1. **STUDY TITLE:** Chronic Alcohol Consumption, Neurocognitive Dysfunction, and Psychological Distress in Adult Survivors of Childhood Cancer

2. **WORKING GROUP AND INVESTIGATORS**

2.1. Working Group: Psychology; Cancer Control

2.2. Investigators:

Tara M. Brinkman	tara.brinkman@stjude.org
E. Anne Lown	alown@arg.org
Margaret L. Stuber	mstuber@mednet.ucla.edu
Marilyn Stovall	mstovall@mdanderson.org
Jordan Gilleland	jordan.gilleland@choa.org
Leslie L. Robison	les.robison@stjude.org
Gregory T. Armstrong	greg.armstrong@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Paul Nathan	paul.nathan@sickkids.ca
Kevin R. Krull	kevin.krull@stjude.org

3. **BACKGROUND AND RATIONALE**

It is well-established that survivors of pediatric malignancies are at-risk for neurocognitive morbidities. Cancer specific risk factors include treatment with neurotoxic agents (i.e., cranial radiation, antimetabolite chemotherapy) or neurosurgery, particularly when these treatments occur at younger age of diagnosis. Importantly, cancer survivors also are susceptible to factors affecting cognition in the general population, including aging, chronic medical conditions, psychological health, and lifestyle factors such as diet and medication use, social engagement, physical activity, sleep, and tobacco and alcohol use. We have recently demonstrated that sleep disturbance and psychoactive medication treatment can exacerbate neurocognitive dysfunction in long-term survivors.[1,2] How other factors contribute to cognitive functioning in adult survivors of childhood cancer survivors beyond treatment-induced impairment is largely unknown.

In the CCSS cohort, 16 percent of adult survivors reported risky drinking patterns and 8 percent reported heavy drinking at baseline.[3] While the chronicity of these drinking patterns has not yet been reported in CCSS, in other adult populations heavy drinking and chronic alcohol use are strongly associated with neurocognitive impairment. These impairments include difficulties with memory, attention, processing speed, problem solving, executive functions, and visuospatial abilities. In addition to observed effects on performance-based neurocognitive tasks, patterns of brain activation as well as reduced gray and white matter volumes have been associated with heavy alcohol use, suggesting neurobiological changes secondary to chronic alcohol consumption.[4]

Individuals who have sustained brain injuries may have increased sensitivity to the effects of alcohol and the additive effects of alcohol use and brain injury have been reported. Specifically, the combined effects of alcohol abuse and brain injury have been associated with reduced prefrontal medial gray matter volume as well as reduced vocational outcomes compared to brain injury or alcohol use alone.[5] Baguley et al[6] demonstrated an additive effect of traumatic brain injury and alcohol abuse on electrophysiologic correlates of

cognition compared to either traumatic brain injury or alcohol abuse alone. Similar to traumatic brain injury, childhood cancer survivors who received neurotoxic cancer treatments have sustained diffuse brain injury and may have increased sensitivity to the effects of alcohol on cognitive processes.

Adult survivors of childhood cancer who initiate alcohol use during adolescence have a two-fold increased risk for later heavy drinking compared to peers who initiated drinking at the same age.[3] The effects of heavy drinking on cognition may be especially salient during adolescence given the continued maturation of the brain during this stage of development. Animal studies have shown decreased neurogenesis in the adolescent forebrain and hippocampus following ethanol exposure.[7] In human adolescents, prefrontal cortex and hippocampus volumes appear reduced in heavy drinkers. Moreover, longitudinal studies have demonstrated that persistent heavy, chronic alcohol use from adolescence to young adulthood is associated with visuospatial and memory deterioration.[8] Thus, survivors of childhood cancer who initiate drinking in early adolescence may be at increased risk for neurocognitive dysfunction due to: 1) increased risk for later heavy drinking and associated cognitive morbidities and/or 2) the direct effects of alcohol on brain maturation in a potentially compromised nervous system following exposure to neurotoxic cancer treatments.

In addition to having adverse effects on cognition, heavy alcohol consumption has been implicated in the emergence, persistence, and worsening of mental health conditions such as depression and anxiety.[9] Epidemiologic data suggest that up to 40% of adults who sought treatment for alcohol use disorders had at least one independent mood disorder[10] and roughly 20% had alcohol-induced mood or anxiety disorders. Results from a 25-year longitudinal study suggest a causal pathway from alcohol abuse or dependence to major depression,[11] though other studies have suggested reciprocal causation. Much evidence also suggests high levels of comorbidity between post-traumatic stress symptoms and alcohol use in the general population, though the mechanism responsible for the relationship has not been elucidated. Previous analyses of CCSS data indicate that among survivors, symptoms of anxiety, depression, and somatization are associated with heavy drinking.[3]

Given survivors' risk for treatment-induced neurocognitive impairment, the identification of modifiable lifestyle factors that may exacerbate or mitigate such deficits is important toward the selection and/or development of cognitive intervention strategies. Moreover, understanding the associations between health behaviors, such as chronic alcohol consumption, and psychological health has the potential to similarly inform mental health interventions for this patient population.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES

4.1. **Aim 1:** To examine the association between alcohol consumption and neurocognitive function in adult survivors of childhood cancer.

Hypothesis 1a: Chronic alcohol consumption will be associated with greater risk of impaired neurocognitive function.

Hypothesis 1b: Younger age at drinking initiation will be associated with increased risk of impaired neurocognitive function.

4.2. **Aim 2:** To examine the association between alcohol consumption and psychological distress in adult survivors of childhood cancer.

Hypothesis 2a: Chronic alcohol consumption will be associated with increased risk for psychological distress and post-traumatic stress symptoms in survivors.

Hypothesis 2b: Chronic alcohol consumption will be associated with persistent and increasing psychological distress symptoms over time.

5. ANALYSIS FRAMEWORK

5.1. **Population:** Survivors who were ≥18 years of age at Baseline and completed the Baseline and 2007 surveys and the Neurocognitive Questionnaire at the 2003 Follow-up survey. Completion of Baseline and 2007 surveys is necessary to define chronic alcohol consumption (see primary predictor below). Neurocognitive data were only collected at the 2003 survey. As such, our analysis plan requires completion of all 3 surveys. **There are 3,590 CCSS participants who responded to the Baseline and 2007 alcohol questions and completed the 2003 NCQ.**

5.2. **Outcomes of Interest:** The primary outcome of interest is neurocognitive functioning as measured by the Neurocognitive Questionnaire (CCSS-NCQ). Neurocognitive data were collected using the NCQ at the 2003 Follow-up. The CCSS-NCQ is a 25-item questionnaire that provides a 3-point Likert scale (0=never a problem to 2=often a problem) for ratings of neurocognitive problems, and is comprised of 4 primary factors: Task Efficiency, Emotional Regulation, Organization and Memory. These factors provide measures of executive functioning (i.e. Emotional Regulation and Organization), attention and processing speed (i.e. Task Efficiency), and short and long-term memory (i.e. Memory). Consistent with previous CCSS studies, impaired performance will be defined as a score falling ≥90th percentile based on values obtained in the sibling cohort.

The secondary outcome of interest is psychological distress as measured by the Brief Symptom Inventory (BSI-18) and the Posttraumatic Stress Diagnostic Scale (PDS). Psychological distress data were collected using the BSI-18 at the time of each survey (Baseline [questions J.16 to J.35], 2003 Follow-up [questions G1 to G18], and 2007 Follow-up [questions L1 to L18]). Scores for Somatization, Depression, and Anxiety subscales and the composite Global Severity Index (GSI) will be examined as binary variables with T-scores ≥63 or above used as a cut-off to categorize survivors as psychologically distressed or not. Psychological distress will be defined as T-scores >63 at the 2003 follow-up. Persistent psychological distress will be defined as clinically significant distress (T-score >63) at Baseline, 2003, and 2007 follow-ups. Increasing psychological distress will be defined as non-significant distress at Basline (T-score <63) that increases at Follow-up 2003 and/or Follow-up 2007. Significant change in distress will be defined as a change greater than the 90% confidence interval of the standard error of the mean for each subscale and global composite. In a recent CCSS longitudinal analysis of psychological symptoms, we found that 8.8% of adult survivors reported persistently elevated distress and 10.3% reported increased distress over the 16-year CCSS follow-up.

Confidence Intervals of the Standard Errors for BSI subscales

	Standard Error	90% C.I.
Depression	4	6.6
Anxiety	4.58	7.56
Somatization	5.66	9.34
Global Severity Index	3.16	5.21

The PDS is a 17-item questionnaire that was included in the 2003 follow-up [questions K1-K17]. Questions are based on the criteria for PTSD in the DSM-IV. Symptoms are rated on a 4 point Likert scale to assess the frequency/severity of symptoms over the past month. Items endorsed at 1 or above will be counted as present. Survivors who report the DSM-IV diagnostic requirements of at least one re-experiencing symptom, two arousal symptoms and three avoidance symptoms (full PTS symptoms) with or without functional impairment (criteria F) will be eligible for this analysis. Previous CCSS data indicate that 16.5% of survivors meet these criteria.

5.3. **Primary Predictors**

5.3.1. Chronic alcohol consumption – (yes vs. no) defined as heavy and/or risky drinking at Baseline and 2007 [Baseline N.6, N.7; 2007 N3, N5, N6]

5.3.2. Heavy drinking

Men ≥6 drinks per day, at least once per month
Women ≥5 drinks per day, at least once per month

5.3.3. Risky drinking

Men >4 drinks per day or 14 drinks per week
Women >3 drinks per day or 7 drinks per week

5.3.4. Age at drinking initiation, years [Baseline N.4; 2007 N2]

We will treat this variable as continuous or by age group (<18 vs. ≥18 years). A decision will be made after reviewing the data and discussing relevant power issues with the assigned statistician.

5.4. **Covariates [for neurocognitive analysis]**

5.4.1. Age (years, continuous at 2003 survey)
5.4.2. Sex
5.4.3. Race/ethnicity (white/non-Hispanic vs. others)
5.4.4. Age at diagnosis (years, continuous)
5.4.5. Radiation

None
Non-cranial
>0Gy to <20Gy max dose to brain
≥20Gy max dose to brain

5.4.6. Cancer Diagnosis (separate model from treatment)

Leukemia
CNS tumors
Hodgkin
Non-Hodgkin
Neuroblastoma
Wilms
Soft tissue sarcoma
Osteosarcoma

5.5. **Covariates [for psychological distress analysis]**

5.5.1. Age (years, continuous at 2003 survey)
5.5.2. Sex
5.5.3. Race/ethnicity (white/non-Hispanic vs. others)
5.5.4. Age at diagnosis
5.5.5. Education (≤high school vs. > high school)
5.5.6. Employment (past year: yes vs. no)
5.5.7. Cancer-related pain (none, small amount vs. medium, a lot, very bad)
5.5.8. Physical health status (poor, fair vs. good, very good, excellent)
5.5.9. Radiation
- None
- Non-cranial
- >0Gy to <20Gy max dose to brain
- ≥20Gy max dose to brain

5.5.10. Cancer Diagnosis (separate model from treatment)
- Leukemia
- CNS tumors
- Hodgkin
- Non-Hodgkin
- Neuroblastoma
- Wilms
- Soft tissue sarcoma
- Osteosarcoma

5.6. **Statistical Modeling**

5.6.1. Frequency distributions will be used to categorize predictors, and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.

5.6.2. We will compare characteristics of survivors who completed the Baseline and 2007 survey with those who did not complete the 2007 survey (see Table 1). We will use these two surveys for comparison as these are the only time points when alcohol data were collected.

5.6.3. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percentages will be calculated for the primary outcomes of interest (neurocognitive function, psychological distress) as well as for the primary predictors (chronic alcohol consumption) and all covariates (Table 2). We will examine univariate associations and correlations among all predictors, covariates, and outcome measures.

5.6.4. To address the first aim, we will utilize logistic regression modeling with robust variance estimates to account for within subject correlation. Multivariable models adjusted for relevant covariates (identified above 5.4) will be fitted and risk ratios and 95% confidence intervals will be reported for each neurocognitive outcome (task efficiency, memory, organization, emotional control). The best fitting and most parsimonious model for each cognitive outcome will be selected using AIC (Table 3). For hypothesis 1a, chronic alcohol consumption (yes vs. no) will be the primary predictor of neurocognitive impairment. No chronic alcohol consumption, including drinkers and nondrinkers will serve as the referent group. For hypothesis 2a, age at drinking initiation, will be the primary predictor of

neurocognitive impairment. If numbers are sufficient, we will examine a potential interaction between age at drinking initiation and chronic alcohol consumption in relation to neurocognitive impairment. Similarly, we will examine potential a interaction between sex and chronic alcohol consumption in relation to neurocognitive impairment.

5.6.5. A similar modeling approach will be taken for the second aim, with indices of psychological distress and posttraumatic stress serving as outcomes for separate multivariable models. For hypothesis 2a, risk ratios will be calculated for the associations between chronic alcohol consumption (yes vs. no) and psychological distress (anxiety, depression, somatization) as measured at 2003 and posttraumatic stress as measured at 2003. We selected the 2003 survey for consistency with measurement of neurocognitive outcomes for Aim 1. For hypothesis 2b, three separate models will be constructed to examine whether chronic alcohol consumption is associated with (increasing/persistent depression, increasing/persistent anxiety, increasing/persistent somatization), adjusted for relevant covariates (identified above 5.5), and the best fitting logistic regression model will be selected using AIC. We will examine a potential interaction between sex and chronic alcohol consumption in relation to psychological distress.

Table 1.Comparision of survivors with and without 2007 survey data

	Survivors with Baseline Survey Only		Survivors with Baseline and 2007 Surveys	
	Mean(SD)	**Range**	**Mean(SD)**	**Range**
Age at diagnosis, years				
Time since diagnosis, years				
Baseline age, years				
Psychological distress at baseline				
Depression				
Anxiety				
Somatization				
	Frequency	**%**	**Frequency**	**%**
Gender				
Male				
Female				
Age at Drinking Initiation				
<18 years				
≥18 years				
Heavy Drinker at Baseline				
Yes				
No				
Risky Drinker at Baseline				
Yes				
No				
Diagnosis				
Leukemia				
CNS Tumor				
Hodgkin Lymphoma				
Non-Hodgkin Lymphoma				
Wilms Tumor				
Neuroblastoma				
Soft tissue sarcoma				
Osteosarcoma				
Radiation Therapy				
None				
Non-cranial				
CRT≤20Gy				
CRT>20Gy				

Table 2. Characteristics of study population (completed baseline, 2003, and 2007)

	M	SD
Age at Baseline		
Age at Diagnosis		
Current Age		
	N	%
Sex		
Female		
Male		
Race/Ethnicity		
White/non-Hispanic		
Other		
Chronic Alcohol Use		
Yes		
No		
Age at Drinking Initiation		
<18 years		
≥18 years		
Educational Attainment		
≤High School		
>High School		
Employed in past year		
Yes		
No		
Cancer-related pain		
None, small amount		
Medium amount, a lot, very bad		
Physical health status		
Poor, fair		
Good, very good, excellent		
Persistent/Increasing Anxiety		
Yes		
No		
Persistent/Increasing Somatization		
Yes		
No		
Persistent/Increasing Depression		
Yes		
No		
Cranial Radiation		
None		
Non-cranial		
<20Gy CRT		
≥20Gy CRT		

Table 3. Chronic Alcohol Use and Neurocognitive Impairment

	Impaired Task Efficiency	Impaired Memory	Impaired Organization	Impaired Emotional Control
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Chronic Alcohol Use				
Yes				
No	Ref	Ref	Ref	Ref
Age				
Age at diagnosis				
Race/ethnicity				
White/Non-Hispanic				
Other	Ref	Ref	Ref	Ref
Sex				
Male	Ref	Ref	Ref	Ref
Female				
Cranial Radiation				
None	Ref	Ref	Ref	Ref
Non-cranial				
>0Gy to <20Gy				
>20Gy				

Table 4. Age at Drinking Initiation and Neurocognitive Impairment

	Impaired Task Efficiency	Impaired Memory	Impaired Organization	Impaired Emotional Control
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Age at first drink				
<18 years				
≥18 years	Ref	Ref	Ref	Ref
Age				
Age at diagnosis				
Race/ethnicity				
White/Non-Hispanic				
Other	Ref	Ref	Ref	Ref
Sex				
Male	Ref	Ref	Ref	Ref
Female				
Cranial Radiation				
None	Ref	Ref	Ref	Ref
Non-cranial				
>0Gy to <20Gy				
≥20Gy				

Table 5. Chronic Alcohol Use and Psychological Distress

	Depression	Anxiety	Somatization	Posttraumatic Stress
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Chronic Alcohol Use				
Yes				
No	Ref	Ref	Ref	Ref
Age				
Age at diagnosis				
Age at first drink				
Race/ethnicity				
White/Non-Hispanic				
Other	Ref	Ref	Ref	Ref
Sex				
Male	Ref	Ref	Ref	Ref
Female				
Education				
≤high school				
>high school	Ref	Ref	Ref	Ref
Employment				
Yes	Ref	Ref	Ref	Ref
No				
Cancer Pain				
None, small amount	Ref	Ref	Ref	Ref
Medium, a lot very bad				
Physical Health Status				
Fair, poor				
≥Good	Ref	Ref	Ref	Ref
Radiation				
None	Ref	Ref	Ref	Ref
Non-cranial				
>0Gy to <20Gy CRT				
≥20Gy CRT				

Table 6. Chronic Alcohol Use and Persistent/Increasing Psychological Distress

	Persistent/Increasing Depression	Persistent/Increasing Anxiety	Persistent/Increasing Somatization
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Chronic Alcohol Use			
Yes			
No	Ref	Ref	Ref
Age			
Age at diagnosis			
Age at first drink			
Race/ethnicity			
White/Non-Hispanic			
Other	Ref	Ref	Ref
Sex			
Male	Ref	Ref	Ref
Female			
Education			
≤high school			
>high school	Ref	Ref	Ref
Employment			
Yes	Ref	Ref	Ref
No			
Cancer Pain			
None, small amount	Ref	Ref	Ref
Medium, a lot, very bad			
Physical Health Status			
Fair, poor			
≥Good	Ref	Ref	Ref
Radiation			
None	Ref	Ref	Ref
Non-cranial			
>0Gy to <20Gy CRT			
≥20Gy CRT			

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