Childhood Cancer Survivor Study

Analysis Concept Proposal

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Project Title

Estimating the Population-Level Burden of Morbidity among Survivors of Childhood Cancer in the United States

Working Group

Epidemiology (Primary)

Chronic Disease (Secondary)

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Background and Rationale

Each year in the U.S., approximately 15,000 children and adolescents are diagnosed with cancer, resulting in an estimated 500,000 survivors of childhood cancer alive as of 2020.[1] While survival from childhood cancer approaches >85%, the decades of life following diagnosis are accompanied by an increased risk of a variety of late effects from therapy and premature death.[2-4] Treatments for childhood cancer have historically lacked specificity compared to treatments for cancer types that affect adults, and are administered during a vulnerable period of biological development. As a result, survivors are at increased risk for many different chronic health conditions (CHCs) such as heart disease, subsequent cancers, and pulmonary, neurologic or endocrine conditions.[2] Additionally, they more frequently experience

neurocognitive, psychosocial, and functional deficits when compared to their peers.[5, 6] As five-year overall survival continues to rise, so too will the number of survivors who are at significant increased risk of multi-morbidity.[7] Therefore, understanding the population-based prevalence of morbidity in survivors of childhood cancer across the U.S. has important implications for the care of survivors, the treatment of current patients, and the policies that impact both.

In a seminal paper by Phillips and colleagues from 2015[8], they leveraged the Childhood Cancer Survivor Study (CCSS) and Surveillance, Epidemiology, and End Results (SEER) data to estimate the burden of morbidity experienced by survivors of childhood cancer. The CCSS is an NCI-funded multi-institutional cohort of five-year survivors diagnosed with childhood cancer between 1970 and 1999. Survivors in this cohort are followed longitudinally to capture health and psychosocial outcomes. Because there is no nationwide surveillance network to monitor survivors of childhood cancer for late effects, Phillips *et al.[8]* utilized morbidity data from the CCSS combined with prevalence estimates from SEER to estimate the number of survivors in the US with various morbidities (CHCs, neurocognitive or functional deficits, etc.). They reported approximately 180,000 survivors of childhood cancer in the US (75% of survivors) had at least one CHC; this prevalence increased with attained age and time since diagnosis.

However, the analysis by Phillips *et al.[8]* has important limitations. First, only data from survivors in the CCSS diagnosed between 1970 and 1986 were evaluated. Therefore, this analysis could not assess how more modern therapy regimens impacted the burden of morbidity among survivors. Second, given limitations in available follow-up at the time of publication, more granular characterizations of organ system-based morbidity burden were not provided. Third, this previous work presented population-level morbidity burden estimates among survivors alive as of January 1, 2011. Comparison of the total morbidity in an aging survivor cohort a decade later with more extensive follow-up is needed. Fourth, while Phillips *et al.[8]* estimated the absolute numbers of survivors who experienced these morbidities, the total burden of morbidity among survivors was not characterized. Given survivors experience multiple morbidities, it would be insightful to estimate the absolute number of morbidity events experienced by survivors on a US population-level scale. Lastly, this previous analysis does not provide an understanding of excess population-level morbidity burden compared with the general population. We recently demonstrated that survivors have a significant excess risk of death relative to a similar age-, race-, and calendar year-matched population.[7] Moreover, when we examined the absolute number of excess deaths by calendar year, the growth of excess deaths occurring ten or more years from diagnosis nearly negated the gains from improvement in 5-year overall survival over the same time frame. These data highlight the importance of estimating the excess population-level morbidity experienced by survivors of childhood cancer.

This proposal aims to estimate the total prevalent population-level burden of morbidity and excess morbidity experienced by survivors of childhood cancer in the US today with data from CCSS survivors diagnosed through 1999 and updated SEER data. By utilizing data from the expanded CCSS cohort with more extensive follow-up, we will be able to: (a) evaluate changes in population-level morbidity by treatment decade and potentially identify any decreases in morbidity associated with more modern therapies; (b) provide a snapshot of population-level organ system-specific morbidities; (c) describe changes in the population-level morbidity burden among aging survivors a decade later; (d) characterize the total prevalent population-level morbidity burden considering multiple morbidities; and (e) estimate the excess

morbidity in survivors of childhood cancer, preliminarily utilizing morbidity data from CCSS siblings. Understanding the true population burden of morbidity in survivors of childhood cancer can inform health policy, coordinated care models, development of novel treatment strategies and future research priorities.

Specific Aims

We hypothesize the population-level burden of morbidity and excess risk experienced by survivors in the US today differs by age at diagnosis (<15, 15+), attained age, sex, cancer type, and treatment decade. We also hypothesize that an updated summary of the population-level burden of morbidity among survivors in the US today will reveal important changes from survivors alive as of January 1, 2011, with notable patterns related to the aforementioned factors. As such, our aims are as follows:

Aim 1: Estimate the total burden of morbidity among five-year survivors of childhood cancer living in the United States as of January 1, 2022.

Given the SEER-informed estimates of the total number of five-year childhood cancer survivors living in the US as of 1/1/2022 and CHC/morbidity data from CCSS, we will estimate the prevalence and absolute number of the following:

a. CHCs overall and by organ system, using the modified NCI CTCAE grading system (v5), with emphasis on evaluation of CHC severity
b. Neurocognitive impairment, using the CCSS Neurocognitive Questionnaire (NCQ)
c. Functional impairment, using self-reported functional limitations

Morbidity burden will be evaluated by age at diagnosis (<15, 15+), attained age, sex, cancer type, and treatment era. Comparisons will be made to previous results published by Phillips *et al[8].*

Aim 2 (Exploratory): Estimate the absolute number of excess CHCs experienced by survivors of childhood cancer in the U.S. using CCSS estimates (Aim 1), where CCSS sibling data will be used to estimate expected rates.

Excess risks for CHCs (overall only) will be examined by age at diagnosis (<15, 15+), attained age, sex, type of cancer, and treatment decade. We will also explore the feasibility of estimating excess risks using nationwide estimates of the prevalence of various conditions in NHANES (see below).

Analysis Framework

- Study Population
    a. CCSS
        i. All CCSS survivors who completed a baseline survey will be included with the following caveats. Consistent with Phillips *et al.[8]*, we will restrict the CCSS sample so that it is more similar to the data available in SEER. Therefore, we will only use data from survivors <20 years at diagnosis, we will exclude germ cell tumors as these were only included in CCSS for CNS patients, and we will also exclude benign CNS tumor survivors from CCSS as these were not captured in SEER until 2004.
    b. SEER

i. We will use data from the SEER 8 registries as this is the only SEER registry that dates back to 1975. SEER 8 covers approximately 8.3% of the U.S. population and includes the following areas: Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, San-Fransisco-Oakland and Seattle-Puget-Sound. From SEER 8, we will select any person diagnosed under the age of 20 from 1975 to 2021. Using the International Classification for Childhood Cancer, we will further restrict the diagnosis site to match those available in CCSS (e.g. exclude retinoblastoma).

c. NHANES
    i. The number of events may be small among siblings. Additionally, siblings in the CCSS may not be representative of either the survivors or the general U.S. population. Therefore, we will also consider national prevalence estimates from NHANES when calculating excess morbidity (Aim 2). We will abstract an age-, sex-, race/ethnicity-matched group from NHANES with no cancer history. NHANES collects information on self-reported medical conditions alongside the age at first onset, many of which are similar to those asked on CCSS questionnaires. We will examine excess morbidity similar to the CCSS analysis if possible; if not, this analysis will be limited to the most common conditions (e.g., by organ system) identified in Aim 1 to data available in NHANES using a framework similar to Esbenshade et al.[9]

- Outcomes of Interest
    a. Chronic health conditions
        i. Participants self-reported the presence of CHCs and the age at onset on the baseline and follow up questionnaires. Participants will be assumed to have the CHC after the first reported instance (i.e., reported onset age), with the exception of subsequent neoplasms where multiple occurrences will be considered. We will utilize CTCAE graded CHCs consistent with previous CCSS papers.[10] We will examine the prevalence of any grade 1-4 condition, any grade 3-4 condition, multiple grade 1-4 or 3-4 conditions, and CHCs by organ system, similar to Bhakta *et al.[2]*
    b. Neurocognitive Impairment
        i. First report of neurocognitive impairment will be assessed using the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ; FU2: J1-J25, FU5: Q1-Q33). The CCSS-NCQ was developed and validated for use in cancer survivors and assesses four specific domains: task efficiency, emotional regulation, organization, and memory. Scores for each of the four domains will be operationalized as binary variables (impaired vs not) for each of the Aims (unless otherwise noted). Participants will be considered impaired if their score is ≥ 90th percentile based on values obtained in the sibling cohort. Participants in the original cohort first completed the NCQ at FU2, participants in the expansion cohort first completed the NCQ at FU5.
        ii. For these analyses our primary outcome will be impairment in any of the four domains. Secondary analyses will examine each domain separately.
    c. Functional Impairment

i. First report of functional impairment will be assessed using items from the SF-36 questionnaire that create the physical component score (PCS) and the mental component score (MCS). Participants will be considered impaired if their score falls below a T-score of 40 (1 standard deviation below the mean) on either component score.

- Sociodemographic Variables
    a. Sex
    b. Attained age (i.e., date of birth and date of last follow-up or death)
    c. Vital status (including date of death)
    d. Primary cancer diagnosis
    e. Age at primary cancer diagnosis (i.e., date of primary cancer diagnosis)
    f. Diagnosis decade (1970s, 1980s, 1990s)
    g. Reported race/ethnicity
    h. Cancer treatment exposures delivered within 5 years of primary cancer diagnosis
        i. Any radiation therapy (RT; yes/no)
            1. Field-specific RT (yes/no), dose for each of the 7 major body regions (cranial, neck, chest, abdomen, pelvic, arm, leg), and maximum cumulative dose across the 7 body regions
            2. Total body irradiation (yes/no and dose)
        ii. Chemotherapy
            1. Any chemotherapy: yes/no
            2. Alkylating agents: yes/no and quantified as cyclophosphamide-equivalent dose (CED)
            3. Anthracyclines: yes/no and quantified as doxorubicin-equivalent dose (DED)
            4. Epipodophyllotoxins: yes/no and cumulative dose
            5. Platinum: yes/no and quantified as cisplatin-equivalent dose
        iii. Hematopoietic cell transplantation (yes/no)

Statistical Analysis

Aim 1: We plan to update the estimated number of five-year survivors diagnosed with childhood cancer between 1970 to 1999 living in the US as of January 1, 2022 using up-to-date data from SEER and methods previously described in detail by Phillips *et al.[8]* Specific updates to assure greater consistency between SEER and CCSS data include the following:

(a) include cases in SEER diagnosed between 0 to 19 years of age from 1970 to 1999, restricting to cancer sites that are also included in CCSS, following Phillips *et al.[8]*; and
(b) include SEER-8 incidence and survival data spanning 1975 to 2021.

In brief, the following steps will be used to obtain the total number of five-year survivors diagnosed between 1970 and 1999 living in the US as of 1/1/2022, consistent with previous work:

1. Age-, sex-, calendar year-, and cancer site-specific cancer incidence and survival data from 1975-2021 in SEER will be used to estimate the prevalence proportions of five-year survivors alive in registry areas using the counting method[11] implemented in SEER*Stat software. These prevalence proportions will be multiplied by the numbers of

individuals alive in age-/sex-/race-/calendar year-matched US populations, accounting for the proportion of the US population covered by SEER. These quantities will be summed to obtain the total.

2. To estimate the total number of five-year living survivors diagnosed with childhood cancer before 1975, the CHILDPREV method[12] will be used to estimate the corresponding prevalence proportions, which uses age and period parametric cancer site-/sex-specific incidence and survival models fitted to SEER data.

Then, we will further estimate: (a) the total number of survivors who experienced each of the morbidity outcomes of interest; and (b) the cumulative numbers of each morbidity event type (including recurrent/multiple events). For analyses described below, the time at risk begins at five years from childhood cancer diagnosis and ends at death or censoring (last follow up).

- For (a): Following methods described by Phillips *et al.[8]*, we will evaluate binarized outcomes (specified below) as of a specific observation time point after the five-year survival milestone (to be defined *a priori*, e.g., 5, 10, 15, etc. years). Because each participant can contribute data at multiple time points (i.e., absence or presence of outcome based on reported age at onset or assessment as of a given observation time point), we will use logistic regression with generalized estimating equations and robust sandwich variance estimates[13] to obtain the predicted probabilities of experiencing the outcomes of interest, adjusting for years after diagnosis, attained age at the observation time point, sex, race, and treatment exposures. These predicted probabilities are estimates of the prevalence proportions of the morbidity event of interest; when multiplied to the number of survivors living in the US as of 1/1/2022 in follow-up/age-/race-/treatment-matched subgroups, we may obtain the estimate of the number of 5-year survivors who experienced the morbidity event of interest. Morbidities that will be evaluated include:
    - At least one CTCAE grade 1-4 CHC
        - At least one organ system-specific CTCAE grade 1-4 CHC (organ systems to be broken out as follows: cardiovascular, respiratory, gastrointestinal, reproductive, endocrine, renal, musculoskeletal, neurological, immunologic/infectious disease, hematology, auditory, ocular, second neoplasms)
    - At least one CTCAE grade 3-4 CHC
        - At least one organ system-specific CTCAE grade 3-4 CHC (see organ system break out above)
    - Multiple (2+) CTCAE grade 1-4 CHCs
        - Multiple (2+) organ system-specific CTCAE grade 1-4 CHCs (see organ system break out above)
    - Multiple (2+) CTCAE grade 3-4 CHCs
        - Multiple (2+) organ system-specific CTCAE grade 3-4 CHCs (see organ system break out above)
    - Any neurocognitive impairment
    - Any domain-specific neurocognitive impairment (four domains: task efficiency, emotional regulation, organization, and memory)
    - Any functional impairment
- For (b): We will estimate the mean cumulative counts (MCCs)[14], a method which estimates the mean number of multiple or recurrent events by a time point of interest in the presence of competing risks, for each of the morbidities of interest. In CCSS, the cumulative burden measure may only appropriately describe subsequent neoplasms (because recurrent events are captured). However, we plan to use the MCC method to

capture the total number of potentially unique events in CCSS (e.g., each row of the CCSS CHC Matrix may be counted once) and all ascertained subsequent neoplasms (with the exception of non-melanoma skin cancers and meningiomas, where up to the first five reported events will be included). When multiplied to the total number of survivors living in the US as of 1/1/2022, we may obtain the estimated total counts of the morbidity events of interest among survivors.

The estimated counts of survivors with specific morbidity events and estimated total counts of morbidity events will be further evaluated by:

- Age at childhood cancer diagnosis (<15, 15+)
- Attained age groups (<30y; 30 to 39 years; 40 to 49 years; 50 years or older)
- Sex
- Cancer diagnosis type
- Treatment decade

We plan to evaluate these multiple factors simultaneously as appropriate, including: attained age and sex; attained age and treatment decade; attained age and cancer type; cancer diagnosis type and treatment decade. Comparisons to the results presented by Phillips *et al.[8]* will be provided.

Aim 2 (Exploratory): This aim focuses on estimating the excess morbidity that survivors of childhood cancer experience using methods similar to Williams et al.[7] To estimate excess morbidity, we need an observed estimate (calculated in Aim 1) and an expected morbidity. The difference of these two estimates will be considered the excess morbidity.

To estimate expected number of individuals in the general population who would develop morbidities of interest, we may estimate the prevalence of events among CCSS siblings using the same methods applied to CCSS survivors (Aim 1). These prevalence estimates will be sex, race, and attained age specific. These estimates are then applied to the total estimated number of 5-year survivors living in the US, in an age, sex, race, and attained age specific manner. We will then subtract this from the observed estimates generated in Aim 1 and this will give us the excess number of survivors with morbidities compared to a similar population. Similar methods will estimate the excess numbers of morbidities of interest using corresponding MCC estimates among siblings.

Morbidities that will examined include:

- At least one CTCAE grade 1-4 CHC
    - If numbers allow: At least one organ system-specific CTCAE grade 1-4 CHC (organ systems to be broken out as follows: cardiovascular, respiratory, gastrointestinal, reproductive, endocrine, renal, musculoskeletal, neurological, immunologic/infectious disease, hematology, auditory, ocular, second neoplasms)
- At least one CTCAE grade 3-4 CHC
    - If numbers allow: At least one organ system-specific CTCAE grade 3-4 CHC (see organ system break out above)
- If there are sufficient numbers of events, we will also examine:
    - Multiple (2+) CTCAE grade 1-4 CHCs
        - Multiple (2+) organ system-specific CTCAE grade 1-4 CHCs (see organ system break out above)
    - Multiple (2+) CTCAE grade 3-4 CHCs
        - Multiple (2+) organ system-specific CTCAE grade 3-4 CHCs (see organ system break out above)

    - Any neurocognitive impairment
        - Any domain-specific neurocognitive impairment (four domains: task efficiency, emotional regulation, organization, and memory)
    - Any functional impairment

We will examine the frequency of events among siblings as well as their sociodemographic characteristics in relation to the survivors as well as the U.S. population. The number of events among siblings may be limited and siblings may not be representative of the national U.S. population as well in terms of sociodemographic factors. Therefore, we will also explore obtaining age-, sex, - and race/ethnicity matched sample from NHANES without a history of cancer to generate prevalence estimates (Aim 1, see Analysis Framework). These estimates will be used to calculate the expected number of individuals with morbidities and the total expected number of morbidities (in comparable subgroups). If data is available in NHANES on all chronic health conditions assessed in CCSS questionnaires, we will also examine the categories noted above (e.g. at least one CHC, etc.).

The estimated excess counts of survivors with specific morbidity events and estimated excess total counts of morbidity events will be primarily presented by attained age. We will also examine them by:

- Age at childhood cancer diagnosis (<15, 15+)
- Sex
- Cancer diagnosis type
- Treatment decade

Special Considerations

None.

Draft Tables and Figures

Table 1: SEER-based estimates of the number of five-year survivors of childhood cancer (diagnosed <20 years of age) in the US and alive as of January 1, 2022 by ICCC site, sex, diagnosis age, attained age, and treatment decade

		By diagnosis age		By attained age						By treatment decade		
Site	Sex	<15	15+	0–19	20–29	30–39	40–49	50–59	60+	1970-1979	1980-1989	1990-1999
All sites	Both											
	Male											
	Female											
Leukemia (I)	Both											
	Male											
	Female											
Acute lymphocytic leukemia	Both											
	Male											
	Female											
Acute myelogenous leukemia (Ib)	Both											
	Male											
	Female											
Hodgkin lymphoma (IIa)	Both											
	Male											
	Female											
Non-Hodgkin lymphoma (IIb,c,e)	Both											
	Male											
	Female											
Brain/central nervous system (III)	Both											
	Male											
	Female											
Neuroblastoma and other peripheral nervous cell tumor (IV)	Both											
	Male											
	Female											
Renal tumors (VI)	Both											
	Male											
	Female											
Malignant bone tumors (VIII)	Both											
	Male											
	Female											
Osteosarcoma (VIIIa)	Both											
	Male											
	Female											
Ewing tumor and related sarcomas of bone (VIIIc)	Both											
	Male											
	Female											
Soft tissue and other extraosseous sarcomas (IX)	Both											
	Male											
	Female											
Germ cell and trophoblastic tumors and neoplasms of gonads (X)	Both											

		By diagnosis age		By attained age						By treatment decade		
Site	Sex	<15	15+	0–19	20–29	30–39	40–49	50–59	60+	1970-1979	1980-1989	1990-1999
	Male											
	Female											

Table 2: Estimates of the number of 5-year survivors alive as of January 1, 2022 with prevalent chronic health conditions, neurocognitive impairment, or functional impairment

		Sex		Age at diagnosis		Attained age				Treatment decade		
		n (%)										
Chronic health conditions (CHCs): Overall and organ system-specific	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any grade 1–4 CHC												
Any grade 3–4 CHC												
Multiple (≥2) grade 1–4 CHCs												
Multiple (≥2) grade 3–4 CHCs												
Neurocognitive impairment	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any neurocognitive impairment												
Task efficiency domain												
Emotional regulation domain												
Organization domain												
Memory domain												
Functional impairment	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any mental or physical impairment (T-score<40)												

Note that denominators are the total number of survivors.

Table 3: Similar to above, but subgroup by childhood cancer diagnosis.

Table 4: Estimates of the number of 5-year survivors alive as of January 1, 2022 with prevalent chronic health conditions, by organ system

		Sex		Age at diagnosis		Attained age				Treatment decade		
		n (%)										
Organ system-specific CHCs	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any grade 1–4 CHC												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												
Any grade 3–4 CHCs												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												

Note that denominators are the total number of survivors.

Table 5: Similar to above, but subgroup by childhood cancer diagnosis.

Table 6: Estimates of the total burden (number) of prevalent CHCs (overall and organ system-specific) among 5-year survivors alive as of January 1, 2022

		Sex		Age at diagnosis		Attained age				Treatment decade		
Organ system-specific CHCs	Overall	Female	Male	<15y	15y+	<30y	30-39y	40-49y	50y+	1970-1979	1980-1989	1990-1999
Any grade 1–4 CHC												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												
Any grade 3–4 CHCs												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												

Table 7: Similar to above, but subgroup by childhood cancer diagnosis.

Table 8: Estimates of the number of **siblings** alive with prevalent chronic health conditions, neurocognitive impairment, or functional impairment by sex, race, and attained age.

		Sex		Attained age			Race		
Chronic health conditions (CHCs): Overall and organ system-specific	Overall (N=)	Female (n=)	Male (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	White (n=)	Black (n=)	Other (n=)
Any grade 1–4 CHC									
Any grade 3–4 CHC									
Multiple (≥2) grade 1–4 CHCs									
Multiple (≥2) grade 3–4 CHCs									
Neurocognitive impairment	Overall (N=)	Female (n=)	Male (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	White (n=)	Black (n=)	Other (n=)
Any neurocognitive impairment									
Task efficiency domain									
Emotional regulation domain									
Organization domain									
Memory domain									
Functional impairment	Overall (N=)	Female (n=)	Male (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	White (n=)	Black (n=)	Other (n=)
Any mental or physical impairment (T-score<40)									

Note that denominators are the total number of survivors.

Table 9: Estimates of the **excess** number of 5-year survivors alive as of January 1, 2022 with prevalent chronic health conditions, neurocognitive impairment, or functional impairment

		Sex		Age at diagnosis		Attained age				Treatment decade		
		n (%)										
Chronic health conditions (CHCs): Overall and organ system-specific	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any grade 1–4 CHC												
Any grade 3–4 CHC												
Multiple (≥2) grade 1–4 CHCs												
Multiple (≥2) grade 3–4 CHCs												
Neurocognitive impairment	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any neurocognitive impairment												
Task efficiency domain												
Emotional regulation domain												
Organization domain												
Memory domain												
Functional impairment	Overall (N=)	Female (n=)	Male (n=)	<15y (n=)	15y+ (n=)	<30y (n=)	30-39y (n=)	40-49y (n=)	50y+ (n=)	1970-1979 (n=)	1980-1989 (n=)	1990-1999 (n=)
Any mental or physical impairment (T-score<40)												

Note that denominators are the total number of survivors.

Table 10: Similar to above but by childhood cancer diagnosis.

Table 11: Estimates of the total burden (number) of prevalent CHCs (overall and organ system-specific) among siblings by sex, attained age and race.

		Sex		Attained age				Treatment decade		
Organ system-specific CHCs	Overall	Female	Male	<30y	30-39y	40-49y	50y+	White	Black	Other
Any grade 1–4 CHC										
Cardiovascular										
Respiratory										
Gastrointestinal										
Reproductive										
Endocrine										
Renal										
Musculoskeletal										
Neurological										
Immunologic/infectious disease										
Hematology										
Auditory or ocular										
Second neoplasms										
Any grade 3–4 CHCs										
Cardiovascular										
Respiratory										
Gastrointestinal										
Reproductive										
Endocrine										
Renal										
Musculoskeletal										
Neurological										
Immunologic/infectious disease										
Hematology										
Auditory or ocular										
Second neoplasms										

Table 12: Estimates of the total burden (number) of prevalent CHCs (overall and organ system-specific) among 5-year survivors alive as of January 1, 2022

		Sex		Age at diagnosis		Attained age				Treatment decade		
Organ system-specific CHCs	Overall	Female	Male	<15y	15y+	<30y	30-39y	40-49y	50y+	1970-1979	1980-1989	1990-1999
Any grade 1–4 CHC												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												

		Sex		Age at diagnosis		Attained age				Treatment decade		
Organ system-specific CHCs	Overall	Female	Male	<15y	15y+	<30y	30-39y	40-49y	50y+	1970-1979	1980-1989	1990-1999
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												
Any grade 3–4 CHCs												
Cardiovascular												
Respiratory												
Gastrointestinal												
Reproductive												
Endocrine												
Renal												
Musculoskeletal												
Neurological												
Immunologic/infectious disease												
Hematology												
Auditory or ocular												
Second neoplasms												

Table 13: Similar to above, but subgroup by childhood cancer diagnosis.

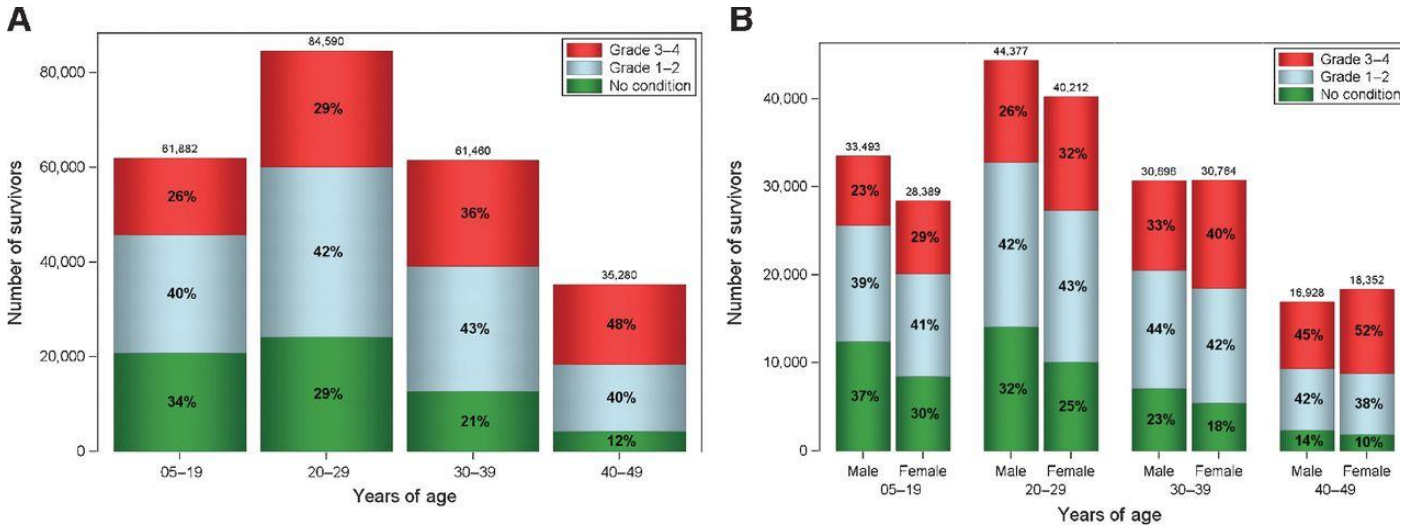

Figure 1: Stacked barplots of number (and proportion) of survivors with no CHCs versus any CHCs (grade 1-4 or grade 3-4) by:

a. Childhood cancer diagnosis group (similar to example A above, but not age subgroups)
b. Sex and attained age (similar to example B above)
c. Attained age and treatment decade (similar to example B above, but different subgroups)
d. Age at diagnosis and attained age (similar to example B above, but different subgroups)

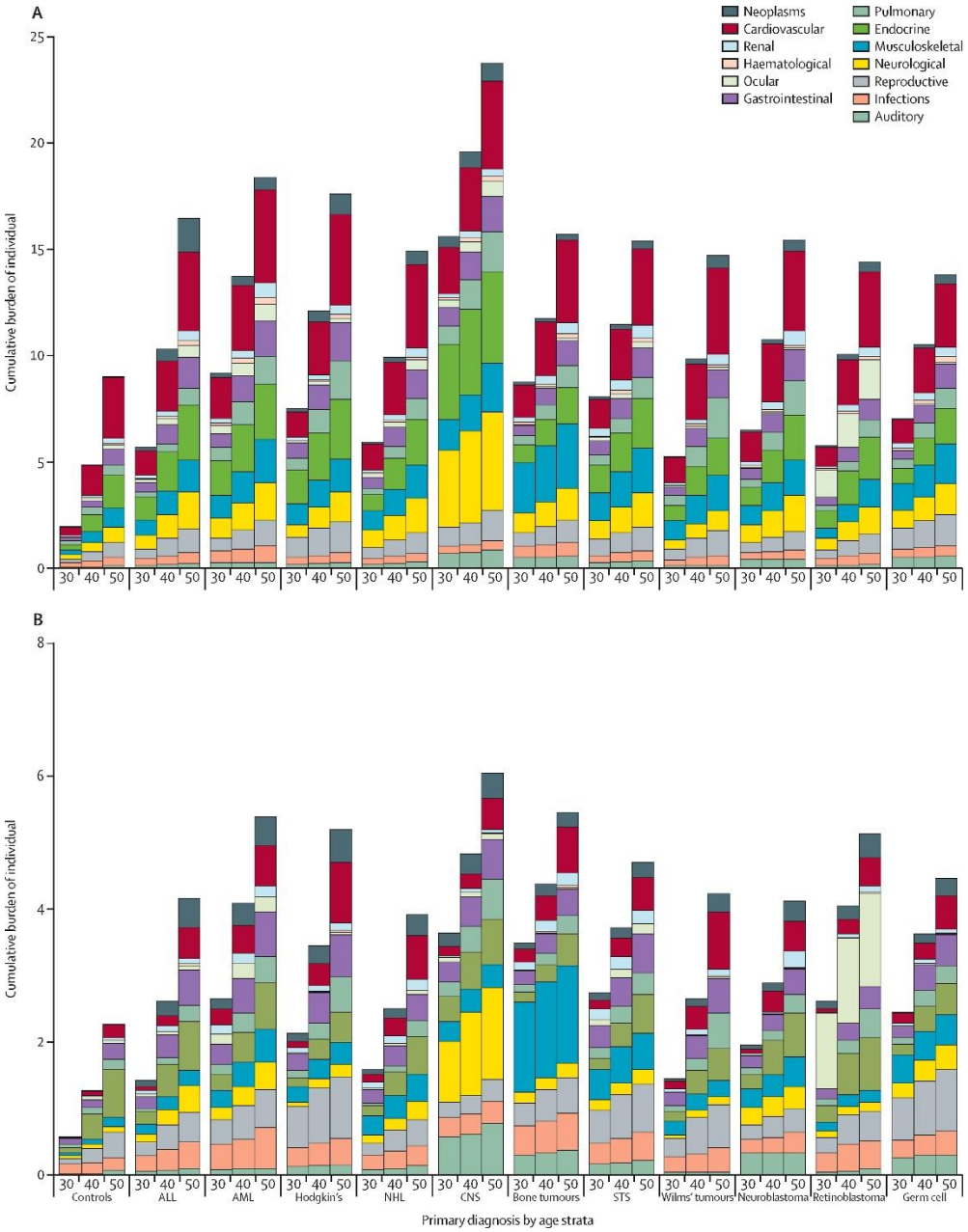

Figure 2: Stacked barplots of the <u>total</u> burden (number) of prevalent CHCs by organ system, attained age group, and primary diagnosis group (similar to example above, but y-axis is not cumulative burden)

a. Instead of primary diagnosis group, subgroup by treatment decade
b. Instead of primary diagnosis group, subgroup by age at diagnosis
c. Instead of primary diagnosis group, subgroup by sex

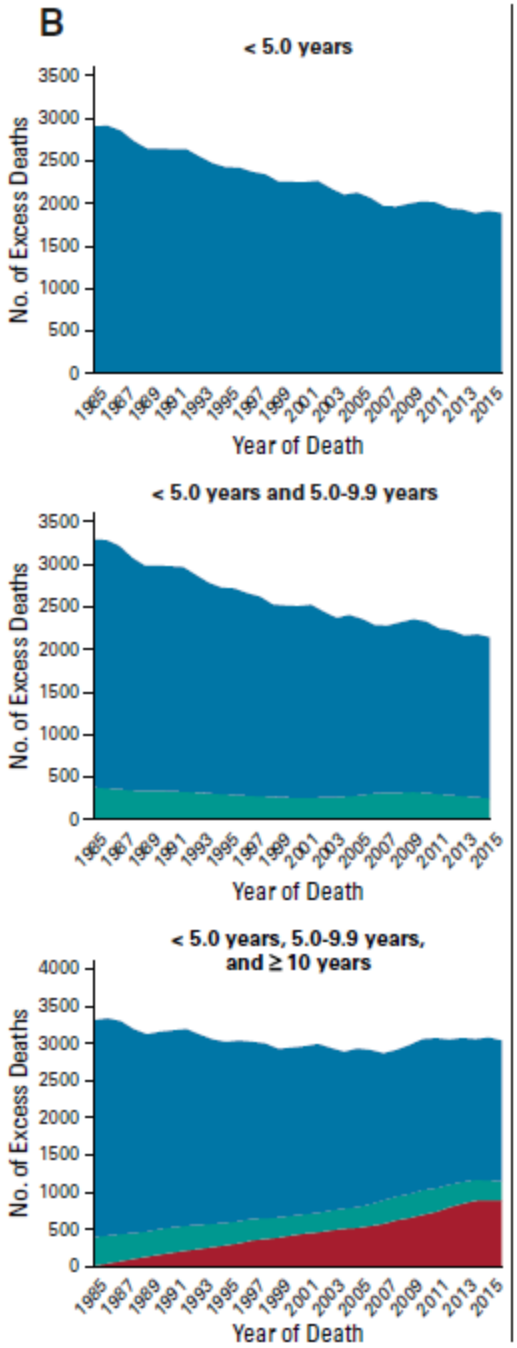

Figure 3: Estimated numbers of excess survivors with a morbidity according to attained age (rather than calendar year on the x-axis) by:

a. Years since diagnosis (similar to above)
b. Childhood cancer diagnosis group
c. Sex
d. Treatment Decade
e. Age at diagnosis

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