Childhood Cancer Survivor Study
Analysis Concept Proposal
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Title:

Long-term outcomes after childhood cancer in infancy, health status and chronic conditions: a report from the Childhood Cancer Survivor Study

Working group and Investigators:

The proposed study will be conducted within the Chronic Disease Working Group. Proposed investigators include:

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Background and Rationale:

Advances in the treatment of childhood cancer have resulted in dramatic increases in survival. However, survivors of childhood cancer have been found to have high rates of chronic illnesses and are at risk for adverse health status.[1] [2] In a previous report from the Childhood Cancer Survivor Study (CCSS), Hudson *et al*. noted that adult survivors of childhood cancer have decreased health status compared to sibling controls across a number of domains including general health, mental health, functional status, and activity limitations.[2] Oeffinger *et al*. reported an increased frequency of chronic illnesses in survivors compared to sibling controls.[1] Ness *et al*. reported in detail on functional limitations across the CCSS cohort, and documented an increased self-report of functional limitations in survivors.[3] Indeed, as the number of childhood cancer survivors grows, it becomes increasingly important to understand the impact of cancer and its therapy. Such an understanding would inform future interventions aimed at decreasing the risk of sequelae and the planning of medical and educational services for survivors.

Proposed is an assessment of survivorship after malignancy in a particular subset of the CCSS cohort, those diagnosed in infancy at less than one year of age, with attention to health status and chronic morbidities. Infancy is a period marked by increases in constitutional growth, the continued development of organ systems including the nervous and pulmonary systems, and the achievement of a rapid succession of developmental milestones. Normal growth and development can be negatively impacted by various disease states, including malignancy.[4] Management of malignancy in this extreme of the pediatric age-range poses particular challenges and infants have been found to have increased risk of acute toxicities from certain therapies. For example, excessive vincristine related neuro-toxicity has been documented in infants undergoing leukemia treatment, increased myelosuppression in infants with Wilms' tumor resulted in the

recommendation for dose reduction of several chemotherapeutic agents in this age group, and an increased risk of hepatopathy with vincristine, dactinomycin, and cyclophosphamide in patients treated for rhabdomyosarcoma at young age has been described.[5] [6] [7] Just as there is concern for high risk of acute toxicities, there is, as well, concern regarding the long-term sequelae for those treated in infancy. However, when faced with caring for survivors treated at very young age, there is little reported that focuses in detail on this potentially vulnerable group.

There are several compelling reasons to examine the infant population. While malignancy in infancy is rare, there has been some suggestion that the incidence has been increasing. Gurney *et al*. utilized population-based data from the Surveillance, Epidemiology, and End Results (SEER) Program and estimated an overall average annual cancer incidence rate of 223 cases per 1 million infants. The greatest proportion of cases was diagnosed in the first month of life (12%). The most common infant malignancies in this report included extracranial neuroblastoma, followed by leukemias, brain and central nervous system tumors, and retinoblastoma. They reported an increase in incidence rates over the study period (1973 to 1992), with an average annual percent increase in rates for all cancers of 2.9%.[8] Kenney *et al*. also described increasing rates of cancers in infancy, utilizing data from the SEER program and from the U.S. Bureau of the Census. They reported that the rate of cancer in infants increased by 15% from 1980-1990, largely due to increased rates of CNS tumors, neuroblastoma, retinoblastoma, and teratomas.[9]

In addition, among cancers of the same histology, infants can demonstrate unique epidemiologic, clinical, and biologic features. For example, infant acute lymphoblastic leukemia (ALL) represents approximately 4% of leukemias in children. ALL in infancy is associated with high white blood cell count and organomegaly at presentation, as well as the presence of MLL gene (11q23) rearrangements, all adverse prognostic features. Indeed, while the outcome of older children with ALL has improved to 80-85% event-free survival (EFS), infants with ALL have much lower EFS at 30-40%, even with use of intensive therapies.[10] [11] In neuroblastoma, on the other hand, infants can have more favorable biologic features when compared to neuroblastoma in older children.[5]

Finally, as noted above, certain therapies for childhood cancer may have particular risk for long-term morbidities for those treated in the infant period. Cranial radiation in the very young child is known to have significant toxicity, and this knowledge has resulted in the attempt to decrease its use in the youngest patients.[12] The impact of other therapies used for the treatment of childhood cancers in the infant period on long-term outcomes could be more fully explored. For example, the use of even low-dose abdominal radiation, intrathecal chemotherapy, chemotherapeutic agents such as high dose cytarabine and platinum agents, and modalities such as hematopoietic stem cell transplantation, may have increased risk for the very young patient. A focused evaluation of outcomes including long-term health-status and chronic illness in patients with malignancy in infancy with regard to particular diagnosis and treatment received would be of value for survivors and families, as well as for providers caring for survivors of cancer in infancy.

The CCSS was established as a resource for investigating the long-term outcomes of a cohort of 5-year survivors of childhood cancer, diagnosed from 1970-1986. The CCSS cohort has over 14,000 active participants, including survivors of leukemia, brain tumors, Hodgkin disease (HD), non-Hodgkin lymphoma (NHL), Wilms' tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. Study participants have provided self-reported health-related information. There were 1,004 participants diagnosed with cancer at less than one year of age. In this group, 52.2% had an underlying diagnosis of neuroblastoma, 18.3% Wilms' tumor, 6.5% brain tumor, 9.4% leukemia, 9.4% soft tissue sarcoma, 1.1% NHL, and 0.2% with a diagnosis of bone tumor.

The goal of this manuscript is to aid health care providers in understanding long-term risks and outcomes for those with cancers in infancy when dealing with patients with new diagnosis and in follow-up. While this group has been included in other analyses from the CCSS, few reports have specifically addressed this population and a detailed overview would be a unique contribution to the literature. Indeed, the severity of outcomes and the quality of survivorship of patients diagnosed with cancer in infancy have not been comprehensively explored across the CCSS cohort. Included will be survivors with completed baseline CCSS surveys who were less than one year of age at the time of their initial cancer diagnosis. This will include those who were over 18 years of age when they completed the baseline survey, as well as those who were less than 18 years of age with a parent completed proxy survey. For the majority of analyses, as described below, the most meaningful control group for establishing relative risks will be siblings. We also plan to include parallel comparisons with those aged 1-1.99 years (N = 1005) at diagnosis and those 2-10 years (N = 7442) at diagnosis. In particular these groups will be used for the analyses addressing treatment risk factors.

Comparisons will be made, as well, using the previously described overall increased risk of adverse health status and chronic health conditions. Of note, Hudson *et al.*, reported 44% of survivors had at least one adverse health status domain, which was true as well for those in the 0-4 year age group. The infant group was not reported separately. We do note that in their analysis, survivors age 35 years or older were more likely to report adverse outcomes in general health, functional status, activity status, or pain as a result of cancer or its treatment, than younger survivors (age 18-24 years.)[2] Oeffinger *et al.* reported an adjusted relative risk of a chronic condition in survivors compared to siblings of 3.3 (95% CI 3.0 to 3.5), and of 8.2 (95% CI 6.9 to 9.7) for a severe or life-threatening condition. They noted that survivors diagnosed at older age were more likely to report chronic health conditions.[1] Based on these results, we recognize that those diagnosed in infancy may not have higher increased risk of chronic health conditions overall when compared to the CCSS cohort as a whole, but believe, nonetheless, that a detailed assessment of this group will be informative. Factors associated with adverse outcome for those at this extreme of the pediatric age range have not been addressed and those with completed questionnaires at less than 18 years of age have not been included in prior analyses of health status or chronic health conditions.

Prior analyses of the CCSS cohort, completed and ongoing, do, in part, address survivorship of malignancy in infancy, and we will take care not to overlap with these analyses. In the analysis of neuroblastoma survivors by Laverdiere *et al*., diagnosis of neuroblastoma at less than one year of age was an independent risk factor for neurologic complications. Our assessment of neurologic outcomes in infants will also utilize a sibling control group. In other analyses, neurocognitive outcomes will be considered with attention to age, though separate consideration of the infant population is not noted. This manuscript will not separately assess neurocognitive status. We plan to report on the use of special educational services in those diagnosed in infancy (less than one year of age) compared to siblings (previously reported with youngest ages grouped as 0-5 years of age.)[13] By considering only those less than one year of age at diagnosis compared to siblings, our analysis will be careful to avoid overlap with a proposal considering the 0-2 year age-group compared to the 3-6 year age-group with regard to school functioning. For those who completed the baseline survey at less than 18 years of age, as a marker of social function, we plan to assess parent report of close friendships in the survivors of cancer in infancy compared to siblings. We do not, however, plan a detailed assessment of psychosocial outcomes.

While those diagnosed in infancy represent a small portion of the entire CCSS cohort, this cohort represents one of the largest of survivors diagnosed in infancy and offers the potential to better understand survivorship after malignancy in this developmentally important age range.

Specific Aims/ Objectives/Research Hypothesis:

The purpose of this analysis will be to examine long-term outcomes of survivors of cancer in infancy. The analysis will include all survivors with completed baseline surveys who were less than one year of age at the time of their initial cancer diagnosis.

Hypotheses:

1) Survivors of cancer in infancy will have a significantly higher prevalence of adverse health status compared to (1) siblings and (2) survivors diagnosed at 1-1.99 years of age and 2-10 years of age with similar diagnosis.

2) Survivors of cancer in infancy will have a significantly higher prevalence and severity (defined by CTCAE 3.0) of morbidities including sensory disorders, neurologic disorders, endocrine disorders, pulmonary disorders, musculoskeletal disorders, and cardiovascular disease, compared to (1) siblings and (2) survivors diagnosed at 1-1.99 years of age and 2-10 years of age with similar diagnosis.

a) Survivors of neuroblastoma in infancy will have higher prevalence and severity of sensory, neurologic, and musculoskeletal disorders compared to (1) siblings and (2) survivors of neuroblastoma diagnosed at 1-1.99 years of age and 2-10 years of age.

b) Survivors of Wilms' tumor in infancy will have higher prevalence and severity of renal problems compared to (1) siblings and (2) survivors of Wilms' tumor diagnosed at 1-1.99 years of age and 2-10 years of age.

c) Survivors of leukemia in infancy will have a higher prevalence and severity of cardiovascular, neurologic, and endocrine disorders compared to (1) siblings and (2) survivors of leukemia diagnosed at 1-1.99 years of age and 2-10 years of age.

d) Survivors of brain tumor in infancy will have higher prevalence and severity of neurologic and endocrine disorders compared to (1) siblings and (2) survivors of brain tumors diagnosed at 1-1.99 years of age and 2-10 years of age.

3) Treatment factors including surgical intervention, exposure to radiation, intrathecal chemotherapy, high dose cytarabine, anthracyclines, and hematopoietic stem cell transplantation will be associated with higher prevalence of chronic morbidities in survivors less than one year of age compared to survivors diagnosed at 1-1.99 years of age and 2-10 years of age with similar diagnoses.

4) Survival will be significantly lower among survivors of childhood cancer in infancy compared to the U.S. population.

5) Survivors of cancer in infancy will have increased use of special education services compared to siblings.

6) Childhood survivors of cancer in infancy will have decreased social functioning compared to siblings, as assessed by parent report of close friendships.

We will determine factors associated with adverse health status and high severity of morbidity in those diagnosed at less than one year of age.

Analysis Framework and Plan:

A. Outcomes of interest:

1. Survival rates

Overall survival analysis will be analyzed from entry into the CCSS cohort using Kaplan-Meier methodology, comparing to expected survival in the U.S. population for age and gender. Hazard ratios comparing survival between different treatment groups will be evaluated using Cox regression models, adjusted for age, gender and treatment era.

2. Health Status

-General health

> 18 years of age at baseline survey: N15 (Would you say your health is excellent, very good, good, fair, poor)

<18 years of age baseline survey: N11: (Would you say that your child's health…)

-Mental health

>18 years of age baseline survey: BSI-18 J, global score

<18 years of age baseline survey: J19, J20, J21

-Physical functional status

> 18 years of age at baseline survey: Developed from N10-12

<18 years of age baseline survey: From N6-8

-Activity limitations

>18 years of age baseline survey: N14

<18 years of age baseline survey: N10

-Pain as a result of previous cancer

>18 years of age baseline survey: J36

<18 years of age baseline survey: J23

-Anxiety as a result of previous cancer

>18 years of age baseline survey: J37

<18 years of age baseline survey: J27

The analysis of health status will be performed using the methodology established by Hudson *et al*., with comparisons made by underlying diagnosis and therapeutic exposures.[2] Comparison will be made for the first 4 domains with the sibling control group. Parallel analyses will be performed comparing to survivors 1-1.99 years of age and 2-10 years of age at diagnosis. Logistic regression models will be utilized to evaluate univariate and adjusted odds ratios.

3. Medical Conditions

Baseline survey: Sections C, D, E, F, G, H, I, J.

The prevalence and severity of chronic medical conditions will be established using the methodology of Oeffinger *et al.*[1] Chronic medical conditions will be examined by organ system and as a group. Complications by organ system will include neurologic problems, sensory problems, endocrine problems, musculoskeletal problems, pulmonary problems, cardiovascular disorders, renal problems, and gastrointestinal problems. Survivors of cancer in infancy will be compared to sibling control groups and to survivors 1-1.99 years of age and 2-10 years of age at diagnosis. Survivors will be compared by primary diagnosis, with particular attention to sensory, neurologic, and musculoskeletal disorders in survivors of neuroblastoma, renal problems in survivors of Wilms' tumor, cardiovascular, neurologic, and endocrine disorders in survivors of leukemia, and neurologic and endocrine disorders in survivors of brain tumors. Cox proportional hazards models will be utilized to evaluate hazard ratios for the risks of grades 1-4, grades 3-4 or ≥2 conditions for the infant group vs. the three control groups. Grade 5 conditions may be compared between survivor groups, but death information is not available for siblings.

4. Use of special education services

Baseline survey: O3

This outcome will be analyzed as a binary outcome (ever in special education program, yes or no), using logistic regression analyses to evaluate univariate and adjusted odds ratios for utilization of special education services. Only the comparison of those less than one year of age at diagnosis to sibling controls will be considered for this analysis.

5. Social functioning

<18 years of age baseline survey only: from J16 About how many close friends does your child have, J17 About how many times per week does your child do things with close friends. The response to these questions will be summarized in tabular form and appropriate groupings formed.

B. Subject population:

Cases will be survivors with completed baseline surveys who were less than one year of age at the time of their initial cancer diagnosis. Sibling controls will be a frequency-matched selection of siblings from the sibling cohort, based on the distribution of age at time of baseline survey for the infant group. For parallel analyses and for analyses addressing certain treatment risk factors, the case group will remain survivors who completed baseline surveys less than one year of age at the time of their initial cancer diagnosis, and the control group will be survivors 1-1.99 years of age and 2-10 years of age at diagnosis. Social functioning will be assessed for those less than one year of age at diagnosis and less than 18 years of age at time of baseline survey.

C. Exploratory variables, covariates of interest:

Age at response to baseline survey
Gender
Underlying Diagnosis
Severity of present illness
Type of treatment
- Radiation
  - Any
  - Brain/Cranio-spinal
  - Abdominal/Pelvic
  - Total body irradiation

Chemotherapy
- Alkylator score
- Anthracycline cumulative dose
- Platinum score
- Vincristine
- High dose cytarabine
- Intrathecal chemotherapy
- Steroid

Surgery
- Any
- Nephrectomy
- Laminectomy
- Craniotomy
- Laparotomy
- Thoracotomy

Bone marrow transplantation

Relapse after primary therapy

Table 1:
Characteristics of Study Participants

	Survivors <1 yrs of age at dx	Siblings	Survivors 1-1.99 yrs at dx	Survivors 2-10 yrs at dx
Age at questionnaire				
Mean				
Range				
Interval from diagnosis				
Mean				
Range				
Sex				
Female				
Male				
Race/Ethnicity				
Highest education level				
High school or less				
Some college				
Diagnosis				
Leukemia				
ALL				
AML				
Brain cancer				
Hodgkins Lymphoma				
NHL				
Wilms tumor				
Neuroblastoma				
Sarcoma				
Bone tumor				
Cancer treatment				
Surgery only				
Radiation only				
Chemotherapy only				
Chemotherapy and XRT				
Chemotherapy and surgery				
Radiation and surgery				
Chemotherapy/Radiation/Surgery				
Bone marrow transplantation				

Table 2.

Percentage of survivors of cancer in infancy and siblings reporting moderate to severe adverse health status

	General Health	Mental Health	Functional Impairment	Activity Limitation	Any Domain
	Survivors/Siblings	Survivors/Siblings	Survivors/Siblings	Survivors/Siblings	Survivors/Siblings
Total population					
Age at survey, years					
≤5					
6-10					
11-15					
16-20					
21-25					
≥26					
Sex					
Male					
Female					
Race/Ethnicity					
White					
Minority					

Table 3.

Percentage of survivors of cancer diagnosed at 1-1.99 years of age and 2-10 years of age reporting moderate to severe adverse health status

	General Health	Mental Health	Functional Impairment	Activity Limitation	Any Domain
	1-1.99yrs/2-10yrs	1-1.99yrs/2-10yrs	1-1.99yrs/2-10yrs	1-1.99yrs/2-10yrs	1-1.99yrs/2-10yrs
Total population					
Age at survey, years					
≤5					
6-10					
11-15					
16-20					
21-25					
≥26					
Sex					
Male					
Female					
Race/Ethnicity					
White					
Minority					

Table 4.

Odds ratios of moderate to severe adverse health outcomes in survivors <1 year of age at diagnosis compared to siblings

	Odds ratios (95% Confidence intervals)				
	General Health	Mental Health	Functional Impairment	Activity Limit	Any Domain
Total Population					
Leukemia					
ALL					
AML					
Brain cancer					
Hodgkins Lymphoma					
NHL					
Wilms tumor					
Neuroblastoma					
Sarcoma					
Bone tumor					

Table 5.

Odds ratios of moderate to severe adverse health outcomes in survivors <1 year of age at diagnosis compared to survivors of cancer diagnosed at 1-1.99 years of age and 2-10 years of age

	Odds ratios (95% Confidence intervals)									
	General Health		Mental Health		Functional Impairment		Activity Limit		Any Domain	
	1-1.99yrs/	2-10yr	1-1.99yrs/	2-10yr	1-1.99yrs/	2-10yr	1-1.99yrs/	2-10yr	1-1.99yrs/	2-10yr
Total Population										
Leukemia										
ALL										
AML										
Brain cancer										
Hodgkins Lymphoma										
NHL										
Wilms tumor										
Neuroblastoma										
Sarcoma										
Bone tumor										

Table 6.

Frequencies, percents, odds ratios, and 95% confidence intervals comparing severe or life-threatening medical complications in survivors < 1 year of age at diagnosis and siblings*

	Survivor		Sibling		OR [95%CI]
	N	%	N	%	
Medical complication (Any Grade 3 or 4)					
Neurologic					
Sensory					
Endocrine					
Pulmonary					
Musculoskeletal					
Cardiovascular					
Renal					
Gastrointestinal					

*Based on Common Terminology Criteria for Adverse Events version3 (CTCAE v3) severity score

Table 7.

Frequencies, percents, odds ratios, and 95% confidence intervals comparing severe or life-threatening medical complications in survivors < 1 year of age at diagnosis and survivors 1-1.99 years of age and 2-10 years of age at diagnosis

	< 1 year at dx		1-1.99yrs		OR [95%CI]	2-10 yrs		OR [95%CI]
	N	%	N	%		N	%	
Medical complication (Any Grade 3 or 4)								
Neurologic								
Sensory								
Endocrine								
Pulmonary								
Musculoskeletal								
Cardiovascular								
Renal								
Gastrointestinal								

*Based on Common Terminology Criteria for Adverse Events version3 (CTCAE v3) severity score

Table 8.

Percent of survivors of cancer in infancy, siblings, survivors 1-1.99 years of age at diagnosis, and 2-10 years of age at diagnosis with chronic physical conditions*

	Survivors < 1 year		Siblings		RR[95%CI]	Survivors 1-1.99 yrs		RR[95%CI]	Survivors 2-10 yrs		RR[95%CI]
	N	%	N	%		N	%		N	%	
No condition											
Any Grade 1 or 2 (Mild or moderate)											
Any Grade 3 or 4 (Severe or life-threatening)											
Grade 5 death											
Multiple conditions											
More than 2											
More than 3											

*Based on Common Terminology Criteria for Adverse Events version3 (CTCAE v3) severity score

Table 9.

Relative Risk of severe/life threatening or multiple chronic health conditions, according to underlying tumor diagnosis and treatment, for survivors diagnosed <1 year age as compared with survivors diagnosed at 1-1.99 years of age and 2-10 years of age.

Cancer diagnosis or treatment exposure	Grade 3 or 4		≥2 Conditions	
	Comparison group		Comparison group	
	(1-1.99 yrs)	2-10 yrs	(1-1.99 yrs)	2-10 yrs
Leukemia				
ALL				
AML				
Brain cancer				
Hodgkins Lymphoma				
NHL				
Wilms tumor				
Neuroblastoma				
Sarcoma				
Bone tumor				
No chemotherapy or radiation				
Chemotherapy				
Any chemotherapy				
Alkylating agent				
Anthracycline				
Platinum				
Vincristine				
High dose cytarabine				
Intrathecal chemotherapy				
Radiation				
CNS radiation				
Abdominal/Pelvic radiation				
Low-dose radiation (non-CNS)				
Total body irradiation				
Bone marrow transplant				
Surgery				
Any				
Nephrectomy				
Laminectomy				
Craniotomy				
Laparotomy				
Thoracotomy				

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