Long-Term Morbidity and Mortality in Infant Survivors of Childhood Cancer
Childhood Cancer Survivor Study
Analysis Concept Proposal

Working Groups and Investigators
Chronic Disease, Biostatistics/Epidemiology, and Subsequent Neoplasm

UCSF

Cristina Perez-Witte, MD	cristina.perez@ucsf.edu
Natalie Wu, MD, MS	natalie.wu@ucsf.edu
Robert Goldsby, MD	robert.goldsby@ucsf.edu
Lena Winestone, MD, MPH	lena.winestone@ucsf.edu

CCSS

Greg Armstrong, MD, MSCE	greg.armstrong@stjude.org
Kevin Oeffinger, MD	kevin.oeffinger@duke.edu
Eric Chow, MD, MPH	ericchow@uw.edu
Lucie Turcotte, MD, MPH, MS	turc0023@umn.edu
Wendy Leisenring, ScD	wleisenr@fredhutch.org
Cindy Im, PhD, MPH	imcindy@umn.edu
Deo Kumar Srivastava, PhD	Kumar.Srivastava@stjude.org

Background and Rationale:

Advances in pediatric oncology treatments have led to remarkable improvements in survival, with five-year survival rates rising from 63% to 85% in recent decades (Sultan et al., 2025). These advances have resulted in a significant increase in the number of childhood cancer survivors. However, with this progress comes a growing recognition of the late effects of cancer therapy, including early mortality as well as chronic health conditions associated with chemotherapy, radiation, and other treatment modalities (Oeffinger et al., 2006; Hudson et al., 2013). These chronic health conditions can vary in severity and have a profound impact on the quality of life of survivors, affecting physical, neurocognitive, and psychosocial development (Geenen et al., 2007).

Among childhood cancer survivors, those diagnosed in infancy (less than 1 year of age) represent a rare but uniquely susceptible population. Infants face distinct risks of mortality and long-term morbidity compared to older children diagnosed with cancer (Esbenshade et al, 2020; Wang et al., 2021). The developmental immaturity of infants - both physiologically and neurologically - at the time of treatment renders them particularly vulnerable to the toxic effects of cancer therapies. For example, radiation therapy, which is often used to treat malignancies including brain tumors, can have devastating effects on neurodevelopment in infants due to the

sensitivity of the developing brain (Armstrong et al., 2016). Radiation exposure during infancy has been associated with long-term deficits in cognitive function; conversely, reducing radiation exposure improves neurocognitive outcomes (Lafay-Cousin et al., 2009). Efforts to reduce radiation exposure and avoid the long-term consequences in younger patients have been implemented over the past several decades.

Chemotherapy is another cornerstone of pediatric cancer treatment, but certain agents carry significant risks of long-term morbidity in infants. Platinum-based agents, such as cisplatin and carboplatin, widely used in the treatment of CNS tumors and neuroblastoma, are known to cause sensorineural hearing loss in young children, with infants being particularly susceptible due to the immaturity of their auditory system at the time of exposure (Knight et al., 2017). Hearing loss can have cascading effects on language acquisition, communication skills, and social development, often leading to lifelong challenges (Landier, 2016). Similarly, anthracyclines, commonly used in treating leukemias and solid tumors, have been linked to an increased risk of cardiotoxicity, which may manifest as arrhythmias, reduced cardiac function, or heart failure later in life (Lipshultz et al., 2013; Kremer et al., 2002).

Infants diagnosed with certain cancers, such as neuroblastoma, may experience more favorable outcomes compared with older children due to the potential for spontaneous tumor regression in low-stage disease (Goldsby et al., 2004). On the other hand, infants diagnosed with other cancers, such as rhabdomyosarcoma, have a worse prognosis compared with older children (Rees et al., 2022). In one German study, infant cancer patients had a fourfold increase in early death (within 30 days of diagnosis) compared with older children, which highlights their distinct susceptibilities (Becker et al., 2020). For infants requiring intensive therapies, including chemotherapy, radiation, or surgical interventions, the risk of treatment-related toxicities remains high and has led to attempts to appropriately modify dosing (Nijstad et al., 2022). Neurological complications are a concerning outcome for infants undergoing radiation or other neurotoxic therapies, as the developing nervous system is highly sensitive to injury during this period (Diller et al., 2009; Packer et al., 2003; Merchant et al., 2009). Motor deficits, seizures, developmental delays, and reduced academic performance are common long-term consequences observed in pediatric cancer survivors treated during infancy (Armstrong et al., 2013; Jacola et al., 2016).

The risk of secondary malignant neoplasms (SMNs) is another critical consideration for infants treated for cancer. While SMNs are a known late effect of cancer therapy in older children and adolescents, infants may have an even greater risk due to their prolonged life expectancy and increased vulnerability to genotoxic effects of therapy (Neglia et al., 2001; Turcotte et al., 2015). This underscores the importance of studying survivorship outcomes in this unique population.

The primary aim of this project is to leverage the Childhood Cancer Survivor Study (CCSS) database to characterize the overall and cause-specific mortality of infant cancer survivors and to

compare these outcomes with survivors who were diagnosed later in childhood. Additionally, we will explore the spectrum and prevalence of treatment-related chronic health conditions in these survivors diagnosed in infancy. Specifically, we will assess the risk of conditions such as sensorineural hearing loss, cardiotoxicity, neurocognitive deficits, and secondary malignancies in survivors diagnosed in infancy and compare these outcomes with those of children diagnosed at older ages with similarly treated malignancies. We hypothesize that infant cancer survivors will exhibit a higher burden of late mortality, as well as chronic health conditions, reflecting increased susceptibility to treatment-related toxicity. Our goal is to contribute to a better understanding of age-related vulnerability that will improve survivorship care and may eventually inform the development of more targeted, less toxic therapeutic strategies for our youngest cancer patients.

Specific Aims:

Aim 1: Determine the overall and cause-specific mortality of infant cancer survivors (diagnosed < 1 year of age) compared with older cancer survivors, and the overall risk of mortality, adjusting for patient demographics, cancer diagnosis and treatment parameters.

Aim 2: Determine the cumulative incidence of chronic health conditions, including subsequent neoplasms, in infant cancer survivors (diagnosed < 1 year of age) compared with older cancer survivors, and the risk for chronic health conditions, adjusting for patient demographics, cancer diagnosis and treatment parameters.

Hypotheses:

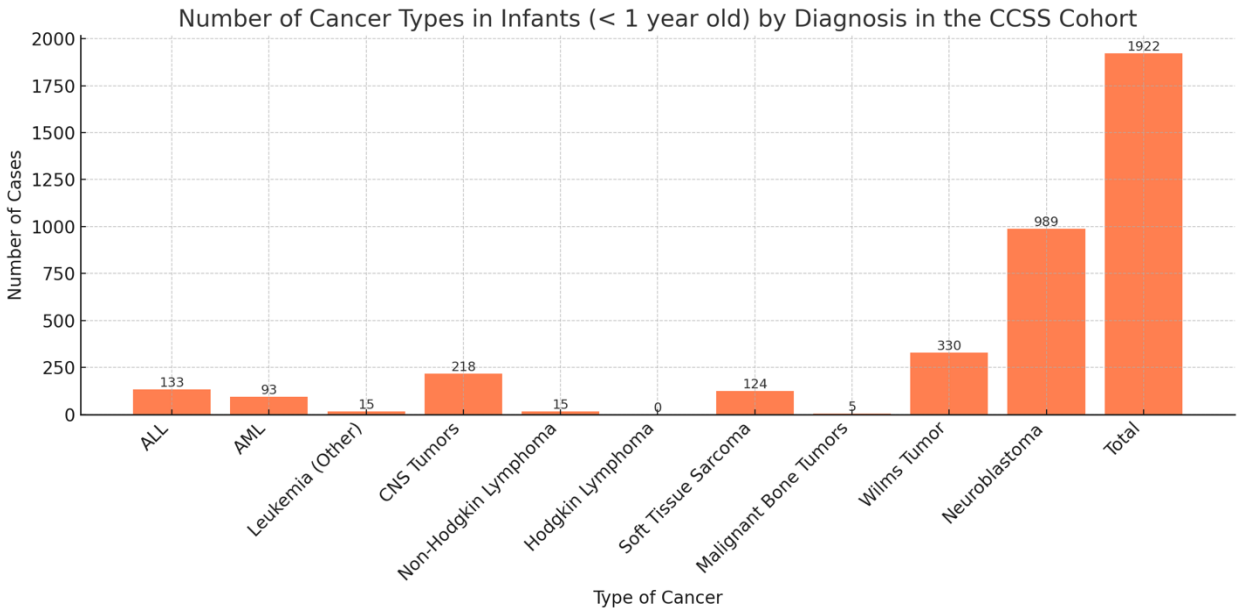
1. Infant childhood cancer survivors will have different survival rates and rates of chronic health conditions compared with older cancer survivors.
2. Specifically, infant survivors will have more severe or life-threatening conditions and subsequent neoplasms compared with older cancer survivors.

Analysis Framework:

Subject population (data from publicly available tables on CCSS website)

- **Inclusion criteria:**
    - The standard CCSS criteria: survived at least 5 years from the following cancer diagnoses (see below)
    - Treated with chemotherapy, surgery, and/or radiation
- **Exclusion criteria:**

- Any individual who did not receive one of the therapeutic modalities (chemotherapy, surgery and/or radiation)
    - For example, there were 380 individuals diagnosed with Neuroblastoma at less than 1 year of age who did not receive any chemotherapy. These individuals would be excluded.



Of the infants, about 73% (1397/1926 of all cancers) experienced a grade 1-5 chronic health condition. About 31% of infants experienced a grade 3 or greater chronic condition (Grade 3 = severe/disabling, Grade 4 = life-threatening, Grade 5 = fatal)

Outcome Variables:

- Overall survival and cause-specific mortality, as defined by Mertens et al. paper (2008) [see Figure 1 and Table 2 for examples]
- Any chronic health conditions (Grade 1-5); severe or life threatening or fatal (Grade 3-5) [see Table 3 for example]
- Chronic health conditions sections as defined by Gibson et al. paper (2018) and subsequent neoplasms, subdivided into malignant neoplasms, benign meningiomas, and non-melanoma skin cancers, as defined by Turcotte et al. paper (2017) [see Table 4 for example]

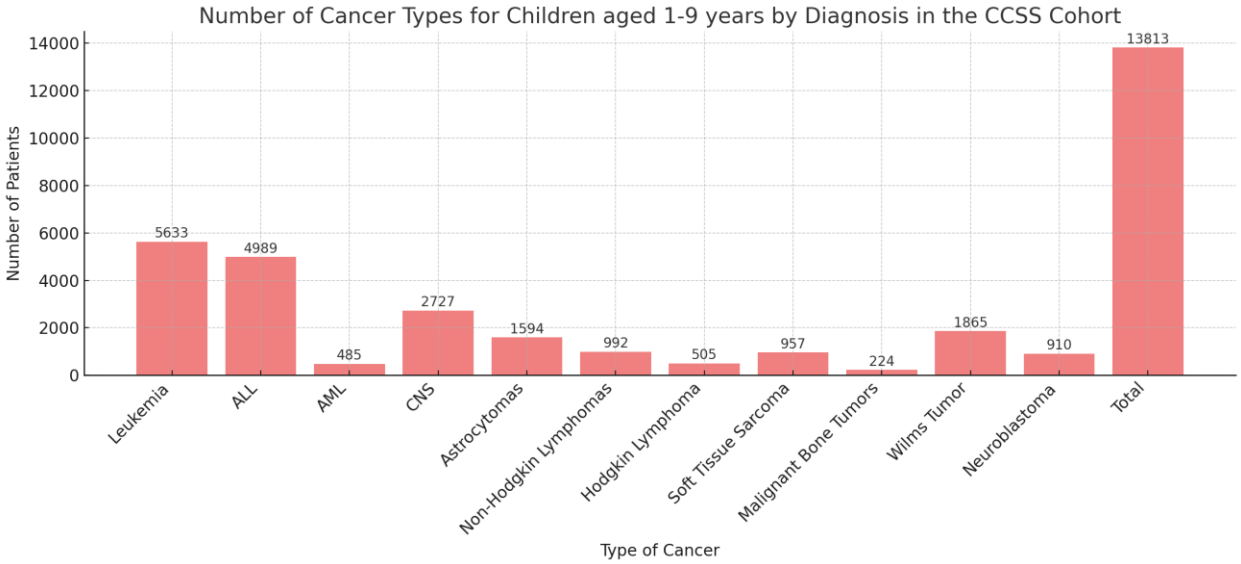
Analyses:

- Underlying clinical and demographic characteristics will be summarized for the infant cancer survivor cohort (diagnosed <1 year of age), child cancer survivor cohort (diagnosed 1-9 years of age), and non-infant cancer survivor cohort (diagnosed 1-21 years of age) [see Table 1 for example].
- Overall survival estimates will be generated for infant cancer survivors, child cancer survivors, and non-infant cancer survivors using the Kaplan-Meier estimator, with comparisons between the three cohorts based on the log-rank test [see Figure 1 for example].
- We will use Cox proportional hazard models to estimate the hazard ratios (HRs) and associated 95% confidence intervals (CIs) for the outcomes of interest between the cohorts of infant cancer survivors, child cancer survivors, and non-infant cancer survivors [see Tables 2 and 3 for examples].
- Cumulative incidence estimates of each endpoint (chronic health condition or subsequent neoplasms) will be evaluated for infant cancer survivors, child cancer survivors, and non-infant cancer survivors overall and within diagnosis groups (hematologic malignancy, CNS tumor, and solid tumors) [see Figure 2 for example], with death from other causes classified as a competing risk event and the follow-up starting at 5 years from the cancer diagnosis and ending with the earliest of development of the primary outcome, death, or for non-affected living participants, their most recent questionnaire completion (censoring). If the date of onset of an irreversible condition, such as blindness, occurs within the first 5 years after the date of diagnosis, the condition will be considered present 5 years after diagnosis and curves will begin at a prevalence higher than zero to reflect the proportion of the population entering with a condition.
- In multi-variable analyses for each outcome of interest, we will assess the effect of age at time of cancer diagnosis in a basic model that will be adjusted for primary cancer diagnosis, attained age (e.g., modeled by natural cubic splines), treatment era, sex, and race/ethnicity. Therapeutic exposures (radiation therapy, chemotherapy exposures such as cyclophosphamide equivalence dose and anthracycline dose, cancer-directed surgeries, bone marrow transplant) will be added to the basic model to examine the impact of treatment on the primary factor of interest (age at time of diagnosis)
- All p-values will be two-sided, and significance levels of 0.05 will be considered significant.

As part of an exploratory analysis, we propose a comparison of infant cancer survivors (diagnosed < 1 year of age) with child cancer survivors (diagnosed 1-9 years of age), matched on cancer diagnosis and treatment parameters. This would allow us to isolate the effect of age at time of diagnosis in similarly treated cancer survivors.

This would entail the creation of a comparison cohort comprised of child cancer survivors (diagnosed between 1-9 years of age). A ratio of up to 4 comparison participants for each infant

subject would be selected from the rest of CCSS cohort by stratified random sampling matching for diagnosis type/group, time since diagnosis and treatment, and treatment received (i.e. alkylator score or cyclophosphamide equivalent dose (CED) of <8,000 mg/m^2 vs ≥8,000 mg/m^2), anthracycline dose (≤250 mg/m^2 vs >250 mg/m^2), surgery, total body irradiation, focal radiation (by site), and bone marrow transplant. Similar methodology was used in a prior CCSS analysis (Goldsby et al., 2018).



Proposal for matching by diagnosis, sex, time since diagnosis, and treatment detail (see below):

- **Hematologic Malignancies** [total = 241] (ALL (133), AML (93), NHL (15)
  - Matching: 1) TBI Y/N, 2) Any radiation (cranial/spinal/testicular) Y/N, 3) Anthracycline Dose (≤250mg/m^2, >250mg/m^2), 4) Alkylator Score (CED <8,000 mg/m^2 vs ≥8,000 mg/m^2), 5) Bone marrow transplant Y/N
- **CNS Tumor** [total = 218)
  - Matching: 1) Any radiation (cranial/spinal) Y/N, 2) Neurosurgery, 3) Anthracycline Dose (≤250mg/m^2, >250mg/m^2), 4) Alkylator Score (CED <8,000 mg/m^2 vs ≥8,000 mg/m^2)
- **Solid tumors** [total = 1068] (Sarcomas/Bone Tumor (129), Renal tumor (330), Neuroblastoma (609)
  - Matching: 1) Surgery 2) Any radiation (location) Y/N, 3) Anthracycline Dose (≤250mg/m^2, >250mg/m^2), 4) Alkylator Score (CED <8,000 mg/m^2 vs ≥8,000 mg/m^2)
  - Please note that the 609 survivors with neuroblastoma referenced above are the survivors who received some form of therapy

For each chronic condition endpoint that will be evaluated, Cox proportional hazards models will be utilized to evaluate prospective comparisons of hazards of events between infant and child survivor cohorts. Age will be utilized as the time scale for analysis, with the time period of evaluation beginning at subject's age at 5 years after diagnosis and ending at the age of occurrence of the event of interest, death, or the end of follow-up (whichever comes first). Subjects included in this analysis will be those entering at 5 years without yet having developed the chronic condition of subsequent neoplasm of interest.

Table 1: Clinical Characteristics of Childhood Cancer Survivors Diagnosed as Infants (<1 year of age), Children (1-9 years of age), and Non-infants (1-21 years of age)

	Infant survivors	Child survivors	Non-infant survivors
	No. (%)	No. (%)	No. (%)
Mean Age in Years			
Sex			
Male			
Female			
Diagnosis			
AML			
ALL			
HL/NHL			
CNS Tumor			
Sarcomas/Bone Tumors			
Wilms			
Neuroblastoma			
Treatment Exposures			
Alkylator agent			
Anthracycline agent			
Radiation Therapy (RT)*			
Surgery			
Treatment Era			
1970-1979			
1980-1989			
1990-1999			
Status			
Alive			
Deceased			

Table 1: Radiation therapy (RT) will be further broken down into the following categories: Any Total Body Irradiation (TBI), Brain RT exclusive of TBI, Spinal RT exclusive of TBI, Abdominal RT exclusive of TBI, and Chest RT exclusive of TBI.*

Table 2: Overall and Cause-specific Mortality in Survivors of Childhood Cancer (Diagnosed as Infants vs Children vs Non-infants)

	Infant Survivors	Child Survivors		Non-infant Survivors	
	No. (%)	No. (%)	HR ** (95% CI)	No. (%)	HR *** (95% CI)
Overall mortality					
Recurrent disease					
Subsequent neoplasms					
Cardiac					
Pulmonary					
External causes					
Other causes					

*Models will be adjusted for primary cancer diagnosis, attained age, treatment era, sex, race/ethnicity, and therapeutic exposures

**Hazard Ratio (HR 95% CI) between Infant Survivors and Child Survivors

***Hazard Ratio (HR 95% CI) between Infant Survivors and all other children (Child and Non-infant Survivors)

Table 3. Chronic Health Conditions in Survivors of Childhood Cancer 5 years after diagnosis (Diagnosed as Infants vs Children vs Non-infants)

	≥ 5 years after diagnosis				
Chronic Condition	**Infant Survivors**	**Child Survivors**		**Non-infant Survivors**	
	No. (%)	**No. (%)**	**HR ** (95% CI)**	**No. (%)**	**HR *** (95% CI)**
No Condition					
Grade 1, mild					
Grade 2, moderate					
Grade 3, severe or disabling					
Grade 4, life-threatening					
Grade 5, fatal					
Any condition					
Grade 1+					
Grade 3+					
Multiple serious health conditions (Grades 3+)					
>2					
≥3					

*Models will be adjusted for primary cancer diagnosis, attained age, treatment era, sex, race/ethnicity, and therapeutic exposures
**Hazard Ratio (HR 95% CI) between Infant Survivors and Child Survivors

***Hazard Ratio (HR 95% CI) between Infant Survivors and all other children (Child and Non-infant Survivors)

Table 4. Chronic Health Conditions by Organ System and Subsequent Neoplasms in Survivors of Childhood Cancers (Diagnosed as Infants vs Children vs Non-infants

	Infant Survivors	**Child Survivors**		**Non-infant Survivors**	
Chronic Health Condition by Organ System	**No. (%)**	**No. (%)**	**HR** (95% CI)**	**No. (%)**	**HR *** (95% CI)**
Endocrine					
Cardiovascular					
Neurological					
Hearing loss					
Visual impairment					
Gastrointestinal					
Musculoskeletal					
Respiratory					
Renal					
Subsequent Neoplasm (Any)					
Malignant Neoplasm					
Benign Meningioma					
Non-melanoma Skin Cancers					

*Models will be adjusted for primary cancer diagnosis, attained age, treatment era, sex, race/ethnicity, and therapeutic exposures
**Hazard Ratio (HR 95% CI) between Infant Survivors and Child Survivors
***Hazard Ratio (HR 95% CI) between Infant Survivors and all other children (Child and Non-infant Survivors)

Figure 1: Kaplan-Meier Survival among 5-year Cancer Survivors Diagnosed in Infancy (age <1 year) vs Childhood (age 1-9 years) vs Non-infancy (age 1-21 years)

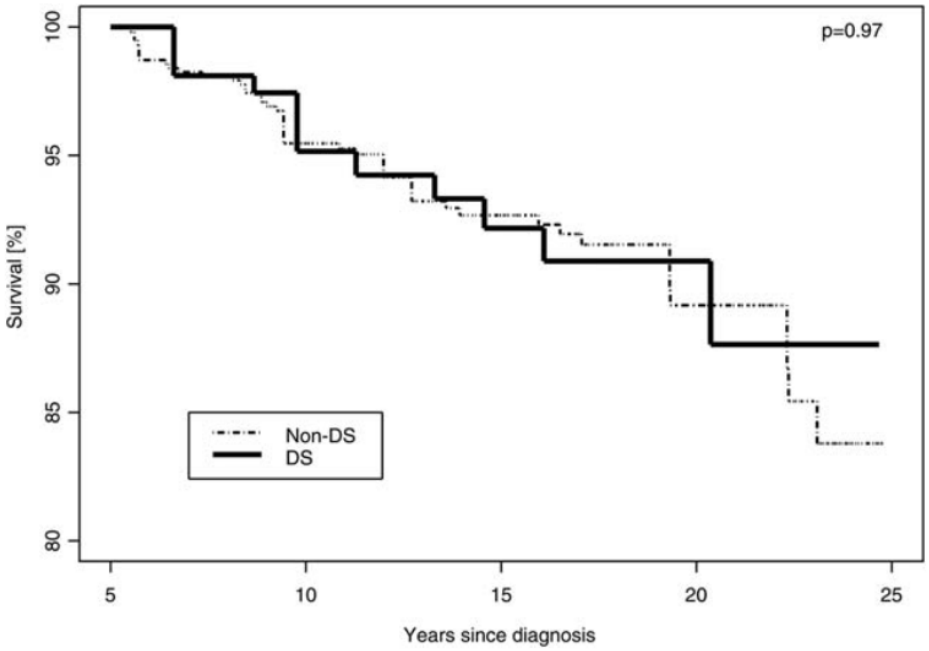


Figure 1. Kaplan-Meier survival among 5-year survivors of leukemia with and without DS.

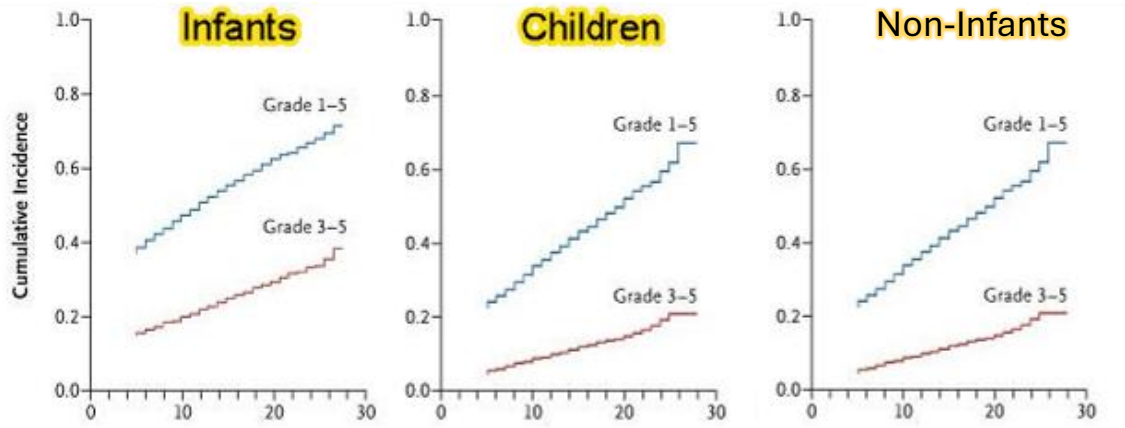
The following Kaplan-Meier curve example was pulled from Goldsby et al., 2018 paper.

Figure 2: Cumulative Incidence of Chronic Health Conditions:

a) Cumulative incidence of grade 1-5 chronic health conditions of infant cancer survivors (diagnosed <1 year of age) vs child cancer survivors (diagnosed 1-9 years of age) vs non-infant cancer survivors (diagnosed 1-21 years of age)

b) Cumulative incidence of grade 3-5 chronic health conditions of infant cancer survivors vs child cancer survivors vs non-infant cancer survivors

c) Cumulative incidence of subsequent neoplasms of infant cancer survivors vs child cancer survivors vs non-infant cancer survivors



Similar to Oeffinger et al., 2006, but would have Grade 1-5 conditions of infants vs children vs non-infant survivors and grade 3-5 conditions of infants vs children vs non-infant survivors

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