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## Requirements to submit AOI

A comprehensive review of previously published data has been completed	Yes
The specific aims are clear and focused	Yes
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.	Yes
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months	Yes

<b>Project Title</b>	Associations Between Smoking, Risky Alcohol Use, and Second Malignant Neoplasms in Childhood Cancer Survivors Compared to their Siblings
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### Planned research population (eligibility criteria)

Childhood Cancer Survivor Study (CCSS) survivors and siblings from the original and expansion cohorts who:

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

### Proposed specific aims

Aim 1: Compare the risk of second cancers between childhood cancer survivors and their sibling controls in relation to smoking behaviors.

--Hypothesis: Childhood cancer survivors with prior or current smoking behaviors have a higher risk of second cancers compared to their sibling controls who have similar smoking exposures.

--Methods: Compare the frequency and type of cancers (SMNs, NMSC, and meningioma) between childhood cancer survivors (second cancers) and their sibling cohort (primary/second cancers). Stratify analysis by

smoking categories (current/history), and assess the relative risk of second cancers between the groups.

Aim 2: Compare the risk of second cancers between childhood cancer survivors and their sibling controls in relation to risky alcohol use.

--Hypothesis: Childhood cancer survivors with risky alcohol use (risky/heavy current or former use) have a higher risk of second cancers compared to their sibling controls who have similar alcohol exposures.

--Methods: Compare the frequency and type of cancers (SMNs, NMSC, and meningioma) between childhood cancer survivors (second cancers) and their sibling cohort (primary/second cancers). Stratify analysis by alcohol use categories (risky/heavy current or former use), and assess the relative risk of second cancers between the groups.

Aim 3: Compare the risk of second cancers between childhood cancer survivors and their sibling controls in relation to poly-substance use (smoking plus risky alcohol use).

--Hypothesis: Childhood cancer survivors with prior or current poly-substance use have a higher risk of second cancers compared to their sibling controls who have similar substance use exposures.

--Methods: Compare the frequency and type of cancers (SMNs, NMSC, and meningioma) between childhood cancer survivors (second cancers) and their sibling cohort (primary/second cancers). Stratify analysis by substance use categories (current/history smoking plus risky/heavy current or former alcohol use), and assess the relative risk of second cancers between the groups.

**Will the project require non-CCSS funding to complete?**

No

**If yes, what would be the anticipated source(s) and timeline(s) for securing funding?**

**Does this project require contact of CCSS study subjects for:**

Additional self-reported information	No
Biological samples	No
Medical record data	No

**If yes to any of the above, please briefly describe.**

N/A

**What CCSS Working Group(s) would likely be involved? (Select all that apply)**

	Primary	Secondary
Second Malignancy		✓
Chronic Disease		
Psychology/Neuropsychology		✓
Genetics		
Cancer Control	✓	
Epidemiology/Biostatistics		

## Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality			✓
Second Malignancy	✓		

## Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco			
Alcohol			
Physical Activity			✓
Medical Screening			✓
Other			

## If other, please specify

Exposure/Independent variables = tobacco and alcohol use data

## Psychosocial

	Primary	Secondary	Correlative Factors
Insurance			✓
Marriage			✓
Education			✓
Employment			✓
Other			

## If other, please specify

## Medical Conditions

	Primary	Secondary	Correlative Factors
Hearing/Vision/Speech			✓
Hormonal Systems			✓
Heart and Vascular			✓
Respiratory			✓
Digestive			✓
Surgical Procedures			✓
Brain and Nervous System			✓
Other			✓

If other, please specify

chronic health conditions (CTCAEv3 - see below)

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## Medications

Describe medications

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			✓
SF-36			✓
CCSS-NCQ			
PTS			
PTG			
Other			

If other, please specify

Other

	Primary	Secondary	Correlative Factors
Pregnancy and Offspring			
Family History			✓
Chronic Conditions (CTCAE v3)			✓
Health Status			✓

## Demographic

	Primary	Secondary	Correlative Factors
Age			✓
Race			✓
Sex			✓
Other			

If other, please specify

## Cancer Treatment

	Correlative Factors
Chemotherapy	✓
Radiation Therapy	✓
Surgery	✓

## Anticipated Sources of Statistical Support

CCSS Statistical Center	Yes
Local Institutional Statistician	No

If local, please provide the name(s) and contact information of the statistician(s) to be involved.

Will this project utilize CCSS biologic samples?

No

If yes, which of the following?

If other, please explain

## Other General Comments

This AOI has been discussed and aims approved for submission by the leads of the Cancer Control (Paul Nathan and Claire Snyder), SMN (Lucie Turcotte), and Psychology (Tara Brinkman) working groups. Dr. Schwartz will be working locally with two substance use researchers, Dr. Andrea King and Dr. Emma Brett, on this study.

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### Agree

I agree to share this information with St. Jude

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