

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

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Title: Late effects and smoking among survivors of childhood cancer: The role of attention, overweight, and pubertal onset in adolescent smoking behavior

Working Group and Investigators:

This proposal is most relevant to the Cancer Control Working Group. Proposed investigators (name/email/fax) will include:

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Background and Rationale:

With a growing population of survivors of childhood cancer, health behavior research has become an essential initiative in pediatric oncology in order to help survivors make informed, healthy decisions for prolonging their disease-free status. Tobacco use is an important focus for intervention, given the known connections between smoking and problematic health consequences in the general population. In order to inform prevention efforts, it is necessary to better understand what factors influence survivors in their decisions about smoking and to consider these factors within the survivors' unique medical context. There remain unanswered questions about tobacco use among adolescent cancer survivors. Finding answers to these questions requires special consideration of the distinct biological, psychological, and social environment of survivorship that frames these adolescents' decisions about smoking.

Tobacco research with healthy adolescent samples has illuminated a range of specific factors that contribute to tobacco use. The extent to which these variables influence smoking decisions of adolescent cancer survivors is not clearly understood. This proposal aims to consider variables that may have particular relevance to the smoking behaviors of adolescent survivors of childhood cancer. These variables include inattention, weight control, and pubertal stage. While these relations have been examined extensively in healthy populations, it remains unclear how such factors influence adolescent cancer survivors and how these factors may be altered by the disease- and treatment-related context of survivorship.

There is a growing body of literature indicating that individuals affected with ADHD are more likely to smoke and are less successful at quitting than their non-ADHD counterparts. Similarities in clinical presentation and response to stimulant medication between survivors who experience attention problems secondary to treatment and their peers who have ADHD from a developmental etiology suggest that these two groups of adolescents may share a similar affinity to the attention-enhancing properties of tobacco. Given that inattention is a commonly reported late effect associated with CNS treatment of childhood cancer, the instrumental value of smoking as a stimulant may explain the onset or maintenance of tobacco use in this survivor population. The association between treatment-related attention problems and tobacco use has not been examined in survivors of childhood cancer. Connecting this cognitive late effect to such an important health behavior decision made by this growing population of medically vulnerable adolescents may illuminate specific channels for prevention and intervention efforts.

The association between smoking and weight control has been well established in the healthy adolescent smoking literature. Given that adolescent survivors of pediatric cancer are at risk for overweight secondary to treatment, it remains possible that survivors struggling with their weight may look to smoking as a means of weight control. Currently, there is no published evidence that survivors who experience post-treatment weight gain have a higher likelihood of engaging in smoking. Still, the difficulty survivors have with weight control and the well-established connection between weight control behaviors and smoking among healthy adolescents suggests that this is a clinically relevant issue that requires investigation. If survivors with weight problems are found to be more vulnerable to engaging in smoking for weight control purposes, it will be important to modify health promotion to target this at-risk group.

Research with healthy adolescents clearly suggests that puberty plays a crucial role in the development of unhealthy behaviors during adolescence. The association between pubertal development and tobacco use has not been examined in adolescent survivors of childhood cancer. Given the high incidence of pubertal disruption in the survivor population, it remains possible that survivors who experience early-onset puberty may be at increased risk for tobacco use. The clinical emphasis of research related to disrupted pubertal development in survivors has focused exclusively on the medical consequences of altered puberty. There is no available research that examines the psychosocial consequences of early puberty for survivors of childhood cancer. Similarly, in a population where health behavior is of paramount importance, there is no available research that considers pubertal onset and substance use in adolescent survivors of childhood cancer.

By studying smoking behavior in the Childhood Cancer Survivor Study cohort, we will be able to determine if the experience of certain late effects places survivors at risk for tobacco use. Late effects of cancer treatment involve lasting physical, cognitive, psychological, and social impairments that place pediatric cancer survivors at risk for a range of complications. Connecting these late effects to important health behavior decisions made by this growing population of medically vulnerable individuals may illuminate specific channels for prevention and intervention efforts.

Specific Aims and Research Hypotheses:

Objective #1: To determine the relation between attention problems and smoking

- Hypotheses: Smoking and attention will be related concurrently and longitudinally.
- a. Parent-report attention problems among adolescents at Baseline will predict self-report smoking at Follow-Up2 and at Teen Health Survey.
 - b. Self-report smoking will be less among survivors who are treated with stimulant medication (i.e., Ritalin).
 - c. Self-reported current smoking at Follow-Up2 will be associated with more problems in executive function at the same time point.
 - d. Survivors with a history of treatment to the brain (including CRT, IT chemotherapy, and/or brain surgery) will be more likely to smoke than survivors who did not receive treatment to the brain. The relation between treatment history and smoking will be mediated by parent-report attention problems at Baseline and by self-report executive function problems at Follow-Up2.

Objective #2: To determine the relation between weight control and smoking

- Hypotheses: Smoking and weight control efforts will be related concurrently.
- a. Self-report of perceived fitness will be associated with smoking on the Teen Health Survey. Survivors who perceive themselves as less physically fit will smoke more than their self-perceived physically fit counterparts.
 - b. Self-report of eating disorder behavior will be associated with smoking on the Teen Health Survey. Survivors who engage in bingeing and purging will smoke more than those who do not engage in those eating disordered behaviors.
 - c. Self-report of exercise will be inversely associated with self-report of smoking on the Teen Health Survey and Follow-Up2. Survivors who engage in regular exercise will smoke less than their less active counterparts.

Objective #3: To determine the relation between pubertal stage and smoking onset among female survivors

- Hypothesis: Self-report of first menstrual period on the Follow-Up1 will be associated with age at smoking onset from Follow-Up2. Specifically, early or precocious puberty will be associated with earlier smoking among female survivors.

Analysis Framework for Objective #1:a) Outcomes of interest:

a. Smoking from Teen Health Survey

Survey	Page	Item #	Item	Construct
Teen Health	13	17	When was the last time you smoked cigarettes?	Smoking

b. Smoking from Follow-Up2

Survey	Page	Item #	Item	Construct
FU2	13	L.2	Do you smoke cigarettes now?	Smoking
FU2	13	L.3	On average, how many cigarettes a day do/did you smoke?	Smoking

b) Subject population:

- a. Cases that were <18 at Baseline AND completed the Teen Health Survey while < 18 years of age. In CCSS, there are 119 cases that fit these criteria.
- b. Cases that were <18 at Baseline AND were >18 at completion of Follow-Up2. In CCSS, there are 2413 cases that fit these criteria.

c) Explanatory variables:

a. Parent-report of attention from Baseline

Survey	Page	Item #	Item	Construct
Baseline<18	10	J.19.g	Has difficulty concentrating, cannot pay attention long	Attention
Baseline<18	10	J.19.h	Is easily confused, seems to be in a fog	Attention
Baseline<18	10	J.19.o	Is impulsive or acts without thinking	Hyperactivity
Baseline<18	10	J.19.s	Is restless or overly active, cannot sit still	Hyperactivity

b. Parent-report use of stimulant medication from Baseline

Survey	Page	Item #	Item	Construct
Baseline<18	5	15	Antidepressants or other prescribed drugs for depression or other mood disorders such as Ritalin, others	Stimulant Medication
Baseline<18	5	16	Other prescribed drugs	Stimulant Medication

c. Self-report of stimulant medication from Follow-Up2

Survey	Page	Item #	Item	Construct
FU2	18	8	Antidepressants or other prescribed drugs for depression or other mood disorders such as Ritalin, others	Stimulant Medication
FU2	18	9	Other prescribed drugs	Stimulant Medication

d. Self-report of executive function from Follow-Up2

Survey	Page	Item #	Item	Construct
FU2	11	J.1	I get upset easily.	Executive Function
FU2	11	J.2	It takes me longer to complete my work.	Executive Function
FU2	11	J.3	I don't think of consequences before acting.	Executive Function
FU2	11	J.4	I am disorganized.	Executive Function
FU2	11	J.5	I forget instructions easily.	Executive Function
FU2	11	J.6	I have problems completing my work.	Executive Function
FU2	11	J.7	I have difficulty recalling things I had previously learned (e.g., names, places, events, activities).	Executive Function
FU2	11	J.8	I get frustrated easily.	Executive Function
FU2	11	J.9	My mood changes frequently.	Executive Function
FU2	11	J.10	I have difficulty coming up with different ways of solving problems.	Executive Function
FU2	11	J.11	I am impulsive.	Executive Function
FU2	11	J.12	I have trouble finding things in my bedroom, closet or desk	Executive Function
FU2	11	J.13	I forget what I am doing in the middle of things.	Executive Function
FU2	11	J.14	I have problems getting started on my own.	Executive Function
FU2	11	J.15	I am an underachiever.	Executive Function
FU2	11	J.16	I am easily overwhelmed.	Executive Function
FU2	11	J.17	I have trouble doing more than one thing at a time.	Executive Function
FU2	11	J.18	I blurt things out.	Executive Function
FU2	11	J.19	My desk/workspace is a mess.	Executive Function
FU2	11	J.20	I have trouble remembering things, even for a few minutes (such as directions, phone numbers, etc.)	Executive Function
FU2	11	J.21	I have trouble prioritizing my activities.	Executive Function
FU2	11	J.22	I read slowly.	Executive Function
FU2	11	J.23	I am slower than others when completing my work.	Executive Function
FU2	11	J.24	I have trouble solving math problems in my head.	Executive Function
FU2	11	J.25	I don't work well under pressure.	Executive Function

A total score will be computed from these items per scoring instructions for the measure from which these items were adapted.

- e. Treatment (CRT and/or IT chemotherapy and/or brain surgery vs. no treatment to the brain)
 - f. Demographic variables (sex, age, race, diagnosis, age at diagnosis, time since treatment)
- d) Specific Tables and Figures:
- a. Smoking rates at Baseline and Follow-Up2 (by age, diagnosis, treatment)
 - b. Rates of attention problems (by diagnosis, treatment)
 - c. Smoking rates by degree of attention problems

Analysis Framework for Objective #2:a) Outcomes of interest:

- a. Smoking from Teen Health Survey (see Objective #1 for items)
- b. Smoking from Follow-Up2 (see Objective #1 for items)

b) Subject population:

- a. Cases that were <18 at Baseline AND completed the Teen Health Survey while < 18 years of age . In CCSS, there are 119 cases that fit these criteria.
- b. Cases that were <18 at Baseline AND were >18 at completion of Follow-Up2 In CCSS, there are 2413 cases that fit these criteria.

c) Explanatory variables:

- a. Self-report of perceived fitness from Teen Health Survey

Survey	Page	Item #	Item	Construct
Teen Health	6	6	I am very physically fit.	Self-concept

- b. Self-report of eating disorder behavior from Teen Health Survey

Survey	Page	Item #	Item	Construct
Teen Health	10	43	In the past 12 months, how many times did you vomit on purpose to lose weight?	Eating Disorder
Teen Health	10	44	In the past 12 months, how many times did you go on an eating binge?	Eating Disorder
Teen Health	19	32	Has a doctor ever said that you had an eating disorder like anorexia or bulimia?	Eating Disorder

- c. Self-report of exercise from Teen Health Survey

Survey	Page	Item #	Item	Construct
Teen Health	11	1	In the past 4 weeks, on how many days did you exercise or play sports hard enough to make you breathe hard, make your heart beat fast, or make you sweat for 20 minutes or more?	Exercise

- d. Self-report of exercise from Follow-Up2

Survey	Page	Item #	Item	Construct
FU2	7	D.1	During the past month, did you participate in any physical activities for exercise?	Exercise
FU2	7	D.2	Do you do vigorous activities for at least 10 minutes at a time?	Exercise
FU2	7	D.3	How many days per week do you do these vigorous activities for at least 10 minutes at a time?	Exercise
FU2	7	D.4	How much total time per day do you spend doing these vigorous activities?	Exercise
FU2	7	D.5	Do you do moderate activities for at least 10 minutes at a time?	Exercise
FU2	7	D.6	How many days per week do you do these moderate activities for at least 10 minutes at a time?	Exercise
FU2	7	D.7	How much time/day do you spend doing these moderate activities?	Exercise

- e. Demographic variables (sex, age, race, BMI at Baseline, BMI at Follow-Up1 diagnosis, age at diagnosis, time since treatment)

d) Specific tables and figures:

- a. Rates of overweight and weight control methods (by age, diagnosis, treatment)
- b. Smoking rates by BMI and use of weight control strategies

Analysis Framework for Objective #3:

a) Outcomes of interest: Age at smoking onset from Follow-Up2

Survey	Page	Item #	Item	Construct
FU2	13	L.1	How old were you when you started smoking?	Smoking

b) Subject population: Female cases that were <18 at Baseline AND were >18 at completion of Follow-Up1. In CCSS, there are 864 cases that fit these criteria.

c) Explanatory variables: Self-report of first menstrual period on Follow-Up1

Survey	Page	Item #	Item	Construct
FU1	13	19.a	At what age did you have your first menstrual period?	Puberty-Female

d) Specific tables and figures:

- a. Smoking rates by onset of menstrual period (early, normal, late)
- b. Age at smoking initiation by onset of menstrual period (early, normal, late)

Statistical Plan:

Multiple regression will be used to examine variables at baseline that are predictive of later smoking behavior. Similarly, regression models will be used to examine variables that are concurrently related to smoking behavior at the Follow-Up2 time point. For example, multiple regression will be used to determine whether parent-report attention symptoms at baseline predict self-report smoking at Follow-Up2. To explore group differences, logistic regression will be used, treating smoking behavior as a dichotomous variable (smoker vs. non-smoker). Other univariate and multivariate techniques (MANOVA, ANOVA) will be used for examining other group differences with continuous variables. We are also proposing to use structural equation modeling to examine the individual and combined influence of attention, weight control, and puberty variables in predicting tobacco use. The large sample size available with this study lends itself well to this technique.

The operational definitions of several variables require explanation as well. Attention at Baseline will likely be treated as a continuous variable resulting from a summation of the 4 indicated parent-report items. The self-report of executive function at Follow-Up2 will be treated as a continuous variable as well, with a total score computed per scoring instructions for the measure from which these items were adapted. Eating disorder symptoms will be considered individually, yielding 3 dichotomous variables from the 3 related questionnaire items. Exercise will likely be defined by the days per week that patients engage in vigorous and/or moderate activity (D.3, D.5). However, it will be important to examine the data to determine the best indicator (or combination of indicators) of exercise. Treatment history will be an important variable to consider, particularly as it relates to the relation between attention and smoking. Treatment history will likely be treated as a dichotomous variable (treatment to the brain vs. no treatment to the brain).

Data will generally be summarized in univariate fashion as demonstrated in Tables 1-5 (attached). The goal in examining the relation between attention and smoking will be to define a group that is experiencing attention problems in a clinical range and to represent this proportion as a percent (as demonstrated in Table 1). The distribution of the available attention variables will be summarized to determine whether a "clinical" group can be defined, as say, an upper quartile of the population. However, in the absence of determining a conceptually meaningful cutoff for attention problems, this data will be presented in terms of mean, median, and range.

Special Considerations:

Lisa Schum submitted a proposal for the Kirschstein-NRSA Fellowship under the sponsorship of Leslie Robinson at the University of Memphis and the co-sponsorship of Pam Hinds and Melissa Hudson at St. Jude Children's Research Hospital. The NRSA Fellowship application was written for the purpose of funding Lisa's dissertation project, originally conceptualized as a single-site retrospective study investigating smoking among adolescent cancer survivors at St. Jude. However, the limited sample size available at St. Jude prompted the research team to consider using the CCSS data for the study. The CCSS questionnaires include items that closely approximate the constructs of interest in our original proposal for the single-site study, and therefore, the current research objectives for this CCSS proposal are largely the same as those submitted in the NRSA Fellowship application.

The NRSA Fellowship application received a priority score of 130 in March of 2005. Although final funding decisions have not yet been determined, there is an expectation that funding will be obtained based on the priority score and summary statements. Funding under this mechanism is intended to fund the student's training, rather than to fund the project itself (i.e., the grant provides no funding for a statistician or other such study-related expenditures but instead pays for tuition, training expenses, and travel).

This project will serve as the doctoral dissertation research for Lisa Schum. As such, it will be required that she perform analyses independently (without the assistance of a statistician) for her dissertation. Lisa's independent analyses will be considered separate from those conducted for publications. Wendy Leisenring, CCSS statistician, will be consulted for all analyses that will be used in manuscripts intended for publication.

Table 1

	Smoking Status and Attention Problems at Baseline		Smoking Status and Attention Problems at FU2	
	No. of Smokers (% with attn probs)	No. of Non-smoker (% with attn probs)	No. of Smokers (% with attn probs)	No. of Non-smoker (% with attn probs)
Total Sample	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Age at Baseline				
8-12	XX (xx)	XX (xx)		
13-17	XX (xx)	XX (xx)		
Age at FU2				
18-22			XX (xx)	XX (xx)
23-27			XX (xx)	XX (xx)
28-32			XX (xx)	XX (xx)
Histology				
ALL	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Other leukemia	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Brain tumor	XX (xx)	XX (xx)	XX (xx)	XX (xx)
HD	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Non-HD lymphoma	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Wilms tumor	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Neuroblastoma	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Soft tissue sarcoma	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Bone malignancies	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Treatment				
CRT	XX (xx)	XX (xx)	XX (xx)	XX (xx)
IT chemo	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Brain surgery	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Chemo (not IT)	XX (xx)	XX (xx)	XX (xx)	XX (xx)
Surgery (not brain)	XX (xx)	XX (xx)	XX (xx)	XX (xx)
RT (not brain)	XX (xx)	XX (xx)	XX (xx)	XX (xx)

Table 2

	Smoking Status and BMI at Baseline		
	No. Underweight (% smokers)	No. Normal Weight (% smokers)	No. Overweight (% smokers)
Age at Baseline			
8-12	XX (xx)	XX (xx)	
13-17	XX (xx)	XX (xx)	
Histology			
ALL	XX (xx)	XX (xx)	XX (xx)
Other leukemia	XX (xx)	XX (xx)	XX (xx)
Brain tumor	XX (xx)	XX (xx)	XX (xx)
HD	XX (xx)	XX (xx)	XX (xx)
Non-HD lymphoma	XX (xx)	XX (xx)	XX (xx)
Wilms tumor	XX (xx)	XX (xx)	XX (xx)
Neuroblastoma	XX (xx)	XX (xx)	XX (xx)
Soft tissue sarcoma	XX (xx)	XX (xx)	XX (xx)
Bone malignancies	XX (xx)	XX (xx)	XX (xx)
Treatment			
CRT	XX (xx)	XX (xx)	XX (xx)
IT chemo	XX (xx)	XX (xx)	XX (xx)
Brain surgery	XX (xx)	XX (xx)	XX (xx)
Chemo (not IT)	XX (xx)	XX (xx)	XX (xx)
Surgery (not brain)	XX (xx)	XX (xx)	XX (xx)
RT (not brain)	XX (xx)	XX (xx)	XX (xx)

Table 3

	Smoking Status and BMI at FU1		
	No. Underweight (% smokers)	No. Normal Weight (% smokers)	No. Overweight (% smokers)
Age at FU1			
18-22	XX (xx)	XX (xx)	
23-27	XX (xx)	XX (xx)	
28-32	XX (xx)	XX (xx)	
Histology			
ALL	XX (xx)	XX (xx)	XX (xx)
Other leukemia	XX (xx)	XX (xx)	XX (xx)
Brain tumor	XX (xx)	XX (xx)	XX (xx)
HD	XX (xx)	XX (xx)	XX (xx)
Non-HD lymphoma	XX (xx)	XX (xx)	XX (xx)
Wilms tumor	XX (xx)	XX (xx)	XX (xx)
Neuroblastoma	XX (xx)	XX (xx)	XX (xx)
Soft tissue sarcoma	XX (xx)	XX (xx)	XX (xx)
Bone malignancies	XX (xx)	XX (xx)	XX (xx)
Treatment			
CRT	XX (xx)	XX (xx)	XX (xx)
IT chemo	XX (xx)	XX (xx)	XX (xx)
Brain surgery	XX (xx)	XX (xx)	XX (xx)
Chemo (not IT)	XX (xx)	XX (xx)	XX (xx)
Surgery (not brain)	XX (xx)	XX (xx)	XX (xx)
RT (not brain)	XX (xx)	XX (xx)	XX (xx)

Table 4

	Smoking Status at Teen Health Survey	
	No. of Smokers (% females)	No. of Non-smoker (% females)
Age at Teen Health Survey		
8-12	XX (xx)	XX (xx)
13-17	XX (xx)	XX (xx)
Eating Disordered Behavior		
Binging	XX (xx)	XX (xx)
Purging	XX (xx)	XX (xx)
ED diagnosis	XX (xx)	XX (xx)
Days of Exercise per Week		
0-1	XX (xx)	XX (xx)
2-3	XX (xx)	XX (xx)
4-5	XX (xx)	XX (xx)
6-7	XX (xx)	XX (xx)

Table 5

	Menstrual Onset		
	No. Early Onset	No. Normal Onset	No. Late Onset
Age at Smoking Onset			
Never smoked	XX (xx)	XX (xx)	XX (xx)
< 10	XX (xx)	XX (xx)	XX (xx)
10-12	XX (xx)	XX (xx)	XX (xx)
13-15	XX (xx)	XX (xx)	XX (xx)
16-18	XX (xx)	XX (xx)	XX (xx)
19-21	XX (xx)	XX (xx)	XX (xx)
22-24	XX (xx)	XX (xx)	XX (xx)
25-28	XX (xx)	XX (xx)	XX (xx)