Analysis Concept Form

Project Title: Health care utilization by survivors of childhood cancer

Working group

- Cancer Control

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Background and Rationale

With improvements in treatment and supportive care, more than 80% of children diagnosed with cancer survive at least 5 years and become long-term survivors (1). However, late effects of childhood cancer are frequent and often serious. Compared to their siblings, survivors of childhood cancer are at a 3.3-fold elevated risk of developing a chronic condition and are 8.2 times more likely to develop a severe or life-threatening condition (2). The St Jude Lifetime Cohort Study (SJLIFE) recently reported that a childhood cancer survivor experiences, on average, 17.1 (95% CI 16.2-18.1) chronic health conditions of any grade by age 50 years. Of these, 4.7 (4.6-4.9) are of grade 3-5 (3). Chronic health conditions lead to increased utilization of health care resources with resultant economic impact on the survivors, their care providers, and the health care system.

Only a limited number of studies have explored the extent of health care services utilized by childhood cancer survivors compared to the general population (4-5), and many of these studies have been limited by sample size, incomplete information regarding treatment exposures, or a focus on only a single health service. Some studies have focused on hospitalization patterns and associated risk factors. The Childhood Cancer Survivor Study (CCSS) reported a survivor hospitalization rate that was 1.6 times (95% CI 1.6-1.7) that of the general population (6). Survivors of Hodgkin disease

had the highest hospitalization rate, twice that of the U.S. general population. Female gender, age less than 4 years at diagnosis, older age at follow-up, low income, radiation treatment, having a chronic health condition and/or a history of relapse or second malignancy were associated with an increased risk of non-obstetrical hospitalization. Studies in Utah (1,499 survivors), British Columbia (1,374 survivors), Scotland (5,229 survivors), and the Netherlands (1,382 survivors) showed similar trends of excess hospitalization, and some reported increased length of stay in those patients who were hospitalized (7-10). However, these studies were performed in relatively small cohorts. A more recent study from ALICCS (Scandinavia) that included 21,297 survivors showed an overall 2-fold risk of being hospitalized and longer hospital stays compared to the general population. Nervous, endocrine, digestive and respiratory system problems accounted for half of the admissions. Survivors of neuroblastoma, hepatic and central nervous system tumors as well as Hodgkin lymphoma had the highest risk (11). Although this study has a substantially larger cohort compared to others, lack of information about treatment precluded detailed analyses of the relationship between treatment factors and utilization. Another study from the Netherlands explored the risk and associated risk factors of hospitalization for neoplasms, circulatory diseases, endocrine/nutritional/metabolic diseases, and eye disorders among 1,382 survivors (12). Radiotherapy was associated with increased hospitalization rates for neoplasms; exposure to anthracycline and radiotherapy to the thorax and/or abdomen was associated with increased hospitalizations for diseases of the circulatory system; and radiotherapy to the head and/or neck was associated with increased of hospitalizations for endocrine/nutritional/metabolic diseases. Even though this study adds unique and important information about treatment-related risk factors for specific indications for hospitalization, it was limited by small sample size.

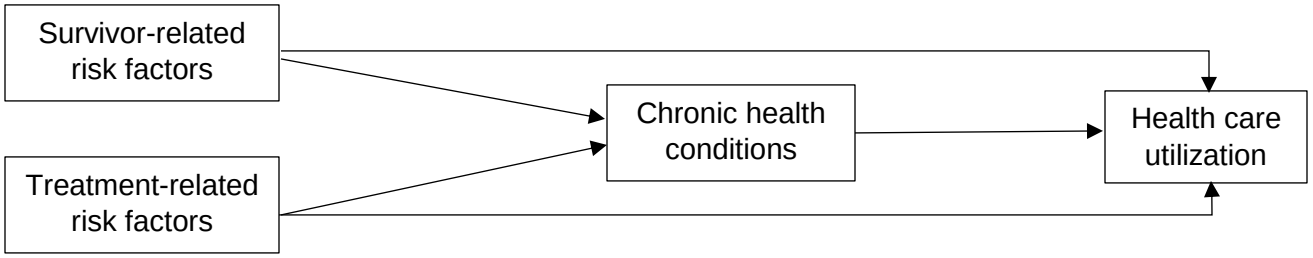
Even fewer studies have focused on emergency department (ED) visits. One study performed in Ontario, Canada showed that attendance at a specialized survivor clinic was significantly associated with decreased ED visits (13).

To our knowledge, no studies have presented data that describes all major types of health care use by describing outpatient physician visits, ED visits, and hospitalizations. The patient, disease, and treatment factors that impact health care utilization by survivors have not been fully elucidated. The link between the development of chronic health conditions and the use of health care resources has been established, but how other factors modify this relationship, and the impact of specific chronic health conditions on utilization require further investigation. For example, the Ontario study of ED use demonstrated that increased rates of ED visits were associated with living in rural areas. This may be due to the fact that people residing in rural areas have fewer

alternatives for after-hours care, such as walk-in clinics, and often use ED services instead of primary care (13).

This study will be the first to provide a detailed picture of the consumption of health services by childhood cancer survivors. Given the growing number of survivors and their burden on the health care system, increasing our knowledge about their use of health services is important for planning allocation of health system resources, and will guide the development of initiatives to support survivors who have a higher burden of health care needs.

Proposed relationship between survivor and treatment related risk factors and health care utilization



Specific aims

1. Describe health care utilization patterns for outpatient physician visits, ED visits, and hospitalizations among childhood cancer survivors as compared to their siblings.

2. Assess variation in health care utilization by survivor, cancer, treatment, and chronic condition characteristics.

Hypotheses

We hypothesize that:

1. Physician visits, ED visits and hospitalizations will all be increased among childhood cancer survivors as compared to their siblings.

2. a) Survivor factors that will predict higher use of health care services in general will include younger age at diagnosis, older age at questionnaire, female gender, lower income, lower education level, having insurance coverage, tobacco use, excessive alcohol intake, and obesity.

b) Cancer diagnosis types that will be associated with higher frequency in use of health care services will include brain tumors and Hodgkin lymphoma.
c) Treatment factors that will be associated with higher frequency in use of health care services in general will include combined modality treatment, any radiation exposure, high cumulative anthracycline dose exposure, and high cumulative alkylator exposure.
d) Grade 3-4 chronic health conditions or multiple chronic health conditions will increase frequency in use of health services in general, particularly disorders of the heart and circulatory system, the brain and nervous system, the respiratory system, and the endocrine system.
e) Increased utilization of follow-up by primary care provider and/or cancer survivor clinics will be associated with a decrease in the frequency of ED visits and/or hospitalizations.
f) Having a cancer survivorship care plan in possession of survivor's primary care doctor will be associated with fewer ED visits and hospitalizations.
g) Some survivor and treatment related risk factors will be associated with an increased use of outpatient physician and ED visits independent of the development of chronic health conditions:
    - Lower education level and lower socioeconomic status will be associated with fewer outpatient visits but more ED visits and hospitalizations.
    - Anthracycline and radiation use will be associated with more outpatient and inpatient visits.
    - Living in a rural location will be associated with more ED visits and fewer outpatient visits.

Methods

<u>Subject population to be included:</u>

- Cases: Original and Expansion Cohort survivors who completed follow-up survey #5
- Controls: Original and Expansion Cohort siblings who completed follow-up survey #5

<u>Outcomes of interest:</u>

1. Health care utilization patterns (all from FU5):
    a. Physician visits: We will assess this by using 3 different outcomes. First, we will assess each type of doctor visit (primary care clinician, clinician at a cancer center, other medical specialist, psychiatrist) during a 2-year period by using binary variables (yes/no) and compare it to siblings. Second, we will assess the total number of doctor visits during a 2-year period by using categorical

variables (none, 1-2, 3-4, 5-6, 7-10, 11-20, more than 20) and compare it to siblings. Third, we will assess the total number of doctor visits related to previous cancer during a 2-year period by using categorical variables (none, 1-2, 3-4, 5-6, 7-10, 11-20, more than 20). We will likely further regroup the categories or define a high vs low use binary variable. However, we would like to see the distribution before deciding on a specific cut-off. [Survivors B1-B3; Siblings B1-B2]

b. Emergency department (ED) visits: number of ED visits during a 12-month period. This is a continuous variable. We will then calculate ED visits rates as ED visits per 1,000 person-years for survivors and their siblings. [Survivors B6; Siblings B3]

c. Non-obstetric hospitalizations: number of admissions to a hospital in a 12-month period [U1-U4c]. This is a continuous variable. We will then calculate hospitalization rates as hospitalizations per 1,000 person-years for survivors and their siblings. Subsequently, we will evaluate the reason for hospitalization as per International Classification of Diseases – Version 10 (ICD-10). We will divide indications for hospitalization into the following ICD-10 groupings:

- infectious diseases;
- neoplasms;
- diseases of the blood, blood-forming organs and certain disorders involving the immune mechanism;
- endocrine, nutritional and metabolic diseases;
- mental and behavioral disorders;
- diseases of the nervous system;
- diseases of the eye and adnexa;
- diseases of the ear and mastoid process;
- diseases of the circulatory system;
- diseases of the respiratory system;
- diseases of the digestive system;
- diseases of the skin and subcutaneous tissue;
- diseases of the musculoskeletal system and connective tissue;
- diseases of the genitourinary system;
- Injury, poisoning, and external causes.

We will then calculate cause-specific hospitalization rates as hospitalizations per 1,000 person-years for survivors and their siblings. In the eventuality that siblings' data are too scarce for some categories, we may consider using data from the general population as our comparison group for this outcome. In this case, we plan to use the National (Nationwide) Inpatient Sample (NIS), a derivative dataset developed by the Healthcare Cost and Utilization Project (HCUP) using State Inpatient Databases (SID) data. Data are available for 2015 (14, 15).

Correlative Factors:

2. Variation in health care utilization by survivor, cancer, treatment, chronic condition characteristics and other possible correlative factors (the final selection of variables and their categorization will depend on data available) (all from FU5):
   a. Survivor characteristics:
      - Sociodemographic characteristics:
        - age at diagnosis
        - attained age at questionnaire
        - race
        - sex
        - living location (rural versus non-rural)
        - health insurance coverage (only 3 levels of insurance coverage were collected on the follow-up survey #5: Canadian resident, American No, American Yes) [A10]
        - marriage status [M1-M3]
        - level of education [A4]
        - employment status (defined as “employed/retired” if “working full-time” or “working part- time” or “caring for home / not seeking paid work” or “retired” or “student”; defined as “unemployed, looking” if “unemployed and looking for work”; defined as “disabled” if “unable to work due to illness or disability”) [A5-A6]
        - household income [A7-A9])
      - Health habits:
        - chronic alcohol intake (yes or no) defined as heavy drinking (men >6 drinks per day, at least once per month, women >5 drinks per day, at least once per month) and/or risky drinking (men >4 drinks per day or 14 drinks per week, women >3 drinks per day or 7 drinks per week) [N1-N6]
        - tobacco use (never, past, current) [N7-N14]
        - body mass index (underweight <18.5 kg/m2, normal 18.5-24.9 kg/m2, overweight 25.0-29.9 kg/m2, obese ≥30 kg/m2) [A1-A2])
      - Health status:
        - general health (fair or poor vs. good, very good or excellent) [O1]
        - mental health (score of 63 or higher on the brief symptom inventory on any of the three subscales vs. no score of

63 or higher on any of the three subscales of the Brief Symptom Inventory) [L1-L18]
- functional impairment (yes vs. no to any of the three questions) [N25-N27]
- activity limitations (limited for more than three months over the past two years vs. limited for 3 months or less/not limited at all to any of the questions) [N29]
- anxiety (very many, a lot, or medium amount of extreme anxiety/fears vs. no or small amount of anxiety/fears) [Survivors L19]
- pain (very bad, a lot, or medium amount of pain vs. no or small amount of pain) [Survivors L20]

b. Cancer diagnosis: Hodgkin's lymphoma, CNS tumor, soft tissue sarcoma, bone tumor, Non-Hodgkin's lymphoma, neuroblastoma, Wilms' tumor, leukemia
c. Treatment exposure:
    - treatment modalities (No chemotherapy, no radiation therapy (+/- surgery), chemotherapy (+/- surgery), radiation therapy (+/- surgery), chemotherapy + radiation therapy (+/- surgery))
    - cardiotoxic therapies (anthracyclines without chest radiation therapy (RT), chest RT without anthracyclines, anthracyclines + chest RT)
    - anthracycline cumulative dose exposure (doxorubicin equivalent dose: none; 0 - <250 mg/m^2; ≥250 mg/m^2)
    - alkylator (cumulative cyclophosphamide equivalent: <4g/m^2; ≥4 - <8 g/m^2; ≥8 g/m^2) (16)
    - bleomycin exposure (yes, no)
    - platinum exposure (yes, no)
    - irradiated area (brain, neck, chest, abdomen/pelvis, total body irradiation (TBI), other, none, unknown)
    - treatment era (1970-79; 1980-89; 1990-99)
d. Severe-life threatening (grade 3-4) chronic conditions (previously graded according to Common Terminology Criteria for Adverse Events (CTCAE v5.0)): We will analyze the data in 2 ways. First, we will use all grade 3-4 chronic conditions reported on or before FU5 to assess the impact of both prevalent conditions and incident conditions that occurred prior to survey completion, including the 1-2 years prior to the survey. Second, we will evaluate only those conditions that developed prior to the 2-year time window for physician visits and prior to the 12-month time window for ED visits and hospitalization. This will allow focus on care of existing conditions, and not care needed to diagnose new

conditions. One of the limitations of our study is that we may underestimate some health care utilization by not counting patients who died with chronic conditions prior completing the follow-up survey #5, but who used health care resources in the period immediately prior to the survey's release. Classes of conditions we will examine include:

- all severe-life threatening chronic conditions (3-4) (yes, no);
- total number of severe/life threatening chronic conditions (3-4);
- severe-life threatening (grade 3-4) organ specific chronic diseases (hearing/vision/speech, urinary system, heart and circulatory system, hormonal system, respiratory system, digestive system, surgical procedures, brain/nervous system) (yes, no for each category)

e. Second malignancy or relapse (yes, no) [S1]
f. Having a cancer survivorship care plan
   - In possession of the survivor (yes, no) [B7];
   - In possession of survivor's local or primary care doctor (yes, no/don't have a primary care doctor) [B8]

Analytic approach:

We will conduct two types of analysis for each health care use outcome: external (in which we compare outcomes between survivors and siblings); and internal (in which we investigate explanatory factors associated with health care use by childhood cancer survivors).

- External analysis:
  a. We will evaluate the proportion with at least one physician visit. Rate ratios (RRs) and associated 95% confidence intervals (CI) comparing proportion of individuals using physician visits between survivors and siblings will be calculated by using a multivariable generalized linear regression models, most likely with a log-link function and Poisson error structure (due to expected high prevalence of outcomes). For physician visits categorized count data, we will evaluate distributions of responses and determine whether to construct binary variables (high/low) or use ordinal outcomes in a proportional odds model. Either way, odds ratios (ORs) and associated 95% confidence intervals will be reported.
  b. We will evaluate ED visits and hospitalizations rates as ED visits per 1,000 person-years and hospitalizations per 1,000 person-years, respectively. We will then evaluate specific health problem related hospitalization rates

as hospitalizations per 1,000 person-years for survivors and their siblings. In the eventuality that siblings' data are too scarce for some of the health problem related hospitalization categories, we may consider using data from general population as our comparison group for this outcome. Relative rates with corresponding 95% confidence intervals (CIs) and absolute excess risks (AERs) per 1,000 person-years will be calculated to compare survivor rates to their siblings using Poisson regression models. Each subject will contribute 1 year to the analysis time, the time frame for which the survey question assesses visits.

c. All models will be adjusted for attained age and sex. We will examine whether stratification by attained age and/or sex are necessary to adequately summarize the data by testing for interactions between survivor/sibling and these variables.

- Internal analysis:

  To identify risk factors/predictors for each of the different health care utilization outcomes among childhood cancer survivors, we will assess potential associations by using similar models as those described above for each outcome (log-linear and Poisson models) but restricted to the survivor population. The potential explanatory factors for health care use are: cancer diagnosis, treatment exposure (though cancer diagnosis and treatment will not be included in the same model, due to high collinearity), chronic conditions, health habits, health status as well as some sociodemographic characteristics, all defined above under Correlative Factors. We will also explore potential associations between certain types of health care use, such as whether higher numbers of physician visits are associated with lower rates of ED visits. For this, we will utilize number of physician visits as a covariate for evaluation in the model for ED visit rates. We will also try to perform more detailed analyses of hospitalization patterns among childhood cancer survivors by exploring which treatment and survivor related factors possibly influence hospitalization rates for specific reasons of hospitalization. All analyses will be adjusted for attained age and sex.

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Examples of tables and figures

Table 1: Demographics and clinical characteristics among childhood cancer survivors and their siblings

	Childhood cancer survivors (N=)		Siblings (N=)		
Characteristic:	**N**	**%**	**N**	**%**	**P-value**
Current age (years):					
<18					
18-24					
25-34					
35-44					
≥45					
Gender:					
Male					
Female					
Race/Ethnicity:					
White, non-Hispanic					
Black, non-Hispanic					
Hispanic					
Other					
Education:					
<High School					
High School Graduate					
College Graduate					
Unknown					
Employment:					
Employed/retired					
Unemployed/looking					
Disabled					
Household income:					
< $40,000					
$40,000-79,999					
≥$80,000					
Unknown					
Insurance Coverage:					
Canadian resident					
American yes					

American no						
Marital Status:						
Married						
Single						
Divorced or separated						
Unknown						
Living Location:						
Rural						
Non-rural						
Cancer Diagnosis:						
Leukemia • ALL • AML • Other						
CNS tumor • Medulloblastoma/PTEN • Astrocytoma • Other						
Lymphoma • Hodgkin lymphoma • Non-Hodgkin lymphoma						
Bone • Osteosarcoma • Ewing sarcoma • Other						
Wilms tumor						
Neuroblastoma						
Soft tissue sarcoma						
Unknown						
Age at Diagnosis (years):						
0-4						
5-9						
10-14						
15-19						
Tobacco Use:						
Never						
Past						
Current						

Chronic Alcohol Intake:					
Yes					
No					
Body Mass Index:					
Underweight <18.5 kg/m^2					
normal 18.5-24.9 kg/m^2					
overweight 25.0-29.9 kg/m^2					
obese ≥30 kg/m^2					
Treatment Modalities:					
No chemotherapy, no radiation therapy (+/- surgery)					
Chemotherapy (+/- surgery)					
Radiation therapy (+/- surgery)					
Chemotherapy + radiation therapy (+/- surgery)					
Radiation Fields:					
Brain					
Neck					
Chest					
Abdomen/pelvis					
TBI					
Other					
None					
Unknown					
Cardiotoxic Therapies:					
Anthracyclines, no chest RT					
Chest RT, no anthracyclines					
Anthracyclines + chest RT					
No anthracyclines, no chest RT					
Anthracyclines (Cumulative Doxorubicin Equivalent Dose)					
None					
>0 - <250 mg/m^2					
≥250 mg/m^2					

Cumulative Cyclophosphamide Equivalent Dose:					
None					
>0 - <4g/m^2					
≥4 - <8 g/m^2					
≥8 g/m^2					
Platinum Exposure:					
Yes					
No					
Bleomycin Exposure:					
Yes					
No					
Treatment Era:					
1970-79					
1980-89					
1990-99					
Health Status - General Health					
Fair or poor					
Good, very good, excellent					
Health Status - Mental Health					
Poor					
Not poor					
Health Status – Functional Impairment					
Yes					
No					
Health Status – Activity Limitations					
Limited for more than 3 months					
Limited for 3 months or less or not limited at all					
Health Status – Anxiety					
very many, a lot, or medium amount of extreme anxiety/fears					

no or small amount of anxiety/fears			[redacted]		
Health Status – Pain					
very bad, a lot, or medium amount of pain					
no or small amount of pain					
Chronic Conditions:					
Any grade 3-4 conditions • Yes • No					
Number of conditions of grade 3-4 (median, range)					
Specific types of chronic conditions (grade 3-4) • Hearing/vision/speech o Yes o No • Urinary system o Yes o No • Heart and circulatory system o Yes o No • Hormonal system o Yes o No • Respiratory system o Yes o No • Digestive system o Yes o No • Surgical procedures o Yes o No • Brain/nervous system o Yes o No					

Second malignancy or relapse • Yes • No					

Table 2: Proportions of each type of physician visits for childhood cancer survivors and their siblings over a 2-year period*

	Childhood Cancer Survivors		**Siblings**		
Physician visits over a 2-year period	**N**	**%**	**N**	**%**	**Rate ratio**
Primary care clinician					
Clinician at a cancer center					
Other medical specialist					
Psychiatrist					

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 3: Number of all physician visits for childhood cancer survivors and their siblings over a 2-year period*

	Childhood Cancer Survivors		Siblings		
	N	**%**	**N**	**%**	**P-value**
Number of physician visits over a 2-year period:					
None					
1-2 times					
3-4 times					
5-6 times					
7-10 times					
11-20 times					
>20 times					
Number of physician visits related to cancer over a 2-year period:					
None					
1-2 times					
3-4 times					
5-6 times					
7-10 times					
11-20 times					
>20 times					

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 4: Proportions of all physician visits regrouped in 2 categories depending on the frequency (high versus low) for childhood cancer survivors and their siblings over a 2-year period (cut-off will depend on the data distribution)*

	Childhood Cancer Survivors		Siblings		
	N	**%**	**N**	**%**	**Rate ratio**
Number of physician visits over a 2-year period:					
High					
Low					
Number of physician visits related to cancer over a 2-year period:					
High					
Low					

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 5: Emergency department (ED) visit rates for childhood cancer survivors and their siblings over a 1-year period*

	Childhood Cancer Survivors			Siblings				
	PY	**ED visits**	**Rate per 1,000 PY**	**PY**	**ED visits**	**Rate per 1,000 PY**	**Relative Rate (95% CI)**	**AER per 1,000 PY**
All survivors								

PY = person-years

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 6: Non-obstetric hospitalization rates for childhood cancer survivors and their siblings over a 1-year period*

	Childhood Cancer Survivors			Siblings				
	PY	Hospitalizations	Rate per 1,000 PY	PY	Hospitalizations	Rate per 1,000 PY	Relative Rate (95% CI)	AER per 1,000 PY
All survivors								

PY = person-years

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 7: Health problem related hospitalization rates for childhood cancer survivors and their siblings over a 1-year period*

	Childhood Cancer Survivors			Siblings				
Health problem	PY	Hospitalizations	Rate per 1,000 PY	PY	Hospitalizations	Rate per 1,000 PY	Relative Rate (95% CI)	AER per 1,000 PY
Infectious								
Neoplasms								
Blood, blood forming organs and immune mechanism								
Endocrine, nutritional								

and metabolic								
Mental and behavioral								
Nervous								
Eye and adnexa								
Ear and mastoid process								
Circulatory								
Respiratory								
Digestive								
Skin and subcutaneous tissue								
Musculoskeletal and connective tissue								
Genitourinary								
External causes								

PY = person-years

According to ICD-10 classification

*Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 8: Survivor Characteristics as predictors for Health care utilization by types of services in CCSS Survivors (multivariable model)*

	Physician visits		**ED visits**		**Hospitalizations**	
	Rate ratio (95% CI)	p-value	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Age at diagnosis (years)						

Current age (years)						
Gender Male Female						
Race/Ethnicity: White, non-Hispanic Black, non-Hispanic Hispanic Other						
Household Income <$40,000 $40,000-79,999$ ≥$80,000						
Educational status <High School High School Graduate College Graduate Unknown						
Employment: Employed/retired Unemployed/looking Disabled						
Insurance Coverage: Canadian American American None						
Tobacco use Never Past Current						
Chronic alcohol use Yes No						
Body Mass Index Underweight Normal						

Overweight Obese						
Health Status - General Health Fair or poor Good, very good, excellent						
Health Status – Activity Limitations Limited for more than 3 months Limited for 3 months or less or not limited at all						
Health Status – Anxiety very many, a lot, or medium amount of extreme anxiety/fears no or small amount of anxiety/fears						
Health Status – Pain very bad, a lot, or medium amount of pain no or small amount of pain						

* This analysis will be done with and without chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions. Depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 9: Comparison of Health care utilization of each type of services between Cancer Diagnosis Groups in CCSS Survivors (multivariable model)*

	Outpatient visits		**ED visits**		**Hospitalizations**	
Cancer diagnosis	Rate ratio (95% CI)	p-value	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Leukemia						
CNS tumor						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Bone sarcoma						
Wilms tumor						
Neuroblastoma						
Soft tissue sarcoma						
Unknown						

* Adjusted for attained age and sex or depending on modelling results, analyses may be stratified on attained age and/or sex.

** This analysis will be done with and without adjusting for chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions.

Table 10: Treatment Characteristics as Predictors for Health care utilization by types of services in CCSS Survivors (multivariable model)
(All factors below will not be included together in a single model as there would be collinearities – these are candidate variables for assessment for a multivariable model).

	Physician visits		**ED visits**		**Hospitalizations**	
	Rate ratio (95% CI)	p-value	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Treatment modalities • No chemotherapy, no radiation therapy (+/- surgery) • Chemotherapy (+/- surgery) • Radiation therapy (+/- surgery) • Chemotherapy + radiation therapy (+/- surgery)						
Cardiotoxic treatment • Anthracyclines, no chest RT • Chest RT, no anthracyclines • Anthracyclines + chest RT • No anthracyclines, no chest RT						
Anthracycline exposure • None • >0 - <250 mg/m2 • ≥250 mg/m2						
Alkylator exposure						

• None • >0 - <4g/m2 • ≥4 - <8 g/m2 • ≥8 g/m2						
Bleomycin exposure Yes No						
Platinum exposure Yes No						
Radiation Fields: Brain Neck Chest Abdomen/pelvis TBI Other None Unknown						
Treatment era 1970-79 1980-89 1990-99						

* Adjusted for sex, attained age or depending on modelling results, some analyses may be stratified on attained age and/or sex.

** This analysis will be done with and without adjusting for chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions.

Table 11: Chronic conditions as Predictors for Health care utilization by types of services in CCSS Survivors (multivariable model)
(All factors below will not be included together in a single model – each will be examined in an adjusted model and only those that are sensible to include together would be combined (i.e types of chronic conditions)).

	Outpatient visits		**ED visits**		**Hospitalizations**	
	Rate ratio (95% CI)	p-value	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Any chronic conditions grade 3-4 Yes No						
Number of chronic conditions grade 3-4						
Specific types of chronic conditions grade 3-4 Hearing/vision/speech Yes No Urinary system Yes No Heart and circulatory system Yes No Hormonal system Yes No Respiratory system Yes No Digestive system Yes						

No						
Surgical procedures						
Yes						
No						
Brain/nervous system						
Yes						
No						

* Adjusted for sex, attained age or depending on modelling results, analyses may be stratified on attained age and/or sex.

Table 12: Other Predictors for Health care utilization by types of services in CCSS Survivors (multivariable model)
(All factors below will not be included together in a single model as there would be collinearities – these are candidate variables for assessment for a multivariable model).

	Outpatient visits		**ED visits**		**Hospitalizations**	
	Rate ratio (95% CI)	p-value	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Second malignancy or relapse						
Yes						
No						
Cancer survivorship care plan in possession of the survivor						
Yes						
No						
Cancer survivorship care plan in possession of survivor's primary care doctor						
Yes						
No/Don't have a primary care doctor						

* Adjusted for sex, attained age or depending on modelling results, analyses may be stratified on attained age and/or sex.
** This analysis will be done with and without adjusting for chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions.

Table 12: Physician visits as Predictor for Health care utilization by types of services in CCSS Survivors (multivariable model)

	ED visits		**Hospitalizations**	
	Relative rate (95% CI)	p-value	Relative rate (95% CI)	p-value
Number of physician visits over a 2-year period				
High				
Low				

* Adjusted for sex, attained age or depending on modelling results, analyses may be stratified on attained age and/or sex.
** This analysis will be done with and without adjusting for chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions.

Table 13: Multivariable models of risk factors for hospitalization for most frequent specific reasons of hospitalizations within childhood cancer survivors (example of specific reasons…)

	Circulatory system		**Respiratory system**		**Neoplasm**	
	Relative rate	**95% CI**	**Relative rate**	**95% CI**	**Relative rate**	**95% CI**
Attained age (years)						
Age at diagnosis (years)						
Gender: Male Female						
Tobacco use: Never Past Current						
Chronic alcohol use: Yes No						
Body Mass Index: Underweight Normal Overweight Obese						
Cancer diagnosis: Leukemia CNS tumor Hodgkin lymphoma Non-Hodgkin lymphoma Bone sarcoma Wilms tumor Neuroblastoma Soft tissue sarcoma						

Unknown						
Anthracycline exposure: None >0 - <250 mg/m2 ≥250 mg/m2						
Alkylator exposure: None >0 - <4g/m2 ≥4 - <8 g/m2 ≥8 g/m2						
Bleomycin: Yes No						
Platinum: Yes No						
Treatment modalities: • No chemotherapy, no radiation therapy (+/- surgery) • Chemotherapy (+/- surgery) • Radiation therapy (+/- surgery) • Chemotherapy + radiation therapy (+/- surgery)						
Cardiotoxic treatment: • Anthracyclines, no chest RT • Chest RT, no anthracyclines						

• Anthracyclines + chest RT • No anthracyclines, no chest RT						
Radiation Fields: Brain Neck Chest Abdomen/pelvis TBI Other None Unknown						
Cancer survivorship care plan in possession of the survivor Yes No						
Cancer survivorship care plan in possession of survivor's primary care doctor Yes No/Don't have a primary care doctor						

* Adjusted for sex, attained age or depending on modelling results, analyses may be stratified on attained age and/or sex.

** This analysis will be done with and without adjusting for chronic conditions to assess if certain factors can have an impact on health care utilization independently from influencing chronic conditions.