compared to SEER by time since diagnosis.

Table 3. Estimates of prevalence as of January 1, 2010 of chronic health conditions in childhood cancer survivors who survived a minimum of 5 years.

Table 4. Estimates of prevalence of chronic health conditions as of January 1, 2010 in childhood cancer survivors who survived a minimum of 5 years by demographic and disease characteristics.

Table 5. Estimates of impaired neurocognitive functioning, adverse overall health status and compromised quality of life as of January 1, 2010 in childhood cancer survivors who survived a minimum of 5 years by demographic and disease characteristics.

Note: Figures will be constructed to illustrate primary findings and take home message of the paper

Table 1. U.S. Childhood Cancer Survivors as of 2010. Number of people previously diagnosed with cancer as children (ages 0-19) in the U.S. alive on January 1, 2010, by age group, time since diagnosis, sex and site

Site	Sex/age	Complete prevalence counts							Time since diagnosis (in years)				
		0-19	20-29	30-39	40-49	50-59	60+	All ages	< 5	5 to 10	10 to <15	15 to <20	≥20
All sites	Both												
	Males												
	Females												
Leukemia	Both												
	Males												
	Females												
ALL	Both												
	Males												
	Females												
Acute myeloid leukemia (Ib)	Both												
	Males												
	Females												
Hodgkin lymphomas (IIa)	Both												
	Males												
	Females												
Non-Hodgkin lymphomas (IIa)	Both												
	Males												
	Females												
Brain/central nervous system (III)	Both												
	Males												
	Females												
Neuroblastoma (IV)	Both												
	Males												
	Females												
Renal tumors (VI)	Both												
	Males												
	Females												

Bone tumors (VIII)	Both												
	Males												
	Females												
Osteosarcomas (VIIIa)	Both												
	Males												
	Females												
Ewing (VIIIc)	Both												
	Males												
	Females												
Soft tissue (IX)	Both												
	Males												
	Females												
Germ cell tumors (X)	Both												
	Males												
	Females												

Table 2. Characteristics of the CCSS sample compared to SEER by time since diagnosis

	Time Since Diagnosis (Years)											
	5 to <10			10 to <15			15 to <20			≥ 20		
Characteristic	**CCSS[†] (N=)**	**SEER[*] (N=)**	***p*-value**	**CCSS[†] (N=)**	**SEER[*] (N=)**	***p*-value**	**CCSS[†] (N=)**	**SEER[*] (N=)**	***p*-value**	**CCSS[†] (N=)**	**SEER[*] (N=)**	***p*-value**
Age at Primary Diagnosis (*M*, SD)												
0-4												
5-9												
10-14												
15-20												
Gender (n, %)												
Male												
Female												
Race (n, %)												
White												
Black												
Other												
Cancer Type (n, %)												
Leukemia												
Brain and central nervous system tumor												
Hodgkin lymphomas (IIa)												
Non-Hodgkin lymphomas (IIa)												
Renal tumors (VI)												
Neuroblastoma												
Soft tissue												
Bone tumors (VIII)												

[†]subject may count in more than one time period depending on length of survival; [*]Limited to those who were alive as of January 1, 2010; were diagnosed with cancer included in CCSS and survived a minimum of 5 years

Table 3. Estimates of prevalence as of January 1, 2010 of chronic health conditions in childhood cancer survivors who survived a minimum of 5 years.

Health Condition	**SEER (N=) n (%)**
No condition	
Grade 1 (mild)	
Grade 2 (moderate)	
Grade 3 (severe)	
Grade 4 (life threatening or disabling)	
Any Condition	
Grades 1-4	
Grades 3 or 4	
Multiple health conditions	
≥ 2	
≥ 3	

Note: All values are calculated based on time since diagnosis and adjusted for age at diagnosis.

Table 4. Estimates of prevalence of chronic health conditions as of January 1, 2010 in childhood cancer survivors who survived a minimum of 5 years by demographic and disease characteristics.

Characteristic	Grade 1-4	Grade 3-4	≥ 2 Conditions	p-value
Time Since Diagnosis in Years				
5 to <10				
10 to <15				
15 to <20				
≥ 20				
Current Age (*M*, SD)				
20-29				
30-39				
40+				
Gender (n, %)				
Male				
Female				
Race (n, %)				
White				
Black				
Other				
Cancer Type (n, %)				
Leukemia				
Brain and central nervous system tumor				
Hodgkin lymphomas (IIa)				
Non-Hodgkin lymphomas (IIa)				
Renal tumors (VI)				
Neuroblastoma				
Soft tissue				
Bone tumors (VIII)				

Note: All values are calculated based on time since diagnosis and adjusted for age at diagnosis.

Table 5. Estimates of impaired neurocognitive functioning, adverse overall health status and compromised quality of life as of January 1, 2010 in childhood cancer survivors who survived a minimum of 5 years by demographic and disease characteristics.

Variables	No.	Impaired Cognitive Functioning (%)	*p*-value	General Health (%)	*p*-value	Mental Health (%)	*p*-value	Functional Impairment (%)	*p*-value	Activity Limitations (%)	*p*-value	Quality of Life (%)			
												MCS	*p*-value	PCS	*p*-value
Total Population															
Current Age (*M*, SD)															
20-29															
30-39															
40+															
Time Since Diagnosis (Years)															
5 to <10															
10 to <15															
15 to <20															
≥ 20															
Gender (n, %)															
Male															
Female															
Race (n, %)															
White															
Black															
Other															
Cancer Type (n, %)															
Leukemia															
Brain and central nervous system tumor															

Hodgkin lymphomas (IIa)															
Non-Hodgkin lymphomas (IIa)															
Renal tumors (VI)															
Neuroblastoma															
Soft tissue															
Bone tumors (VIII)															

Note: All values are calculated based on time since diagnosis and adjusted for age at diagnosis.

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