CHILDHOOD CANCER SURVIVOR STUDY- Analysis Concept Proposal

1. TITLE: Tobacco Use Among Adult Siblings of Childhood Cancer Survivors

2. WORKING GROUP INVESTIGATORS: This proposed study will be within the Cancer Control Working Group (primary) and Psychosocial Working Group (secondary).

David Buchbinder	dbuchbin@uci.edu
Kevin Krull	Kevin.krull@stjude.org
Jennifer Ford	fordj@mskcc.org
Jacqueline Casillas	jcasillas@mednet.ucla.edu
Lonnie Zeltzer	lzeltzer@mednet.ucla.edu
Anne Lown	annelownhecht@gmail.com
Wendy Leisenring	wleisenr@fhcrc.org
Greg Armstrong	Greg.Armstrong@stjude.org
Leslie Robison	les.robison@stjude.org
Kevin Oeffinger	oeffingk@mskcc.org

3. BACKGROUND AND RATIONALE:

Having a sibling with childhood cancer may influence psychological and behavioral outcomes in adulthood. Childhood experiences with significant stress have the ability to undermine capacity for adaptation, the development of coping skills, and social networks [1-3]. Furthermore, stressful childhood experiences are associated with the development of adverse health behaviors as adults [1-3]. Research with siblings of children on active therapy for cancer demonstrates that siblings experience impaired psychosocial health including post-traumatic stress reactions, adverse emotional reactions, and impairment in quality of life [4-7]. The National Cancer Institute, Office of Cancer Survivorship states that "family members, friends, and caregivers are part of the survivorship experience [8]. Despite the demonstration of sibling psychosocial impairment and the acknowledgement of importance of characterizing the impact of the cancer experience on family members, little is known about these siblings when they reach adulthood.

Previous literature has reported some siblings of childhood cancer survivors to be at higher risk for post-traumatic stress symptoms [4-7] and adverse health behaviors including heavy and risky alcohol use behaviors [9-10]. Research documents that approximately one-third of siblings exhibit moderate to severe post-traumatic stress reactions consisting of intrusive thoughts, avoidance behaviors, physiologic reactivity, and hyper vigilance in the context of the cancer experience [4-7]. The correlation between post-traumatic stress reactions and adverse health behaviors such as risky or heavy alcohol use has also been documented in the general population [11-12]. Not surprisingly, siblings of childhood cancer survivors demonstrate greater risky and heavy alcohol use when compared to survivors and controls [9-10]. Sibling factors associated with risky and heavy alcohol use included younger age, male sex, lower educational attainment, and psychological distress including depression and anxiety. The possibility of a causal relationship between adverse stress reactions and negative health behaviors exists.

Tobacco use among siblings of childhood cancer survivors has not been systematically evaluated. Tobacco use is an adverse health behavior that has been associated with significant morbidity and mortality, as well as enormous costs in the general population including an increased risk of cancer [13-16]. The strong association with cancer risk is particularly worrisome given the increased risk of cancer that has been demonstrated among siblings of childhood cancer survivors [17-18]. Despite research characterizing the tobacco use practices of survivors themselves [19-

22], siblings were utilized as a control group when focusing on the tobacco use practices of childhood cancer survivors [21]. Compared to survivors, siblings were more likely to use tobacco. However, in-depth analysis of the sibling data was not done. Risk factors for tobacco use have been defined in the general population including sociodemographic factors such as age, sex, race/ethnicity, educational attainment, household income, and employment status [13-15]. Although many of these risk factors for tobacco use in the general population are also seen in cancer survivors, the distribution of these risk factors and possible additional risk factors that are unique to siblings have not been defined. Cancer-related factors including diagnosis, treatment intensity, and the presence of late effects may be associated with ongoing sibling distress [23]. As a result, cancer-related factors may serve as modifiers of tobacco use among siblings of childhood cancer survivors.

Further information, drawn from large, diagnostically diverse samples, is needed to best identify siblings at greatest risk for tobacco use in adulthood. This Childhood Cancer Survivor Study (CCSS) is the largest cohort of siblings of childhood cancer survivors. The CCSS has the potential to be a vital resource in understanding the impact of childhood cancer upon siblings. Thus, given the paucity of information with respect to tobacco use in siblings affected by childhood cancer, the proposed analysis is a starting point for characterizing understanding the tobacco use behaviors and predictors of tobacco use in siblings of childhood cancer survivors.

4. SPECIFIC AIMS:

The proposed study will utilize data from two sources: the CCSS and the National Health Interview Survey (NHIS) survey administered in 1993. The CCSS data in this analysis are from a 24 page baseline questionnaire completed by self-report or telephone utilizing a trained interviewer, conducted primarily between 1995 and 1996. The NHIS questionnaire administered in 1993 included a tobacco use section as part of Year 2000 Supplement. Tobacco use variables between the CCSS and the NHIS administered in 1993 are closely comparable and allow for assessment of tobacco use specifics across both populations at time points that will ensure the stability of tobacco use behaviors. The prevalence of tobacco use among the adult siblings of childhood cancer survivors will be compared with controls from a national sample. Predictors for tobacco use will be examined among the siblings of childhood cancer survivors.

4.1 Aim 1: To describe the prevalence of tobacco use (measures described in Appendix A include current smoker, former smoker, never smoked, quantity of cigarettes, smokeless tobacco use, any tobacco use) of adult siblings of childhood cancer survivors and compare them to national controls. *We hypothesize that current smoking, former smoking, the quantity of cigarettes, smokeless tobacco use, and any tobacco use, among adult siblings of childhood cancer survivors will be greater and never smokers will be fewer when compared with national controls.*

4.2 Aim 2: To identify sibling and survivor characteristics (described in Appendix A) associated with any tobacco use (current smoker, former smoker, smokeless tobacco use) among adult siblings of childhood cancer survivors. *We hypothesize that sibling sociodemographic factors including older age, male sex, White race/ethnicity, lower household income and educational attainment will be associated with reports of any tobacco use among siblings. Sibling characteristics including impairment in sibling general health, psychological distress, heavy alcohol use, bereavement, and younger sibling age at the time of diagnosis will be associated with increased reports of any tobacco use among siblings. Survivor characteristics including impairment in survivor general health, survivor psychological distress, heavy alcohol use among the survivor, any tobacco among the survivor use, survivor diagnosis, greater treatment intensity, and late effects will be associated with an increase in reports of any tobacco use in siblings.*

5. ANALYSIS FRAMEWORK:

5.1 Sample:

A random sample of the 14,363 participating survivors was asked to provide contact information for their nearest aged sibling. Of the 5,791 eligible siblings 4,869 (84.1%) Of the participating siblings, these analyses will utilize those who were $\geq$ 18 years of age at the time of completion of the baseline questionnaire resulting in data from 3,083 siblings.

As a sibling comparison group participants from the NHIS survey completed in 1993 (n=20,860) will be selected and weighted to match the CCSS sibling sample by age, sex, socioeconomic status, and race/ethnicity. The NHIS is annual survey focused on the assessment of health in the United Sates which is conducted by the National Center for Health Statistics (NCHS) and the Center for Disease Control (CDC). A random sample of households within the United States is interviewed with respect to basic health and demographic characteristics utilizing a questionnaire. Appendix A demonstrates that the tobacco use variables are closely comparable between the CCSS baseline questionnaire and the NHIS survey administered in 1993 which included a supplement (Year 2000 Supplement) with questions focusing on tobacco use. This similarity allows for assessment of tobacco use across both populations at time points that ensure stability of tobacco use practices.

5.2 Outcomes of Interest and Predictor Variables:

Aim 1: Outcomes of interest

A. Sibling Current Smoker- defined as exposure to at least 100 cigarettes and smoking on a regular basis
B. Sibling Former Smoker- defined as exposure to at least 100 cigarettes and no longer smoking
C. Sibling Never Smoked- defined as exposure to less than 100 cigarettes
D. Quantity of Cigarettes-defined as none vs. $\leq$20 per day vs. $\geq$20 per day
E. Smokeless Tobacco Use- defined as current use of snuff or chewing
F. Any Tobacco Use-defined as current smoker, former smoker, or smokeless tobacco use

Predictor Variable:
Not applicable (descriptive data)

Aim 2: Outcomes of interest

A. Any Tobacco Use-defined as current smoker, former smoker, or smokeless tobacco use

Predictor Variables

A. Sibling Sociodemographic Characteristics
    a. Age at baseline questionnaire
    b. Sex
    c. Race/ethnicity
    d. Household income
    e. Educational attainment

B. Sibling Characteristics
    a. Sibling general health status

b. Sibling psychological distress as measured by the Brief Symptom Inventory 18 (BSI-18) including the global severity index and subscales of depression and anxiety.
c. Heavy alcohol use defined as > 5 drinks / day for females and > 6 drinks / day for males at least one time per month.
d. Sibling bereavement defined as survivor death after entry
e. Sibling age at diagnosis

C. Survivor Characteristics
a. Survivor general health status
b. Survivor psychological distress as measured by the BSI-18 including the GSI and subscales of depression and anxiety.
c. Survivor heavy alcohol use as defined above.
d. Survivor any tobacco use
e. Survivor diagnosis
f. Survivor treatment intensity
g. Survivor chronic health conditions (including second cancer)

5.3 Statistical analysis plan:

Specific Aim #1

Table 1 will provide descriptive statistics of the two populations (CCSS siblings and NHIS controls) including demographic characteristics, such as, age of the sample, sex, race/ethnicity, household income, and educational attainment.

Tables 2-4 will provide further descriptive statistics of the study outcomes focused on siblings including: current smoker, former smoker, never smoked, quantity of cigarettes, smokeless tobacco use, and any tobacco use. These outcomes will be presented by sibling sociodemographic characteristics including age of the sample, sex, race/ethnicity, household income, and educational attainment. Outcomes will also be presented by sibling characteristics including: sibling general health status, sibling psychological distress, sibling heavy alcohol use, sibling bereavement (survivor death following study entry), and sibling age at the time of diagnosis. Outcomes will also be presented by survivor characteristics including survivor general health status, survivor psychological distress, survivor heavy alcohol use, and any tobacco use among survivors, diagnosis, treatment intensity, and survivor late effects including chronic health conditions and second cancers.

Table 5 will provide the results of logistic regression analyses which will be used to evaluate adjusted comparisons of the tobacco use behaviors between the CCSS siblings and the participants from the NHIS (weighted to match the CCSS sample by age, sex, socioeconomic status, and race/ethnicity). Adjusted odds ratios with 95% confidence will be reported.

Specific Aim #2

Among CCSS siblings, adjusted univariate analyses will be completed and presented in Tables 6-7. Individual sibling and survivor characteristics will each be evaluated in a separate model adjusted by sibling sociodemographic characteristics including age of the sample, sex, race/ethnicity, insurance status, income, education. Those factors that are statistically significant at the $p < 0.10$ level will be included in the final multivariable model, with some evaluations to

eliminate inclusion of factors that are collinear with one another in the full model. Table 8 will present the result of a single final multivariable logistic regression model which will evaluate associations between any tobacco use and key sibling and survivor characteristics. The construction of this model will include those factors that are felt to be important predictors of tobacco use in the general population including the sibling sociodemographic characteristics such as age of the sample, sex, race/ethnicity, insurance status, income, education which will be forced into the model. Other factors will be included if they are significant at the $\alpha = 0.05$ level or if their inclusion markedly modifies the effects of another variable. Adjusted odds ratios with 95% confidence will be reported. Analysis will be carried out using the SAS statistical software (SAS Institute, Cary, NC).

APPENDIX A

Equivalency of Tobacco Use Questions between the Childhood Cancer Survivor Study and the National Health Interview Survey

Childhood Cancer Survivor Study	**National Health Interview Survey (Section Year 2000, YB-Tobacco) – 1993**
N.1 Have you smoked at least 100 cigarettes in your entire life? No Yes	1 Have you smoked at least 100 cigarettes in your entire life? Yes No Don't know
N.1d Do you smoke cigarettes now? No Yes	3. Do you now smoke cigarettes every day, some days, or not at all? Everyday Some days Not at all
N.1b On average, how many cigarettes a day do/did you smoke? Number of cigarettes ___	4. On the average, about how many cigarettes a day do you now smoke? ___ Number of cigarettes a day Don't know
N.2 Have you ever used any of the tobacco products listed below? Chewing tobacco Yes, regularly use Yes, occasionally use Yes, no longer use Never used Snuff tobacco Yes, regularly use Yes, occasionally use Yes, no longer use Never used	8. Do you use snuff now? 9. Do you use chewing tobacco now? Yes No Don't know

Control Variables

Question	Childhood Cancer Survivor Study	NHIS 1993
Age	A.1 What is your date of birth? Code date	1 (Household composition page). Age? Code age in years
Sex	A.2 What is your sex? Male Female	A. Household composition page Sex? Male Female
Race/ethnicity	A.4 To which one of the following groups do you belong? White Black American Indian or Alaskan Native Asian or Pacific Islander Other (specify)	L1 Demographic page 3a. What is the number of the group or groups which represents ___ race? White Black Indian (American) Eskimo Aleut Filipino Hawaiian Korean Vietnamese Japanese Asian Indian Samoan Guamanian Other API Other 3b. Which of those groups; that Is, (entries in 3a) would you say best represents ____ race?
Income	Q.8 Over the last year, what is the total income of the household you live in? Less than $9,999 $10,000 - $19,999 $20,000 - $ 39,999 $40,000 - $59,999 Over $60,000	L1 Demographic page 8a. Was the total combined family income during the past 12 months – that is, yours more or less than $20,000? $20,000 or more Less than $20,000

Education	O.1 What is the highest grade of level of schooling that you have completed? 1- 8 years (grade school) 9 – 12 years (high school), but did not graduate Completed high school Training after high school, other than college Some College College graduate Post Graduate Level	L1 Demographic page What is the highest grade or year of regular school ___ has ever attended? 2a. Never attended school or kindergarten 1 through 8 (Elementary) 9 through 12 (High school) 1-6+ (College)

APPENDIX B

TABLE 1: Demographics by dataset

Variable	Siblings N = (%)	NHIS* N = (%)
Age 18-20 20-29 30-39 40+		
Gender Male Female		
Race/ethnicity White Non-white		
Household Income <$9,999 $10,000-19,999 $20,000-39,000 $40,000-59,999 Over $60,000		
Education High school graduate or less More than high school graduate		

*Weighted to CCSS sibling sample in order to match age, gender, socioeconomic status, and race/ethnicity.

TABLE 2: Sibling tobacco use outcomes by sibling sociodemographic characteristics

Variable	**Current Smoker** N (%)	**Former Smoker** N (%)	**Never Smoked** N (%)	**Quantity Cigarettes** **0** **<20** **>20** N(%) N(%) N(%)	**Smokeless Tobacco** N(%)	**Any Tobacco** N(%)
Age 18-20 20-29 30-39 40+						
Gender Male Female						
Race/ethnicity White Non-white						
Household Income <$9,999 $10,000-19,999 $20,000-39,000 $40,000-59,999 Over $60,000						
Education High school graduate or less More than high school graduate						

TABLE 3: Sibling tobacco use outcomes by sibling characteristics

Variable	**Current Smoker** N (%)	**Former Smoker** N (%)	**Never Smoked** N (%)	**Quantity Cigarettes** **0** **<20** **>20** N(%) N(%) N(%)	**Smokeless Tobacco** N(%)	**Any Tobacco** N(%)
Health Status Fair/poor Good/very good/excellent						
Psychological Distress GSI Yes No Depression Yes No Anxiety Yes No						
Heavy Alcohol Use Yes No						
Bereaved Yes No						
Sibling Age at Diagnosis Not born yet 0-5 5-10 10-15 15-20 20-25 >25						

TABLE 4: Sibling tobacco use outcomes by survivor characteristics

Variable	**Current Smoker** N (%)	**Former Smoker** N (%)	**Never Smoked** N (%)	**Quantity Cigarettes** **0 <20 >20** N(%) N(%)N(%)	**Smokeless Tobacco** N(%)	**Any Tobacco** N(%)
Survivor Health Status Fair/poor Good/very good/excellent						
Survivor Psychological Distress GSI Yes No Depression Yes No Anxiety Yes No						
Survivor Heavy Alcohol Use Yes No						
Survivor Any Tobacco Use Yes No						
Diagnosis Brain tumor Leukemia Hodgkin Lymphoma Non-Hodgkin Lymphoma Kidney tumor Neuroblastoma Sarcoma Bone tumor						
Treatment Intense Yes No						
Survivor Chronic Health Conditions Yes No						

TABLE 5: Tobacco use by dataset. Percent with each among sibling and NHIS participants. Adjusted odds ratios for CCSS siblings compared to their NHIS peers.

Variable	Sibling N = (%)	NHIS N = (%)	Adjusted OR* (95% CI) Sibling vs. NHIS
Current Smoker Yes No			
Former Smoker Yes No			
Never Smoker Yes No			
Quantity Cigarettes >20 <20			
Smokeless Tobacco Use Yes No			
Any Tobacco Use Yes No			

*Adjusted by age, sex, race/ethnicity, household income, educational status

TABLE 6: Adjusted univariate analyses of any tobacco use among siblings by sibling characteristics.

Variable	**Any Tobacco Use vs. None** Adjusted OR* (95% CI)
Health Status	
Fair/poor	
Good/very good/excellent	
Psychological Distress	
GSI	
Yes	
No	
Depression	
Yes	
No	
Anxiety	
Yes	
No	
Heavy Alcohol Use	
Yes	
No	
Bereaved	
Yes	
No	
Sibling Age at Diagnosis	
Not born yet	
0-5	
5-10	
10-15	
15-20	
20-25	
>25	

*Adjusted by age, sex, race/ethnicity, household income, educational status

TABLE 7: Adjusted univariate analyses of any tobacco use among siblings by survivor characteristics.

Variable	**Any Tobacco Use vs. None** Adjusted OR* (95% CI)
Survivor Health Status	
Fair/poor	
Good/very good/excellent	
Survivor Psychological Distress	
GSI	
Yes	
No	
Depression	
Yes	
No	
Anxiety	
Yes	
No	
Survivor Heavy Alcohol Use	
Yes	
No	
Survivor Any Tobacco Use	
Yes	
No	
Diagnosis	
Brain tumor	
Leukemia	
Hodgkin Lymphoma	
Non-Hodgkin Lymphoma	
Kidney tumor	
Neuroblastoma	
Sarcoma	
Bone tumor	
Treatment Intense	
Yes	
No	
Survivor Chronic Health Conditions	
Yes	
No	

*Adjusted by age, sex, race/ethnicity, household income, educational status

TABLE 8: Multivariable model of any sibling tobacco use. (actual variables shown will depend on modeling results).

Variable	**Any Tobacco Use vs. Not** Adjusted OR* (95% CI)
DEMOGRAPHICS	
Age 18-20 20-29 30-39 40+	
Gender Male Female	
Race/ethnicity White Non-white	
Household Income <$9,999 $10,000-19,999 $20,000-39,000 $40,000-59,999 Over $60,000	
Education High school graduate or less More than high school graduate	
SIBLING CHARACTERISTICS	
Health Status Fair/poor Good/very good/excellent	
Psychological Distress GSI Yes No Depression Yes No Anxiety Yes No	
Heavy Alcohol Use Yes No	
Bereaved Yes No	
Sibling Age at Diagnosis Not born yet 0-5 5-10 10-15 15-20 20-25 >25	
SURVIVOR CHARACTERISTICS	
Survivor Health Status Fair/poor Good/very good/excellent	
Survivor Psychological Distress GSI Yes	

No Depression Yes No Anxiety Yes No	
Survivor Heavy Alcohol Use Yes No	
Survivor Any Current Tobacco Use Yes No	
Diagnosis Brain tumor Leukemia Hodgkin Lymphoma Non-Hodgkin Lymphoma Kidney tumor Neuroblastoma Sarcoma Bone tumor	
Treatment Intense Yes No	
Survivor Chronic Health Conditions Yes No	

REFERENCES:

1. Garner AS, Shonkoff JP, Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics 2012; 129: e224-31.

2. Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012; 129: e232-46.

3. Taylor SE, Way BM, Seeman TE. Early adversity and adult health outcomes. Dev Psychopathol. 2011; 23: 939-54.

4. Murray JS. Siblings of children with cancer: a review of the literature. Journal of Pediatric Oncology Nursing 1999; 16: 25-34.

5. Houtzager BA, Grootenhuis MA, Last BF. Adjustment of siblings to childhood cancer: a literature review. Support Care Cancer 1999; 7: 302-320.

6. Wilkins KL, Woodgate RL. A Review of Qualitative Research on the Childhood Cancer Experience from the Perspective of Siblings: A Need to Give Them a Voice. Journal of Pediatric Oncology Nursing 2005; 22: 305-319.

7. Alderfer MA, Long KA, Lown EA, et al. Psychosocial adjustment of siblings of children with cancer: a systematic review. Psycho-Oncology 2010; 19:789-805.

8. About Cancer Survivorship Research: Survivorship Definitions. (2009) Retrieved August 8, 2009 from the National Cancer Institute Office of Cancer Survivorship Website: http://cancercontrol.cancer.gov/ocs/definitions.html.

9. Lown EA, Goldsby R, Mertens AC, et al. Alcohol consumption patterns and risk factors among childhood cancer survivors compared to siblings and general population peers. Addiction 2008; 103: 1139-1148.

10. Lown EA, Goldsby R, Mertens AC, et al. Prevalence and predictors of risky and heavy alcohol consumption among adult siblings of childhood cancer survivors. Psychooncology 2012. [Epub ahead of print].

11. Breslau N, Davis GC, Schultz LR. Posttraumatic Stress Disorder and the Incidence of Nicotine, Alcohol, and Other Drug Disorders in Persons Who Have Experienced Trauma. Arch Gen Psychiatry 2003; 60: 289-294.

12. Brown PJ, Wolfe J. Substance abuse and post-traumatic stress disorder co morbidity. Drug and Alcohol Dependence 1994; 35: 51-59.

13. Current Cigarette Smoking Prevalence Among Working Adults—United States, 2004-2010. MMWR 2011; 60: 1305-1309.

14. Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses --- United States, 2000—2004. MMWR 2008; 57: 1226-1228.

15. Smith SS, Fiore MC. The epidemiology of tobacco use, dependence, and cessation in the United States. Primary Care: Clinics in Office Practice 1999: 26; 434-461.

16. Surveillance for Cancers Associated with Tobacco Use – United States, 1999-2004. MMWR 2008; 57: SS8,

17. Friedman DL, Kadan-Lottick NS, Whitton J, et al. Increased Risk of Cancer among Siblings of Long-term Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 2005; 14: 1922-1927.

18. Winther JF, Sankila R, Boice JD, et al. Cancer in Siblings of Children With Cancer in the Nordic Countries: a Population Based Cohort Study. Lancet 2001; 358: 711-717.

19. Nathan PC, Ford JS, Henderson TO, et al. Health Behaviors, Medical Care, and Interventions to Promote Healthy Living in the Childhood Cancer Survivor Study Cohort. JCO 2009; 27: 2363-2373.

20. Emmons K, Li FP, Whitton J, et al. Predictors of Smoking Initiation and Cessation Among Childhood Cancer Survivors: A Report From the Childhood Cancer Survivor Study. JCO 2002; 20: 1608-1616.

21. Tao ML, Zeltzer LK, Byrne J, et al. Smoking in Adult Survivors of Childhood Acute Lymphoblastic Leukemia. JNCI 1998; 90: 219-225.

22. Emmons K, Butterfield RM, Puleo E, et al. Smoking among participants in the childhood cancer survivors cohort: The Partnership for Health Study. JCO 2003; 21: 189-196.

23. Buchbinder D, Casillas J, Krull KR, et al. Psychological Outcomes of Siblings of Cancer Survivors: A Report from the Childhood Cancer Survivor Study. Psycho Oncology 2011; 20: 1259-680.