1. STUDY TITLE: Predictors of smokeless and dual tobacco use among survivors of childhood cancer (Concept # 10-06)

2. WORKING GROUP AND INVESTIGATORS: This proposed publication will be done within the Cancer Control working group. Proposed investigators will include:

James Klosky, PhD	james.klosky@stjude.org
Karen Emmons, PhD	karen_emmons@dfci.harvard.edu
Deo Kumar Srivastava, PhD	kumar.srivastava@stjude.org
Melissa Hudson, MD	melissa.hudson@stjude.org
Kevin Oeffinger, MD	oeffingk@mskcc.org
Ashley Hum, MS	ashley.hum@stjude.org
Kiri Ness, PT, PhD	kiri.ness@stjude.org
Bob Klesges, PhD	bob.klesges@stjude.org
Marilyn Stovall	mstovall@mdanderson.org
Les Robison, PhD	les.robison@stjude.org

3. BACKGROUND AND RATIONALE:

Over the past 50 years, survival rates for childhood cancer have dramatically improved.[1] However, survivorship is commonly affected by complications resulting from cancer treatment. These potential complications could be exacerbated by deleterious health behaviors such as tobacco use. An investigation from the Childhood Cancer Survivor Study (CCSS) estimated that 42% of pediatric cancer survivors will experience serious, disabling, or life-threatening illnesses by 30 years post diagnosis including cardiovascular disease, stroke, kidney failure, pulmonary fibrosis, and second malignancies, conditions that can be worsened by tobacco use.[2] Several antineoplastic therapies commonly used in the treatment of pediatric malignancies have independently been associated with cardiopulmonary toxicities and organ compromise that can be potentiated by tobacco use. Adults who continue to smoke after diagnosis of head and neck cancer, for example, experience increased rates of tobacco-related complications, diminished efficacy of radiation therapy, reduced survival time, and greater risk of disease reoccurrence/second primary tumor as compared to those who stop smoking post diagnosis.[3-5]

While smoking has been well examined among survivors of childhood cancer, smokeless tobacco use has been understudied in this high risk population.[6-11] Currently, the two most commonly used smokeless tobacco products in the United States are snuff and chewing tobacco.[12-13] Snuff is finely shredded or ground tobacco that is placed between the gum and cheek.[12] Chewing tobacco is produced in the form of a loose leaf, plug, or twist and is put in the cheek. Like any form of tobacco use, smokeless tobacco use is dangerous, especially to childhood cancer survivors due to their susceptibility for health problems. Smokeless tobacco includes up to 28 carcinogens, and results in several adverse health consequences, such as cancer and cardiovascular disease.[13-14]

Despite the risk associated with smokeless tobacco use, Emmons et al. (2002) reported that 6% of male childhood cancer survivors in the CCSS cohort were currently using chewing tobacco, with 3% using snuff. [6] Similarly, Foster et al. examined smokeless tobacco use among survivors of retinoblastoma and found that 2.9% of survivors reported occasional or regular use of chewing tobacco whereas 1.8% reported occasional or regular use of snuff.[18] Among survivors of acute myeloid leukemia, Schultz et al. found that 4% of the young adult survivors and 3% of the adolescent survivors endorsed using chewing tobacco or snuff in last 30 days.[19] Across cancer studies, less than 1% of females report using either chewing tobacco or snuff, which is consistent with the rates in the general US population.[13,15] Disturbingly, rates of smokeless tobacco use among childhood cancer survivors appear to be similar to those found in the general US population and may be on the rise.[13]

Research also found that survivors are concurrently using both cigarettes and smokeless tobacco, which could compound the risks associated with both forms of tobacco use.[11,18] In the aforementioned retinoblastoma study, current smokers were 3.39 times more likely than never smokers to have used other tobacco products.[16] Klosky et al. reported that 11% of survivors had a history of concurrently smoking cigarettes and using smokeless tobacco.[17] Research among the general population has demonstrated that individuals who are dual tobacco users have a harder time with tobacco cessation, and are more likely to engage in other risky health behaviors, e.g., alcohol use.[11] Thus, smokeless tobacco use and dual tobacco use among pediatric cancer survivors is a pertinent area for research in order to accurately identify and address these behaviors and the associated health consequences.

The aims of this study are to examine the following among childhood cancer survivors: (1) the prevalence of smokeless tobacco use and dual tobacco use; (2) the predictors of current smokeless tobacco use, “ever” smokeless tobacco use, and dual tobacco use; and (3) the predictors of cessation among those who “ever” used smokeless tobacco.

It’s important to note that CCSS investigators have previously examined predictors of cigarette smoking in both male and female CCSS participants. Yet the examination of predictors associated with smokeless and dual tobacco use has not taken place in this cohort.[6] Additionally, this study will utilize data from the 2007 follow-up questionnaire which will provide more current rates of tobacco use in the survivorship population.

4. SPECFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES

4.1. SPECIFIC AIMS

4.1.1. Describe the prevalence of smokeless tobacco use and dual tobacco use among a national cohort of adults surviving childhood cancer.

Hypothesis 4.1.1.1. Rates of smokeless tobacco use and dual tobacco use among childhood cancer survivors will approach those of the general US population.

4.1.2. Examine predictors of smokeless tobacco (current and "ever") use and dual tobacco use among adult survivors of childhood cancer.

Hypothesis 4.1.2.1. Predictors of current smokeless tobacco use, "ever" smokeless tobacco use, and dual tobacco use will be similar to those of cigarette use as previously reported by Emmons et al.[6] Specific relationships are expected to be found between older age at cancer diagnosis, absence of cranial irradiation, absence of pulmonary-toxic treatment, lower education, being nonblack, and lower income and current/"ever" smokeless tobacco and dual tobacco use.

4.1.3. Examine predictors of cessation among "ever" smokeless tobacco users.

Hypothesis 4.1.3.1. The predictors of smokeless tobacco cessation will be similar to those reported by Emmons et al.[6]

5. ANALYSIS FRAMEWORK:

5.1. Outcomes of interest (dependent variables): 1) current smokeless tobacco use, 2) "ever" smokeless tobacco use, 3) dual tobacco use, and 4) smokeless tobacco use cessation.

It is important to note that dual tobacco use will be defined in this study as the current use of at least one smokeless tobacco product in addition to the current use of at least one smoked tobacco product. Both types of tobacco use must be present to meet the standard for dual tobacco use.

5.1.1. **Current Smokeless Tobacco Use** will be measured by the CCSS Long-Term Follow-up Study 2007 survey.

5.1.1.1. Smokeless tobacco use will be measured by question N.13: "In the past year, have you ever used any of the tobacco products?"

Participants indicated their use of the following tobacco product options:

- chewing tobacco
- snuff tobacco

- pipes
- cigars

The response options were the following:

- "never used"
- "no longer use,"
- "occasionally use"
- "regularly use"

Only those endorsing chewing tobacco and/or snuff will be included as smokeless tobacco users. Specifically, those who responded "Occasionally use" or "Regularly use" in regard to chewing tobacco or snuff within the past year will be considered current smokeless tobacco users.

5.1.2. **"Ever" Smokeless Tobacco Use** will be measured by the CCSS Long-Term Follow-up Study 2007 survey.

5.1.2.1. "Ever" smokeless tobacco use will be measured by question N.14: "For any of those that you have used or are currently using, how long have you used it?"

Participants indicated their use of the following tobacco product options:

- chewing tobacco
- snuff tobacco
- pipes
- cigars

The response options were the following:

- "less than one year"
- "1-2 years"
- "3-4 years"
- "5-10 years"
- "11+ years"

Only those who endorse a history of chewing tobacco or snuff will be included as "ever" smokeless tobacco users.

5.1.3. **Dual tobacco use** will be measured by the CCSS Long-Term Follow-up Study 2007 survey.

5.1.3.1. Dual tobacco use will be measured by both questions N.13 (smokeless tobacco use, see above for a description of item) and N.9 (cigarette use). Specifically, participants will be classified as

current dual tobacco users if they respond “Yes” to occasional or regular chew or snuff use on item N.13. AND they respond “Yes” to item N.9 “Do you smoke cigarettes now?”

5.1.4. **Smokeless tobacco cessation** will be measured by the CCSS Long-Term Follow-up Study 2007 survey.

5.1.4.1. Smokeless tobacco cessation will be assessed via the response option “no longer use” or “never used” from question N.13 in regards to either chewing tobacco or snuff in the past year, but only for those who indicated a history of smokeless tobacco use on N.14.

5.2. Independent (exploratory) variables

5.2.1. Demographic, diagnostic and treatment variables

a. Race/ethnicity (categorical: white/non-Hispanic, white Hispanic, black/non-Hispanic, black Hispanic, American Indian/Alaska native, Asian or Pacific Islander, Other)

b. Age (continuous, but will also be examined in this format: 18-20 years, 21-24 years, 25-29 years, 30-34 years, 35-39 years, 40-49 years)

c. Sex (categorical: male, female)

d. Education (categorical: 1-12 years (not high school (HS) grad), HS grad/ post HS training, college grad/post grad). Other categories of education may be used based on the distribution of these data.

e. Household income (categorical: less than $20,000, $20,000-$59,000, over $60,000). Other categories of household income may be used based on the distribution of these data.

f. Marital status (categorical: single, married or living as married (2 categories combined), divorced or separated (2 categories combined)

g. Age at time of cancer diagnosis

h. Cancer type (dichotomous (yes/no) for each variable assessed: leukemia, CNS, Hodgkin’s Disease, non-Hodgkin’s lymphoma, Kidney (Wilms), neuroblastoma, soft tissue sarcoma, bone cancer)

i. Cancer treatment (dichotomous (yes/no) for each variable assessed: bleomycin, carmustine (BCNU), lomustine (CCNU), anthracyclines, chest irradiation, cranial irradiation, neck irradiation)

5.2.2. Psychological/Health status variables

a. **Psychological distress** will be measured by the Brief Symptom Inventory-18[20] (BSI-18; CCSS Long-Term Follow-up Study 2007 survey, items L1-18). The BSI-18 is composed of three subscales[21] including depression (items L 4, 6-8, 13, 18), somatization (items L 2-3, 10-12, 14), and anxiety (items L 1, 5, 9, 15-17). This scale also provides a Global Severity Index. Psychological distress will be characterized using the total and factor scores of the BSI-18. The relationship between the BSI-18 subscale and total scores and smokeless/dual tobacco use, and smokeless tobacco cessation will be assessed. T-scores will be used to categorize participants according to cut-off scores ($\geq$ 63 [90th percentile]) indicating clinically significant levels of distress.[22]

b. **Participants' health status** will also be examined via the following concepts from the CCSS Long-Term Follow-up Study 2007 survey

b.1. Limitations on activities due to impairment or health problems will be measured by items N.22-24 and N.26. The response options for N.22 – N.24 are yes and no.

b.1.a.Question N.22: "Because of any impairment or health problems, do you need the help of other persons with <u>personal care</u> needs, such as eating, bathing, dressing, or getting around your home?"

b.1.b.Question N.23: "Because of any impairment or health problems, do you need the help of other persons in handling <u>routine needs</u>, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?"

b.1.c.Question N.24: "Does any impairment or health problem keep you from holding a job or attending school?"

b.1.d.Question N.26: "Over the last 2 years, how long (if at all) has your health limited you in each of the following activities? (Mark one box on each item):"

- "The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports"
- "The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling"
- "Walking uphill or climbing a few flights of stairs"
- "Bending, lifting, or stooping"
- "Walking one block"
- "Eating, dressing, bathing, or using the toilet"

The response options for each activity were the following:

- "Limited for more than 3 months"
- "Limited for 3 months or less"
- "Not limited at all"

b.2. **Participants' general health** statuses will be measured by item L.19: "In general, would you say that your health is:" with the following response options:

- "Excellent"
- "Very good"
- "Good"
- "Fair"
- "Poor"

b.3. **Participants' pain** will be measured by item L.21: "How much bodily pain have you had during the past 4 weeks?" with the following response options:

- "None"
- "Very mild"
- "Mild"
- "Moderate"
- "Severe"
- "Very severe"

b.4. **Participants' anxieties/ fears** as a result of cancer; leukemia, tumor or similar illness or its treatment will be measured by item L.20: "Do you currently have anxieties/fears as a result of your cancer, leukemia, tumor or similar illness or its treatment?" with the following response options:

- "No anxieties/ fears"
- "Small amount of anxieties/ fears"
- "Medium amount of anxieties/ fears"
- "A lot of anxieties/ fears"
- "Very many, extreme anxieties/ fears"

b.5. **Other Issues** will be measured by items O 1-6: "Please rate how concerned you are about the following:"

- Your future health
- Your ability to have children
- Developing a cancer
- Your ability to get health insurance
- Your ability to get life insurance
- Any other issues

The response options for each issue were the following:

- "Very concerned"
- "Somewhat concerned"
- "Concerned"
- "Not very concerned"
- "Not at all concerned"

5.2.3. Medications and Alcohol Use

a.1. Classes of medications/ drugs taken in two year period (April 2006 to April 2008) for more than one month will be measured by question C.8 from the CCSS Long-Term Follow-up Study 2007 survey (items 1-10). The following drugs medicine/ drugs were listed as options (participants were instructed not to endorse medicine/ drugs that they obtained "over the shelf at the drug store"): birth control pills, estrogens or progesterones, testosterones (male hormones), pills or insulin

for diabetes, medications for high blood pressure or hypertension, medications to lower cholesterol or triglycerides, medications for heart conditions, including angina, coronary heart disease, congestive heart failure, or irregular heartbeat, thyroid medications, medications for depression, and other prescribed drugs.

The response options for each class of medications/ drugs were the following:

- "no"
- "yes"
- "not sure"

We will only consider Antidepressants and "Medications for high blood pressure or hypertension" in our model.

b.1. Alcohol use will be examined as risky alcohol consumption, heavy alcohol consumption, and current alcohol consumption.[23,24] Participants who indicated on question N.1 that they had had at least two drinks of any kind of alcoholic beverage in their lifetime answered further questions on alcohol use.

Question N.3: "During the last 12 months, <u>how many</u> alcoholic drinks did you have on a typical day when you drank alcohol?" Three categories of alcohol (wine, beer, mixed drinks) were provided and the response options for each were continuous.

Question N.4: "During the last 12 months, what is the largest number of drinks you had on any single day? Was it…"

The response options were the following:

- "24+ drinks"
- "12-23 drinks"
- "8-11 drinks"
- "5-7 drinks"
- "4 drinks"
- "3 drinks"
- "2 drinks"
- "1 drink"

Question N.5: "During the last 12 months, <u>how often</u> did you usually have any kind of drink containing alcohol?"

The response options were the following:

- "Everyday"

- "5 to 6 times a week"
- "3 to 4 times a week"
- "twice a week"
- "once a week"
- "2 to 3 times a month"
- "3 to 11 times in the past year"
- "1 or 2 times in the past year"
- "Never in the past year"

Question N.6: "During the last 12 months, how often did you have 5 or more (males) or 4 or more (females) drinks containing any kind of alcohol in a single day?"

The response options were the following:

- "Every day"
- "5 to 6 days a week"
- "3 to 4 days a week"
- "two days a week"
- "one day a week"
- "2 to 3 days a month"
- "one day a month"
- "3 to 11 days in the past year"
- "1 or days in the past year"
- "Never in the past year"

Risky alcohol consumption for women is defined as having more than three drinks per day or more than seven drinks per week.[24] Risky drinking for men is defined as having more than four drinks per day or more than fourteen drinks per week.[24] For the purposes of the analyses, we will categorize participants as those who do and do not engage in risky drinking.

Heavy drinking for women is defined as having five or more drinks per day at least once a month during the last year.[23,25] Heavy drinking for men is defined as having six or more drinks per day at least once a month during the last year. [23,25] For the purpose of the analyses, we will categorize participants as those who are and are not heavy drinkers.

Current alcohol consumption is defined as consumption of alcohol during the past year. Using the item below, we will categorize participants as those who are and are not current drinkers.

Question N.3: "During the last 12 months, how many alcoholic drinks did you have on a typical day when you drank alcohol?" Participants who endorsed one or more drinks will be identified as current drinkers.

5.3. Subject population: Data is available on 8015 adult survivors of childhood cancer who participated in the CCSS Long-Term Follow-up Study 2007 survey. Participants were 18 years of age or older at the time of survey completion. The expected number of current smokeless tobacco users is 481 based on preliminary data reported in Emmons et al.[6]

5.3.1.. Exclusion criteria

- Being ineligible for the Long-Term Follow-up Study 2007 survey
- Paralysis
- Mental Retardation

5.4. STATISTICAL ANALYSIS:

The primary objective of the study is to estimate the prevalence rates of smokeless tobacco use (STU) and dual tobacco use (DTU) as defined in Section 5.1. Then in an exploratory manner we will also identify the factors, listed in Section 5.2. that may be predictors of STU and DTU. In addition, we will also evaluate the factors that may be associated with "ever" smokeless tobacco use (ESTU) and smokeless tobacco cessation (STC) among "ever" smokeless tobacco users.

5.4.1. Descriptive statistics, including means and standard deviations, medians and ranges and frequencies and percents will be used to describe the cohort in terms of demographic, diagnosis and specific treatment factors.

5.4.2. Differences in outcome measures, classified as Yes/No for STU, DTU, ESTU and STC with respect to demographics, diagnosis and specific treatment variables will be analyzed using chi-square test (for categorical factors) or t-test or its robust rank based analogs for the continuous measures.

5.4.3. The relationship between each of the outcome measures STU, DTU, ESTU and STC and the predictors will be evaluated using PROC GENMOD in statistical software package SAS with log link. We will conduct the analysis in a stepwise manner, i.e. we will first conduct an analysis in which one factor at a time will be evaluated in the model and all the factors that are significant at p-value less than 0.15 will be incorporated into the multiple

regression model. Then, starting with the full model we will adopt a backward selection process and eliminate the least significant factor (largest p-value) and continue in this manner until we have only the significant factors in the model, i.e. those with p-values less than 0.05. For all the significant factors in the model the p-values and PRs (Prevalence Ratios) along with their 95% confidence intervals will be provided.

Table 1

Demographics among CCSS Cohort Members in 2007 (N=8015)

			Sex				Smokeless Tobacco Use Status						Dual Tobacco Use Status			
	Total Population		Male		Female		Current User		Former User		Never User		Current User		Former or Never	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All persons																
Age 18-20 years 21-24 years 25-29 years 30-34 years 35-39 years 40-49 years 50-59 years																
Race/ethnicity African-Amer. White, not Hisp White Hispanic Black not Hisp Black Hispanic Amer. Indian Asian/Pac Is. Other Not specified																
Household incm. < $20,000 $20K-59,999 >$60,000																

Not specified																
Marital Status Single Married/live as Divorced/separ Not specified																
Education status 1-12 years Comp HS/pt HS Col grad/pt grad Not specified																
Cancer diagnosis Leukemia CNS HD NHL Kidney/Wilms' Neuroblastoma Soft tissue sar Bone cancer																

Abbreviations: HS, high school; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma

Table 2

Frequency of Survivors by Tobacco Use Status and Previous Pulmonary/Cardiac Toxic Therapy

	Bleomycin				BCNU/CCNU				Anthracyclines			
	Yes		No		Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Smokeless Tobacco User												
Never User												
Ever User												
Current User												
Former User												
Dual Tobacco User												
Never User												
Ever User												
Current User												
Former User												

	Cranial Irradiation				Chest Irradiation				Neck Irradiation			
	Yes		No		Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Smokeless Tobacco User												
Never User												
Ever User												
Current User												
Former User												
Dual Tobacco User												
Never User												
Ever User												
Current User												
Former User												

EXAMPLE Table 3. Multiple Regression for POTENTIAL Variables Predicting Current Smokeless Tobacco Use among Adult Survivors of Childhood Cancer.

	β	statistic	P value	Risk Ratio	95% Confidence interval (CI)
Variable					
Intercept					
Household income < 20,000 20,000-59,999 ≥60,000					
Education 1-11 years HS/ some post HS College graduate					
Race Black Other					
Age at cancer diagnosis 0-9 years 10-20 years					
Pulmonary-toxic treatment Yes No					
Cranial irradiation Yes No					

EXAMPLE Table 4. Multiple Regression for POTENTIAL Variables Predicting "Ever" Smokeless Tobacco Use among Adult Survivors of Childhood Cancer.

	β	statistic	P value	Risk Ratio	95% Confidence interval (CI)
Variable					
Intercept					
Household income < 20,000 20,000-59,999 ≥60,000					
Education 1-11 years HS/ some post HS College graduate					
Race Black Other					
Age at cancer diagnosis 0-9 years 10-20 years					
Pulmonary-toxic treatment Yes No					
Neck irradiation Yes No					

EXAMPLE Table 5. Multiple Regression for POTENTIAL Variables Predicting Dual Tobacco Use among Adult Survivors of Childhood Cancer.

	β	statistic	P value	Risk Ratio	95% Confidence interval (CI)
Variable					
Intercept					
Household income < 20,000 20,000-59,999 ≥60,000					
Education 1-11 years HS/ some post HS College graduate					
Race Black Other					
Age at cancer diagnosis 0-9 years 10-20 years					
Pulmonary-toxic treatment Yes No					
Chest irradiation Yes No					

EXAMPLE Table 6. Multiple Regression for POTENTIAL Variables Predicting Smokeless Tobacco Cessation among Adult Survivors of Childhood Cancer.

	β	statistic	P value	Risk Ratio	95% Confidence interval (CI)
Variable					
Intercept					
Household income < 20,000 20,000-59,999 ≥60,000					
Education 1-11 years HS/ some post HS College graduate					
Race Black Other					
Age at cancer diagnosis 0-9 years 10-20 years					
Pulmonary-toxic treatment Yes No					
Brain irradiation Yes No					

6. SPECIAL CONSIDERATION:

6.1. Contingent on the decision by Dr. Leisenring, statistical analysis will be completed by the biostatistical team at St. Jude Children's Research Hospital under the supervision of Deo Kumar Srivastava, PhD. All analyses and methods will be given to a member of the statistical coordinating center for review throughout the data analysis process and prior to submitting our manuscript(s) to the CCSS publications committee for review.

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