Study title: Effects of Substance Use on Long-Term Health Outcomes in Childhood Cancer Survivors

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Working groups: Cancer Control (Primary), Chronic Diseases (Secondary), Subsequent Neoplasm (Secondary), Psychology (Secondary)

Background and rationale: Currently, over 500,000 long-term survivors of childhood cancer live in the United States (US), and this number is increasing.[1] Unfortunately, young survivors have a markedly elevated incidence of poor health outcomes despite cure. This includes a higher rate of subsequent malignant neoplasms, with cumulative incidence of 20.5% at 30 years after the childhood cancer diagnosis.[2] This risk is especially high in female patients diagnosed at older ages, in earlier treatment eras, and who were treated with radiation. Risk persists beyond age 50, with survivors continuing to have an SMR of 4.7 for death due to new cancer even after reaching that age.[3] Childhood cancer survivors also face a 4.2-5.6-fold increased risk of developing severe, life-threatening, or fatal (CTCAE grade 3-5) chronic health conditions (CHC) compared to their siblings. These include elevated risks specifically in cardiovascular,[4] pulmonary,[5] gastrointestinal,[6] and endocrine[7] conditions compared to siblings. Furthermore, despite receiving similar treatments, not all survivors experience the same late effects profile. This suggests

modifiable risk factors, like health behaviors, may influence long-term health outcomes and could be targeted in interventions.[8]

Few studies have directly and discretely measured the contribution of substance use to excess risk for poor health outcomes, including CHCs and SMNs, in survivors. This is despite the fact that substance use, like tobacco smoking and heavy alcohol consumption, are well-established carcinogens and causes of chronic disease in the general population.[9-14] Use of these substances may further-increase risk for heart disease, pulmonary dysfunction, GI/endocrine disorders (such as diabetes, hepatic dysfunction, and dyslipidemia) and subsequent cancers in survivors beyond known cancer treatment exposures.[15-18] It has also been suggested that alcohol and tobacco could act synergistically with each other and/or with cancer treatment (e.g. receipt of radiation therapy) to elevate subsequent cancer risk in survivors. While, it is recommended that survivors avoid excess substance use,[19] there is concern that childhood cancer survivors – who often received mutagenic treatments early in life – are ***more*** susceptible to health effects of substance use compared to those without certain cancer exposures or a history of cancer at all.

Taken together, current evidence highlights an important research gap. The role of substance use (e.g., tobacco smoking, alcohol use) in driving excess CHC and SMN risk has not been directly quantified, and may differ amongst cancer survivors with certain diagnoses/treatment exposures as well as versus siblings without a history of cancer. Since risky health behaviors tend to cluster and can exacerbate other late effects, it is critical to evaluate whether smoking and alcohol use further increase survivors' already elevated CHC and SMN risk. Determining effects of these modifiable health behaviors would provide both clinical insight and justification into prevention opportunities for this vulnerable population.

Specific aims/objectives/research hypotheses:

Aim 1: Evaluate morbidity risk among childhood cancer survivors in relation to their smoking behaviors.

Aim 1.1 (survivor vs sibling comparison): Compare morbidity risk between survivors and siblings in relation to smoking behaviors.

- **Hypothesis 1.1:** Survivors with prior or current smoking behaviors have a higher SMN, cardiometabolic and pulmonary CHCs risk, compared to their siblings with similar smoking exposures.

Aim 1.2 (within survivors): Assess how smoking is associated with adverse health outcomes among survivors.

- **Hypothesis 1.2a:** Survivors with current smoking behaviors have a higher risk of SMN, cardiometabolic and pulmonary CHCs compared to survivors who never smoked, with former smokers' risk closer to non-smokers compared to current smokers.
- **Hypothesis 1.2b**: The risk of SMN, cardiometabolic CHCs, and pulmonary CHCs, is increased in a dose response fashion (e.g., cumulative pack-years history) among survivors.

Aim 2: Evaluate morbidity risk among childhood cancer survivors in relation to their alcohol use.

Aim 2.1 (survivor vs sibling comparison): Compare morbidity risk between survivors and siblings in relation to alcohol use.

- **Hypothesis 2.1:** Survivors with risky alcohol use (risky/heavy current or former use) have a higher SMN, cardiometabolic CHC, and total burden of CHC risk compared to their siblings with similar alcohol exposures.

Aim 2.2 (within survivors): Assess how alcohol use is associated with adverse health outcomes among survivors.

- **Hypothesis 2.2a:** Survivors with current risky alcohol use (risky/heavy current) have a higher SMN, cardiometabolic CHC, and total burden of CHC risk compared to survivors without risky alcohol use, with former users risk closer to non-drinkers compared to current risky drinkers.
- **Hypothesis 2.2b:** The risk of SMN, cardiometabolic CHCs, and pulmonary CHCs, is increased in a dose response fashion (e.g., estimated years of current risky/heavy drinking reported across baseline/FU surveys) among survivors.

Aim 3: Evaluate morbidity risk among childhood cancer survivors in relation to their poly-substance use (current/former smoking plus risky alcohol use).

Aim 3.1 (survivor vs sibling comparison): Compare morbidity risk between survivors and siblings in relation to poly-substance use.

- **Hypothesis 3.1:** Survivors with prior or current poly-substance use have a higher SMN, cardiometabolic CHC, pulmonary CHC, and total burden of CHC risk compared to siblings with similar substance use exposures.

Aim 3.2 (within survivors): Assess how poly-substance use is associated with adverse health outcomes among survivors.

- **Hypothesis 3.2a:** Survivors with prior or current poly-substance use have a higher SMN, cardiometabolic CHC, pulmonary CHC, and total burden of CHC risk compared to survivors without poly-substance use.
- **Hypothesis 3.2b:** The risk of SMN, cardiometabolic CHCs, and pulmonary CHCs, is increased in a dose response fashion (e.g., estimated years of current poly-substance use reported across baseline/FU surveys) among survivors.

Analysis framework:

Population of interest: We will include Childhood Cancer Survivor Study (CCSS) survivors and siblings from the original and expansion cohorts who ***(Figure 1)***:

- Were alive at Baseline/Expansion Baseline assessments
- Have substance use data (e.g., alcohol, smoking behaviors) available at Baseline/Expansion Baseline, FU2, FU4, FU5 and/or FU7 assessments
- Have subsequent CHC/SMN (survivor cohort) or primary/subsequent cancer+CHC (sibling cohort) data at Baseline/Expansion Baseline assessments as well as any FU assessment

Exposure variable(s) of interest: Self-reported

- *Smoking:* Current smokers are defined as individuals who reported being current smokers on the survey queried and had a history of consuming at least 100 cigarettes in their lifetime. Former smokers are defined as individuals who had

smoked a minimum of 100 cigarettes in their lifetime but were not presently smoking on the survey queried. Nonsmokers are defined as individuals who reported having smoked less than 100 cigarettes throughout their lifetime in the survey queried. We will also calculate approximate "pack-years" across Baseline/Expansion Baseline and FU surveys to create a dose-response/cumulative smoking exposure variable. This will be assessed continuously.

- *Risky or heavy drinking*: Heavy drinking is defined as consumption of six or more drinks per day for men or five or more drinks per day for women, occurring at least once per month. Similarly, risky drinking is defined as the consumption of at least four drinks per day or 14 drinks per week for men, and at least three drinks per day or seven drinks per week for women. These definitions are based on NIAAA guidelines and analogous to other CCSS analyses. We will also calculate approximate "risky drinking years" across Baseline/Expansion Baseline and FU surveys to create a dose-response/cumulative risky drinking exposure variable. This will be assessed continuously.

Outcome variables of interest: The first primary outcome is subsequent malignant neoplasms (SMN), defined by CCSS as any self- or proxy-report primary invasive cancer (SEER site codes) occurring ≥5 years after the original diagnosis (excluding recurrences) and validated from pathology reports, medical records or death certificates.[20] We will also examine incidence of:

- Non–melanoma skin cancers (NMSC)
- Meningioma (benign intracranial meningiomas)

Additionally, we will define CHCs overall and by

- Any grade (1-5) CCSS' adaptation of Common Terminology Criteria for Adverse Events (CTCAE, version 5)
- Severe or life-threatening (grades 3-5)
- Cardiometabolic conditions (any grade+grade 3-5)
    - Hypertension
    - Dyslipidemia
    - Major adverse cardiovascular events (heart failure CTCAE grade 3+, coronary artery disease CTCAE grade 3+, stroke CTCAE grade 4+)
    - Diabetes
    - Cirrhosis (grade 3), needing a liver transplant (Grade 4), or fatal liver disease (Grade 5)
- Pulmonary conditions (any grade+grade 3-5)

Exploratory variables:

- Age at childhood cancer diagnosis, Baseline/Expansion Baseline, and most recent FU survey that CHC, SMN or substance use reported
- Sex (female/male)
- Race and ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, other)
- Marital status: Will represent as a dichotomous variable, separating participants who are married/living with a partner versus those who are single/widowed/divorced/separated/no longer living as married. If data are available at multiple time points, the variable will represent whether participants were married/living with a partner at any point during the study period. Depending

on the distribution of this variable across time points, the proportion of time points in which participants were married/living with a partner during the study period may also be considered.

- Insurance (yes/no): If data are available at multiple time points, the variable will represent whether participants were un-insured at any point during the study period.
- Education (less than high school, high school graduate, college graduate, post-graduate, unspecified): If data are available at multiple time points, the variable will represent highest educational attainment at any point during the study period.
- Employment (employed, unemployed/looking for job, student/retired, unspecified): If data are available at multiple time points, the variable will represent whether participants were employed at any point during the study period.
- Primary/Childhood cancer diagnosis (survivor participants only)
- Cancer treatments (survivor participants only): presented descriptively for survivor participants will include: Radiation therapy (total body irradiation (TBI), head, neck, chest, abdomen, pelvis, legs, arms – yes/no; cumulative Gy), surgery (brain, thoracic, laparotomy, amputation, limb-sparing, splenectomy, nephrectomy – yes/no), hematopoietic stem cell transplant (yes/no), alkylating agents (yes/no; total cumulative Cyclophosphamide-equivalent mg/m2 dose[21]), anthracyclines (yes/no; total cumulative Doxorubicin-equivalent mg/m2 dose[22]), Platinum agents (yes/no, total cumulative mg/m2 dose[23,24]), epipodophyllotoxins (yes/no, total cumulative mg/m2 dose), vinca alkaloids (yes/no, total cumulative mg/m2 dose), and glucocorticoids (yes/no, total cumulative mg/m2 dose)

Methods/Statistical Analyses:

Descriptive statistics will summarize characteristics of the analytic cohort (survivors and siblings), including age, sex, cancer diagnosis and treatment exposures (survivors only), and prevalence of substance use behaviors (smoking status, alcohol use, and polysubstance use). Differences in exposure prevalence and demographic characteristics between survivors and siblings will be evaluated using chi-square tests for categorical variables and t-tests or ANOVA for continuous variables, as appropriate. The frequency and type of cancer (SMNs, NMSC, and meningioma) and CHCs among survivors and siblings will be described overall and stratified by substance use exposure categories.

Survivor–Sibling Susceptibility Analyses (Aims 1.1, 2.1, and 3.1)

- To compare morbidity risk between survivors and siblings in relation to substance use, we will use Cox proportional hazards regression models with attained age as the time scale. To account for changes in substance use habits over time, smoking status, risky alcohol use, and polysubstance use will be modeled as time-varying covariates based on data across Baseline, FU2, FU4, FU5, and FU7 surveys.
- Models will include survivor status (survivor vs sibling), the respective substance use exposure, and a survivor × exposure interaction term to directly test for differential susceptibility.

  For outcomes evaluating the "total burden" of CHCs (Aims 2.1 and 3.1), time-to-event analyses will be conducted with the outcome defined as time to first occurrence of high or severe CHC burden. Hazard ratios (HRs) and 95%

confidence intervals (CIs) will be estimated using Cox proportional hazards regression models. Robust sandwich variance estimators will be applied to account for within-family correlation between survivors and siblings. Models will be adjusted for relevant demographic and socioeconomic variables.
As an alternative approach, the distribution of burden score categories across follow-up assessments will be examined. If sufficient numbers are observed across burden categories over follow-up, associations between substance use exposures and CHC burden severity will be evaluated using mixed-effects ordinal logistic regression models, with burden category as the outcome and participant-specific random effects included to account for repeated measures within individuals over time.

Within-Survivor Analyses (Aims 1.2, 2.2, and 3.2)

- To evaluate the longitudinal associations between substance use and adverse outcomes restricted to the survivor cohort, we will construct time-varying Cox proportional hazards models for distinct endpoints (SMNs, specific cardiometabolic, and pulmonary CHCs).
- For total CHC burden outcomes (Aims 2.2 and 3.2), time-to-event analyses will be conducted with the outcome defined as time to first occurrence of high or severe CHC burden. Hazard ratios (HRs) and 95% confidence intervals (CIs) will be estimated using Cox proportional hazards regression models. Models will adjust for demographic, socioeconomic, and detailed treatment-related covariates (e.g., radiation fields/doses, specific chemotherapy agent classes, and surgery).
  As an alternative approach, the distribution of burden score categories across follow-up assessments will be examined. If sufficient numbers are observed across burden categories over follow-up, associations between substance use exposures and CHC burden severity will be evaluated using mixed-effects ordinal logistic regression models, with burden category as the outcome and participant-specific random effects included to account for repeated measures within individuals over time.

- To evaluate the dose-response hypotheses (1.2b, 2.2b, and 3.2b), cumulative exposure variables (continuous pack-years, continuous risky drinking years, and cumulative years of poly-substance use) will be calculated across longitudinal waves. These will be entered into models as continuous variables to evaluate linear trends. To explore potential non-linear thresholds or acceleration of risk, we will additionally fit models using restricted cubic splines.

Special considerations: None

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Figure 1: CONSORT diagram for study participation

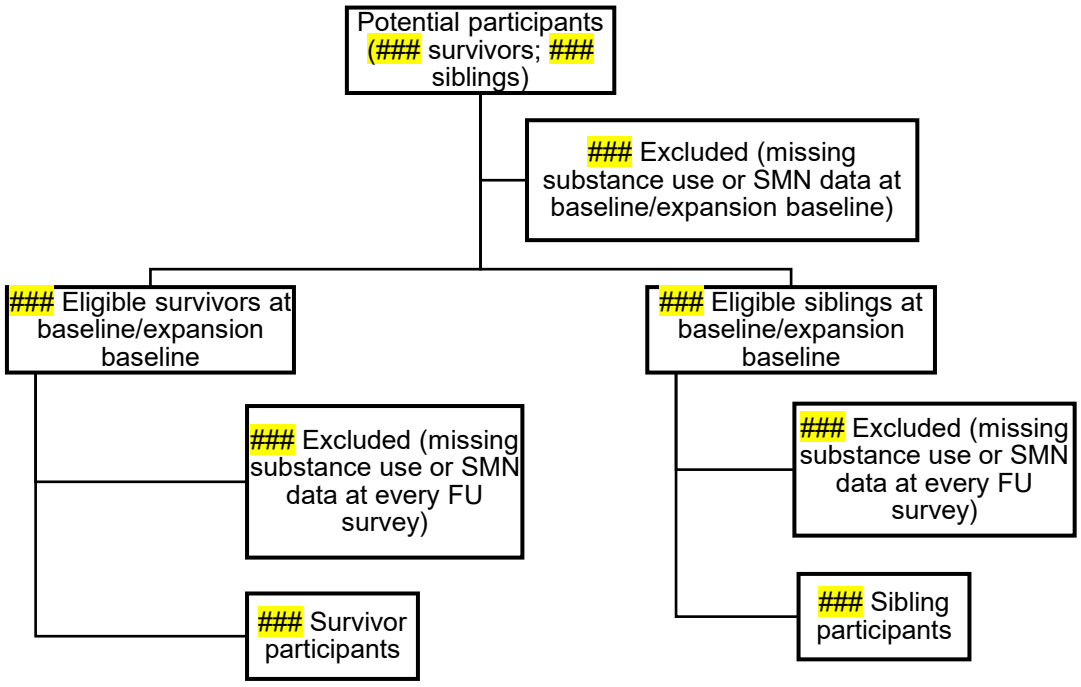

Figure 2. Cumulative incidence of SMN by exposure status. For example, two panels or lines: survivors who ever smoked vs never, and siblings who ever smoked vs never (or overlay four curves: survivor-smoker, survivor-nonsmoker, sibling-smoker, sibling-nonsmoker)

Figure 3. Forest plot of adjusted hazard ratios for SMN by exposure, comparing survivors and siblings. This figure would display adjusted HRs (with 95% CI) for each exposure category (e.g. former vs never smoker, current vs never smoker, risky-drinker vs not) for survivors (point markers) and for siblings. Interaction terms p-values could be annotated.

Table 1: Characteristics of childhood cancer survivors and siblings

	Survivors (n=***)	Siblings (n=***)	*p*-value
Age at diagnosis (M, SD)			
Age at baseline/expansion baseline (M, SD)			
Age at last FU (M, SD)			
Sex (n, %)			
Male			
Female			
Race/Ethnicity (n, %)			
Non-Hispanic white			
Non-Hispanic Black			
Hispanic, any race			
Other			
Marital Status (n, %)			
Married/Living with a partner			
Single/widowed/divorced/separated/no longer living as married			
Insurance (n, %)			
Education (n, %)			
Less than high school			
High school graduate			
College graduate			
Post-graduate			
Unspecified			
Employed			
Unemployed/Looking for job			
Student/Retired			
Unspecified			
Primary Cancer Diagnosis (n, %)			
Leukemia			
Lymphoma			
CNS tumors			
Neuroblastoma			
Bone/Soft tissue sarcomas			

Kidney tumors			
Radiation (n, %)			
Total Body Irradiation (with dose in cGy, M, SD)			
Head/Neck (with dose in cGy, M, SD)			
Dose ≥ 20 Gy (n, %)			
Chest (with dose in cGy, M, SD)			
Dose ≥10 Gy (n, %)			
Dose ≥15 Gy (n, %)			
Abdomen/Pelvis (with dose in cGy, M, SD)			
Legs/Arms (with dose in cGy, M, SD)			
Hematopoietic stem cell transplant (n, %)			
Chemotherapy (n, %)			
Alkylating agents (with total cumulative Cyclophosphamide-equivalent mg/m2 dose, M, SD)			
Busulfan / Cyclophosphamide / Carmustine / Lomustine exposure (n, %)			
Anthracyclines (with total cumulative Doxorubicin-equivalent mg/m2 dose, M, SD)			
Total dose ≥250 mg/m2			
Epipodophyllotoxins (with total cumulative mg/m2 dose, M, SD)			
Glucocorticoids (with total cumulative mg/m2 dose, M, SD)			
Platinum agents (with total cumulative mg/m2 dose, M, SD)			
Vinca-alkaloids (with total cumulative mg/m2 dose, M, SD)			
Surgery			
Brain			
Thoracic			
Laparotomy			
Amputation			
Limb-sparing			
Splenectomy			
Nephrectomy			
Substance use			
Smoking (n, %)			
Current			
Former			
Never			
Alcohol (n, %)			
Current			
Risky			
Heavy			

Subsequent malignant neoplasms (SMNs; survivors only) or primary invasive cancer (siblings)			
Non–melanoma skin cancers (NMSC)			
Meningioma (benign intracranial meningiomas)			
CHCs			
Any grade			
Grade 3-5			
Cardiometabolic conditions (any grade+grade 3-5) -Hypertension -Dyslipidemia -Major adverse cardiovascular events (heart - failure CTCAE grade 2+, coronary artery disease CTCAE grade 3+, stroke CTCAE grade 4+) -Diabetes -Cirrhosis -Need for liver transplant -Fatal liver disease			
Pulmonary conditions (any grade+grade 3-5)			

Table 2. Adjusted hazard ratios (HRs) for SMN/primary invasive cancer by smoking and alcohol exposure

	Survivors HR (95% CI)	Siblings HR (95% CI)	*p*-value
Smoking status			
- Never smoker (ref)	1.00	1.00	—
- Former smoker	***	***	***
- Current smoker	***	***	***
Risky alcohol use			
- No (ref)	1.00	1.00	—
- Yes	***	***	***
Combined exposure			
- Neither (ref)	1.00	1.00	—
- Smoking only	***	***	***
- Risky drinking only	***	***	***
- Heavy drinking only	***	***	***
- Both smoking and risky drinking	***	***	***
- Both smoking and heavy drinking	***	***	***

Table 3. Adjusted hazard ratios (HRs) for CHCs by smoking and alcohol exposure

Structure TBD