

CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal

Title: Socioeconomic status and associations with subsequent malignant neoplasms among survivors of childhood cancer

Working Groups: Subsequent Neoplasms, Biostatistics/Epidemiology, Cancer Control

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Background and Rationale

Through significant advances in treatment and supportive care measures, 5-year survival rates for childhood cancer now exceed 85% and there are half a million survivors of pediatric cancer now alive in the United States.¹ However, it is important to recognize that cancer disparities exist in regard to cancer incidence and outcomes, both in adults and pediatrics, resulting in unequal survival benefit, as well as inequity in engagement of survivorship care after a diagnosis of childhood cancer that can impact outcomes in long-term survivors.² For example, a recent study demonstrated the largest increase in incidence of pediatric cancers is occurring among non-Hispanic American Indian and Alaska native children and adolescents, and the smallest increase is among non-Hispanic White children and adolescents.³ Similarly, this study showed across different pediatric cancer types, that incidence of pediatric cancers was rising at a more rapid rate among lower socioeconomic (SES) quintiles, whereas among higher SES quintiles the incidence rates remained relatively stable.³

In regards to outcomes, multiple studies have demonstrated that children from racial and ethnic minority groups and those from lower SES have inferior outcomes compared to their non-minority and higher SES counterparts.⁴⁻⁸ Specifically, it has been noted that low SES is associated with poorer recurrence-free and overall survival rates for various childhood cancers including leukemias (acute lymphoblastic leukemia and acute myeloid leukemia), brain tumors (medulloblastoma), lymphomas (Hodgkin lymphoma), and solid tumors (rhabdomyosarcoma, bone tumors, neuroblastoma, and liver tumors), among others.^{7,8} These disparities are most notable among adolescents and young adults, who already face worse outcomes compared to their younger counterparts.⁸ Additionally, disparities persist long-term for survivors of childhood cancer, and include poorer patient-reported outcomes, increased rates for chronic health conditions, as well as decreased long-term survival rates.⁹⁻¹¹ Etiologies for these disparities, may include impaired access and/or utilization of health care, lower representation in clinical trials, biological differences (cancer biology and pharmacogenomics), language barriers, treatment non-adherence, partaking in risky health behaviors (smoking, alcohol, poor diet), and cultural beliefs, among others.⁷⁻¹³

One plausible explanation for how low SES may increase cancer risk is that low SES has been demonstrated to cause chronic stress.^{14,15} This in turn might impair the immune response as a result of decreases in the cytotoxic T-cell and natural killer cell activities that affect immune surveillance processes against tumor formation.¹⁶ The impact of chronic stress on the immune system and its function can also modulate the development and the accumulation of mutational changes, as well as DNA damage, growth and angiogenic factors, and reactive oxygen species, which have all been associated with tumor development.¹⁷⁻¹⁹ Thus, recognizing that survivors of childhood cancer can be impacted by financial hardship at both the individual and neighborhood levels, it is plausible that survivors of childhood cancer can, as a result of lower SES, have increased risk for subsequent malignant neoplasm (SMN) development.²⁰

Given the multitude of studies demonstrating disparities in incidence and outcomes of pediatric primary cancers, we aim to evaluate the impact of SES on incidence and outcomes of SMNs. SMNs are the most prevalent cause of premature mortality (after cancer recurrence) reported by the Childhood Cancer Survivor Study (CCSS).^{21,22} Additionally, studies have demonstrated that lower income and SES were associated with later-stage diagnosis, which may impact mortality of specific SMNs, which we plan to evaluate in a sub-population of survivors in this proposal.^{23,24} Specifically, certain SMNs such as breast and colorectal cancer have specific screening recommendations for childhood cancer survivors to improve early detection rates and increase survival benefit; there may be differences in mortality for these SMNs based on SES factors due to decreased access to health care.²⁵⁻²⁹ Similarly, other SMNs, such as thyroid cancer that are not routinely symptomatic and may only be found through screening assessments, may have higher incidence in individuals with higher income and SES, who may have increased access to health care and screening services.³⁰

To measure SES in this study, we plan to utilize measures of neighborhood-level deprivation. Research has shown that neighborhood characteristics can be a key determinant of health, and shape opportunities for and barriers to health outcomes (including cancers), as a result of

material deprivation, physical and psychological stressors, toxic and/or harmful environmental exposures, and limited access and resources for healthy behaviors.^{20,31,32} There are several different metrics that have been developed for measuring neighborhood-level deprivation. Prior studies (published and currently in press) in the setting of survivors of childhood cancer have utilized Area Deprivation Index (ADI).¹¹ We propose to utilize three different neighborhood-level metrics in this study as they evaluate different social determinants of health that may differentially impact incidence and outcomes of SMNs. Our goal is to determine if differences in our findings, based on which neighborhood-level metric is utilized, could guide specific public health interventions in the future to improve long-term care and survival of survivors of childhood cancer. We therefore plan to utilize ADI, the social vulnerability index (SVI), and modern redlining, to capture neighborhood deprivation and evaluate for multiple social determinants of health.

The Area Deprivation Index was originally created as a metric of neighborhood-level socioeconomic adversity to reflect the degree of social disparities in overall health and mortality.³³ The ADI is composed of 17 education, employment, housing-quality and poverty factors drawn from Census data and subsequently updated to incorporate American Community Survey data and is available as a single composite score at the US Census block group level.³⁴ The Social Vulnerability Index, was developed to determine which communities, based on US Census data, may need support surrounding a hazardous event as a result of increased vulnerability based on 15 different social factors that reflect the four overall domains of socioeconomic status, household composition, race/ethnicity status (including primary language), and housing type and transportation.³⁵ SVI is available as an overall measure, but also as four sub-measures based on the domains and is available at the US census tract or county level.³⁶ While ADI places more emphasis on poverty levels and housing costs, SVI includes additional measures of population demographics within the community, including data on race/ethnicity that is lacking in ADI.³⁶⁻³⁸ High SVI and ADI scores correspond to a higher degree of adversity and deprivation.

In contrast to ADI and SVI, modern redlining allows us to evaluate the impact of long-standing structural racism and inequity at a neighborhood-level on resulting contemporary health outcomes as a result of previous disparate mortgage lending practices.³⁹ Redlining has led to segregation of Black and other minority populations in the US, resulting in decreased access to healthcare resources for these populations, which can have implications for preventative medicine for health conditions including screening for malignancies.³⁹ This could be of significant consequence to childhood cancer survivors following screening recommendations for SMNs, such as those for breast and colorectal cancer. Recently, there have been several studies demonstrating poorer health outcomes as a result of redlining.³⁹ In particular, recent published work has demonstrated redlining to be associated with later-stage diagnosis and poorer survival of breast cancer.^{40,41}

Finally, as an exploratory aim we plan to evaluate changes in these SES measures between initial and follow-up to evaluate the association between changes in SES over time and SMN among survivors of childhood cancer.

Specific Aims and Hypotheses:

1. Describe neighborhood-level socioeconomic status, based on initial ADI, SVI, modern redlining of survivors of childhood cancer with and without SMNs, overall and by subtype

Hypothesis: Survivors with higher ADI, SVI (composite and sub-measures) and modern redlining will have higher cumulative incidence and burden of SMNs overall as well as certain SMNs, such as breast cancer and colorectal cancer. Survivors with lower ADI, SVI (composite and sub-measures) and modern redlining will have higher cumulative incidence and burden of other SMNs, such as thyroid cancer that rely more heavily on screening evaluations to detect disease.

2. Evaluate adjusted associations between incident SMN risk (overall and specific types) and initial geocode-based neighborhood level SES (based on ADI, SVI, and modern redlining) using incremental models adjusting for basic clinical and demographic factors, personal socioeconomic factors, and lifestyle factors.

Hypothesis: Survivors with higher ADI, SVI (composite and sub-measures) and modern redlining will have greater risk for SMNs overall as well as certain SMNs, such as breast cancer and colorectal cancer, even when adjusted for other individual-based characteristics.

3. Describe how neighborhood-level SES impacts cause-specific mortality outcomes after SMN among survivors. In this aim we will look at specific SMNs, with specific focus on breast cancer and colorectal cancer by ADI, SVI and modern redlining, to assess how systemic and neighborhood disadvantage and long-term inequity impacts mortality of known SMNs with significant rates of mortality. We will utilize most recent geocoding data prior to SMN diagnosis for this aim. This is an analysis of conditional mortality restricted to survivors who have developed an SMN.

Hypothesis: Survivors with high index scores of ADI, SVI (composite and sub-measures), and modern redlining will have higher mortality rates related to various SMNs, including breast cancer and colorectal cancer.

4. Evaluate adjusted associations between SMN cause-specific mortality risk and the most recent neighborhood level SES before SMN (based on ADI, SVI, and modern redlining).

Hypothesis: Survivors with higher ADI, SVI (composite and sub-measures) and modern redlining will have higher cause-specific mortality risk after specific SMNs, such as breast cancer and colorectal cancer, even when adjusted for other individual-based characteristics.

Exploratory aim 1. Evaluate staging at diagnosis of breast cancer and relapse based on ADI, SVI (composite and sub-measures) and modern redlining. There are ~430 secondary breast cancer cases that have staging data available. We aim to assess the impact of SES at the time of subsequent breast cancer diagnosis on staging and relapse.

Hypothesis: Survivors with highest contemporaneous ADI, SVI (composite and sub-measures), and modern redlining will have higher breast cancer staging at diagnosis.

Exploratory aim 2. Explore whether SMN diagnosis results in longitudinal change in socioeconomic disadvantage based on ADI, SVI (composite and sub-measures), and modern redlining. We will utilize most recent geocoding prior to SMN diagnosis, and most recent geocoding data after SMN diagnosis for participants with available data.

Hypothesis: Survivors will have higher ADI, SVI, and modern redlining index scores after SMN diagnosis

Analysis Framework:

1. Population of interest: Survivors enrolled in the CCSS cohort (1970-1999) who completed the baseline questionnaire. The subset of adult survivors of childhood cancers with Baseline and Follow-up 5 data from the CCSS expansion cohort will be used for Exploratory Aim 2 (longitudinal).
2. Outcome of interest: Diagnosis with any SMN \geq 5 years from childhood cancer diagnosis. Subsequent malignant neoplasm (SMN) will be defined as all subsequent invasive neoplasms and classified as International Classification of Disease for Oncology (ICD-O).
3. Descriptive characteristics of the cohort from initial survey:
 - a. Basic survivor data: age at childhood cancer diagnosis, sex, race and ethnic group, childhood malignancy, attained age at last follow up, decade of diagnosis (1970s, 80s, 90s), vital status and cause of death (including major SMN types)
 - b. Subsequent malignant neoplasm data: age at diagnosis of subsequent malignant neoplasm, time from initial diagnosis, subsequent malignancy diagnosis
 - c. Area deprivation index (divided into highest quintile (most deprived) vs rest as per other recent studies)
 - d. Social vulnerability index (divided into highest quintile (most vulnerable) vs rest)
 - a. Sub-measures: socioeconomic status, household composition, race/ethnicity status, and housing costs and transportation (divided into highest quintile vs rest)
 - e. Modern redlining index score (high (score \geq 2) vs rest)⁴¹
 - f. Additional individual level sociodemographic variables: Health Insurance Status (yes/no), Household Income, Education level (< college degree vs \geq college degree); Marital Status (Never married vs Ever married); Lives independently (Yes vs No); Employment (Unemployed vs Employed). A category of "NA" will be created for some of these variables not appropriate for participants younger than 25 years.
 - g. Environmental/lifestyle exposures:
 - i. Smoking status (yes [ever smoked]/no)
 - ii. BMI (underweight, normal, overweight, obese)
 - iii. Physical activity (yes/no)
 - h. Family cancer history (yes/no/unknown)
 - i. Therapeutic exposures
 - i. Therapeutic radiation (Any: Yes/No; site; cumulative dose)
 - ii. Chemotherapy class and cumulative doses
 - a. Platinating agents (yes/no/cumulative dose^{42,43})

- b. Alkylating agents (yes/no/cumulative dose, reported as cyclophosphamide equivalent dose ⁴⁴)
- c. Anthracyclines (yes/no/cumulative dose, reported as doxorubicin equivalent dose⁴⁵)
- d. Epipodophyllotoxins (yes/no/cumulative dose)
- iii. Hematopoietic cell transplantation (yes/no)

4. Statistical analysis plan:

- a. Descriptive statistics: Present the clinical characteristics and various neighborhood-level measures of social determinants of health of survivors included in analyses, especially by outcomes of interest (SMNs, cause-specific mortality). For the analysis of aim 3, this will be an analysis of conditional mortality restricted to survivors who have developed an SMN.
- b. Cumulative incidence: Estimate cumulative incidence and cumulative burden and 95% confidence intervals for subsequent malignant neoplasms (all, leukemia, sarcoma, breast cancer, thyroid, lymphoma, colorectal cancer, other solid tumors, melanoma) based on ADI, SVI (composite and sub-measures), and modern redlining. Time from initial geocoding date will be used as the time scale and death will be treated as a competing risk event. Subsets of subjects may be presented if numbers permit/interesting findings are identified. Cumulative incidence will also be estimated for cause-specific mortality within ADI, SVI and modern redlining categories (defined by the most current geocode before SMN diagnosis) after development of specific subsequent malignant neoplasms treating deaths from other causes as competing risks, with time from subsequent malignant neoplasm diagnosis used as the time scale.
- c. Multivariable models: Cox proportional hazards models will be used to assess associations between the risk of subsequent malignant neoplasms and categorical ADI, SVI, and modern redlining variables. Multivariable analyses evaluating associations between specific SMN risks and neighborhood-level SES will be based on the following models. Model 1 (baseline model): adjust for basic clinical and demographic factors (age at initial diagnosis, sex, initial cancer diagnosis, race/ethnicity for ADI-specific model). Model 2 (add personal socioeconomic factors): model 1 and further adjust for educational attainment, health insurance, employment, income. Model 3 (add lifestyle factors): model 1 and model 2, as well as adjusting for smoking status, BMI, physical activity. Model 4 (to be utilized in analysis for cause-specific mortality) will include variables from Model 1 and chronic health condition (CHCs) burden (lower vs higher than median CHC burden). Cox regression models will be used to assess mortality risk associations with each ADI, SVI, and modern redlining exposure group. Age will be used as the time scale with entry to analysis (age at initial geocode timepoint or SMN diagnosis) and censoring at age of last follow-up (or death for analysis of SMN risk) or date of National Death Index data abstraction for analysis of mortality risk.
- d. Exploratory Aim 1: Present the cross-sectional association of staging (early vs late) at diagnosis of secondary breast cancer (~430 cases) and risk for relapse and various

neighborhood-level measures of social determinants of health of survivors included in analyses. Multivariable logistic regression models adjusting for demographic characteristics (age at initial diagnosis, sex, initial cancer diagnosis, time since initial cancer diagnosis, race/ethnicity for ADI-specific model) will be assessed.

- e. Exploratory Aim 2: Present changes in neighborhood-level SES variables after SMN diagnosis. Utilizing most-recent geocoding prior to SMN diagnosis and most-recent geocoding after SMN diagnosis, assess for positive or negative changes in neighborhood-level SES measures related to SMN diagnosis.

Proposed Tables and Figures:

Table 1. Basic demographic and treatment characteristics of survivors

	With geocoding data		No geocoding data	
	N	%	N	%
Mean age at primary diagnosis, years				
Age at primary diagnosis, years				
0-4 y				
5-9 y				
10-14 y				
≥ 15 y				
Sex				
Male				
Female				
Race and ethnicity				
White, NH				
Black, NH				
Hispanic				
Other (Asian, Native American/Pacific Islander)				
Unknown				
Decade of diagnosis				
1970-79				
1980-89				
1990-99				
Childhood cancer diagnosis				
ALL				
AML				
Other leukemia				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
CNS malignancy				
Wilms tumor				
Osteosarcoma				
Ewing sarcoma				
Other bone cancer				
Neuroblastoma				
Soft tissue sarcoma				
Chemotherapy				
Anthracycline (mg/m ²)				
None				
1-100				
101-300				
>300				

	With geocoding data		No geocoding data	
	N	%	N	%
Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000				
Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+				
Platinum agents (mg/m2) None 1-400 401-750 >750				
Radiation Yes No				
Hematopoietic cell transplantation Yes No				
Vital status Alive Deceased				
Survival after childhood cancer diagnosis, years 5-9 10-14 15-19 20-24 25-29 30-34 ≥35				
Number of person-years since cohort entry				
Mean years of follow up from diagnosis, years				
Smoking status Non-smoker Current smoker Ever smoked				
BMI, n (%) Underweight Normal Overweight Obesity				
Physical Activity (as per CDC criteria) Yes No				
Health Insurance Status Yes No				
Household Income < 20,000				

	With geocoding data		No geocoding data	
	N	%	N	%
20-39,999 40-59,999 60-79,999 80-99,999 ≥ 100,000				
Marital Status Currently married Never married Ever married NA				
Living Independently Yes No NA				
Employment Yes No NA				
Educational Attainment ≥ college degree < college degree NA				
ADI Q1 Q2 Q3 Q4 Q5				
SVI Q1 Q2 Q3 Q4 Q5				
Redlining index Redlining Index < 2 Redlining Index ≥ 2				

ADI, Area Deprivation Index; NH, Non-Hispanic; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CED, Cyclophosphamide Equivalent Dose

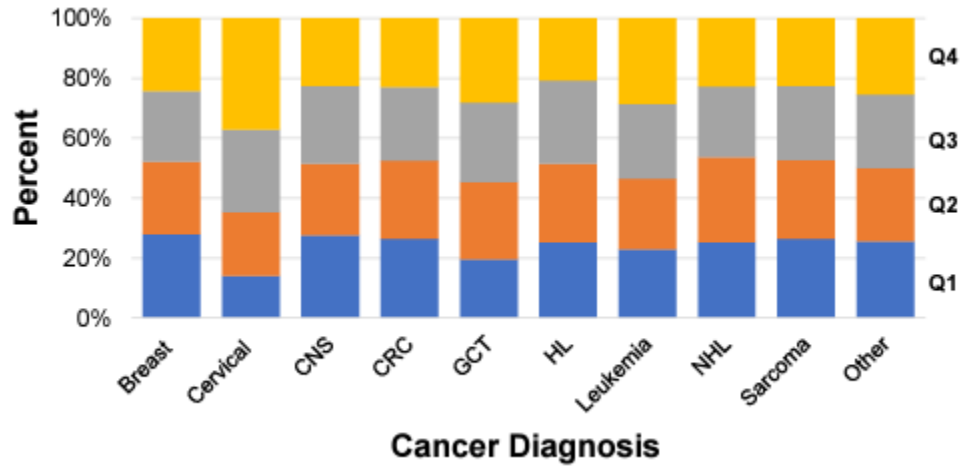


Figure 1: Neighborhood-level SES factor distribution by SMN type (illustrative example above with ADI quartiles, Q1-Q4)

- Add columns for “no SMN” and “any SMN”
- Specific SMN types shown in Table 2
- Three panels, each dedicated to: ADI quintiles, SVI quintiles, and redlining index grades

Table 2. Characteristics of subsequent malignant neoplasm (SMN) cases by initial geocode-based neighborhood-level SES factors

	ADI (repeat for SVI, redlining index)				
	Q1	Q2	Q3	Q4	Q5
Time from childhood cancer diagnosis to SMN diagnosis, years: % (N) 5-10 10.1-15 >15					
Age at SMN diagnosis, years: % (N) ≤30 31-50 >50					
SMN subtype, 15-year cumulative incidence (95% CI) Any SMN Leukemia Sarcoma Breast Cancer Thyroid Cancer Lymphoma Colorectal Cancer Other Solid Tumors Melanoma					
SMN subtype, cumulative burden by age 40y (95% CI) Any SMN Leukemia Sarcoma Breast Cancer Thyroid Cancer Lymphoma Colorectal Cancer Other Solid Tumors Melanoma					

ADI, Area Deprivation Index; SMN, Subsequent Malignant Neoplasm

Figure 2: Cumulative incidence and burden for overall and specific subsequent malignant neoplasms for survivors based on area deprivation index

Figure 3: Cumulative incidence and burden for overall and specific subsequent malignant neoplasms for survivors based on social vulnerability index (composite and sub-measures)

Figure 4: Cumulative incidence and burden for overall and specific subsequent malignant neoplasms for survivors based on modern redlining

Table 4. Mortality after SMN diagnosis by neighborhood-level SES factors

	ADI (repeat for SVI, redlining index)				
	Q1	Q2	Q3	Q4	Q5
Vital status Deceased, % (N)					
Cause-specific mortality cumulative incidence after breast SMN 5-year (95% CI) 10-year (95% CI) 15-year (95% CI)					
Cause-specific mortality cumulative incidence after colorectal SMN 5-year (95% CI) 10-year (95% CI) 15-year (95% CI)					

Figure 5. Cumulative incidence of cause-specific mortality after diagnosis of specific subsequent malignant neoplasms for survivors based on area deprivation index

Figure 6. Cumulative incidence of cause-specific mortality after diagnosis of specific subsequent malignant neoplasms for survivors based on social vulnerability index (composite and sub-measures)

Figure 7. Cumulative incidence of cause-specific mortality after diagnosis of specific subsequent malignant neoplasms for survivors based on modern redlining

Q1 (ref.) Q2 Q3 Q4 Q5								
Redlining index <2 (ref.) ≥2								

Table 6. Association between breast cancer stage at diagnosis and ADI, SVI, and modern redlining (Exploratory Aim)
 Adjusted for sex, age at childhood cancer diagnosis, race/ethnicity, time since initial cancer diagnosis

	OR (95% CI) Early-stage	OR (95% CI) Late-stage
Low ADI	Ref.	Ref.
High ADI		
Low SVI (composite)	Ref.	Ref.
High SVI (composite)		
Low SVI (socioeconomic status)	Ref.	Ref.
High SVI (socioeconomic status)		
Low SVI (household composition)	Ref.	Ref.
High SVI (household composition)		
Low SVI (race/ethnicity)	Ref.	Ref.
High SVI (race ethnicity)		
Low SVI (housing/transportation)	Ref.	Ref.
High SVI (housing/transportation)		
Redlining Index < 2	Ref.	Ref.
Redlining Index \geq 2		

ADI, Area Deprivation Index; SVI, Social Vulnerability Index;

Table 7. Association between breast cancer relapse and ADI, SVI, and modern redlining Adjusted for sex, age at childhood cancer diagnosis, race/ethnicity, time since initial cancer diagnosis

	OR (95% CI)	<i>p</i> -value
Low ADI	Ref.	
High ADI		
Low SVI (composite)	Ref.	
High SVI (composite)		
Low SVI (socioeconomic status)	Ref.	
High SVI (socioeconomic status)		
Low SVI (household composition)	Ref.	
High SVI (household composition)		
Low SVI (race/ethnicity)	Ref.	
High SVI (race ethnicity)		
Low SVI (housing/transportation)	Ref.	
High SVI (housing/transportation)		
Redlining Index < 2	Ref.	
Redlining Index ≥ 2		

ADI, Area Deprivation Index; SVI, Social Vulnerability Index;

Table 8. Description of Changes to Neighborhood Socioeconomic Deprivation with SMN diagnosis (Exploratory Aim)

	N=
ADI Score Decrease No change Increase	
SVI Composite Score Decrease No change Increase	
SVI Socioeconomic Score Decrease No change Increase	
SVI Household Composition Score Decrease No change Increase	
SVI Race/Ethnicity Score Decrease No change Increase	
SVI Housing/Transportation Score Decrease No change Increase	
Modern Redlining Index Decrease No change Increase	

ADI, Area Deprivation Index; SVI, Social Vulnerability Index; SMN, Subsequent Malignant Neoplasm; SD, Standard Deviation

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