CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1) **TITLE** Patterns and Predictors of Clustered Risky Health Behaviors Among Adult Survivors of Childhood Cancer

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3) **BACKGROUND AND RATIONALE**

Progress in survival among children diagnosed and treated for cancer has resulted in an increasing research focused on later health complications in this population.[1] Late effects include a variety of chronic health conditions such as secondary malignancies, cardiovascular disease (ischemic coronary artery disease, cerebrovascular disease, and hypertension), obesity, diabetes, osteoporosis, dyslipidemia and kidney dysfunction that may be exacerbated by unhealthy behaviors. Late effects are commonly experienced by adults treated for cancer during childhood, and appear to increase in prevalence with aging. In the Childhood Cancer Survivor Study (CSSS), Oeffinger[1] estimated a cumulative incidence of 73.4% for at least one chronic health problem by 30 years after the diagnosis among the 10,397 adults participants (mean age, 26.6 years); over 40% will experience a chronic condition that is severe, life-threatening or fatal. For vulnerable groups, careful medical follow-up and healthy lifestyles are critical to minimize the risk and severity of late effects and maximize well-being.

Risky health behaviors including smoking, alcohol abuse and physical inactivity cause significant morbidity in the general population.[2] Risky health behaviors can have synergistic health-damaging effects,[3] yet over 50% of people engage in 2 or more risky behaviors.[4,5] These behaviors will adversely affect outcomes in childhood cancer survivors, a population already at risk for higher rates of chronic disease and second neoplasms. Recognizing that the behaviors are modifiable, further study is warranted.

Previous reports have shown conflicting results describing the prevalence of some risky health behaviors in adult survivors of childhood cancer compared to their peers. For instance, some studies indicate higher alcohol consumption among young adult survivors[6] while others report lower rates of alcohol use.[7] In the CCSS cohort, alcohol use was evaluated in 1994-1998 among 10,398 adult survivors, and compared to sibling controls (n=3034) and a national sample of healthy peers from the National Alcohol Survey (n=4774).[8] Survivors were slightly less likely to demonstrate either risky drinking (for women to exceed three drinks per day or seven drinks per week, and for men more than four drinks per day or 14 drinks per week) [adjusted odds ratio (ORadj) = 0.9; 95% confidence interval (CI) 0.8–1.0] or heavy drinking (five or more drinks per day for women and six or more drinks per day for men at least once a month in the past year) (ORadj = 0.8; CI 0.7–0.9), and were more likely to be current drinkers compared to healthy peers. In addition, survivors were less likely to be current, risky or heavy drinkers when compared to sibling controls. In another CCSS report, black and Hispanic survivors were less likely to engage in heavy drinking than non-Hispanic white survivors when adjusted for socioeconomic status.[9] This finding is consistent with drinking patterns observed in the general population.[10]

Most studies indicate that smoking rates among childhood cancer survivors are similar to or modestly lower than their counterparts in the general population.[11] Emmons et al. reported that 28% of the CCSS survivor cohort was ever smokers, and 17% were current smokers. When compared to the U.S. population, the observed to expected (O/E) ratios for cigarette smoking among survivors were 0.72 (95% CI 0.69-0.75) among all survivors and 0.71 (CI 0.68-0.74) and 0.81 (CI 0.70-0.93) among whites and nonwhites, respectively. Survivors who smoked were more likely than siblings to quit (O/E, 1.22; 95% CL, 1.15, 1.30).[12] Conversely, another study that compared childhood cancer survivors from responders to a general population survey noted that survivors were significantly more likely to be smokers (ORadj=2.33, 95% CI 1.98-2.73) compared to controls. [13]

In another study from CCSS, Florin et al[14] used data from the baseline questionnaire and compared it to data from the 2003 Behavior Risk Factor Surveillance System (BRFSS) questionnaire to determine if physical activity patterns differed between childhood cancer survivors and the general population. Among 2648 adult survivors of childhood ALL, 53% did not meet the physical activity criteria outlined by the Centers for Disease Control and Prevention (CDC);(i.e. at least 30 minutes of moderate-intensity physical activity on 3 days or more per week) and were more likely to be inactive compared to the general population. Ness et al[15] also documented the physical activity patterns in the entire CCSS cohort and reported that adult survivors of childhood cancer (n=9301) were less likely than siblings (n=2886) to meet physical activity guidelines (46% vs 52%) and more likely than siblings to report inactive lifestyle (23% vs 14%). Medulloblastoma and osteosarcoma survivors reported the highest rates of physical inactivity. Other risk factors associated with an inactive lifestyle were cranial radiation, amputation, female gender, black race, older age, lower education, underweight or obesity, smoking and depression.[15]

Collectively, research supports that survivors either engage in risky drinking at rates similar to or modestly lower than peers, and that they are less likely to be physically active. Unhealthy behaviors among long-term survivors may exacerbate other treatment-related health risks. Risky health behaviors do not happen in isolation, but cluster in individuals in specific combinations[16],[17]. Fine et al[4] analyzed the data from the 2001 National Health Interview Survey to report the prevalence of multiple risk behaviors and clustering in the US general population. Among 29,183 participants, the mean number of risk factors was 1.68 (95% CI 1.66 –1.70), and

17% had three or more risk factors from among cigarette smoking, risky alcohol consumption, physical inactivity and overweight.

Despite this potentially large impact, there are very few reports on prevalence of risk behavior clustering among childhood cancer survivors. Overlapping risk factors are widely reported in healthy populations. Use of alcohol is strongly associated with subsequent and continued smoking[18] as is low physical activity.[19] No or low physical activity was associated with greater risk of alcohol use among adolescents.[20] In the National Health Interview Survey multiple RHB were more common among those reporting psychological distress.[4]
Butterfield[21] reported multiple health risk behaviors among a selected group of smokers recruited from CCSS. These authors demonstrated that childhood cancer survivors who smoke have a number of other risk factors for the development of preventable disease, and that the presence of these risks was associated with factors that decrease the likelihood of quitting smoking. However, patterning of multiple health risk behaviors in the entire CCSS cohort has not been reported.

It is important to describe the pattern of multiple health risk behaviors among childhood cancer survivors because of the possible synergistic effects of risky behavior on health outcomes. Understanding the behavioral clusters and associated demographic covariates can provide support for existing screening guidelines, planning for future prevention programs, and the opportunity to design multiple lifestyle intervention approaches to modify late effects. It is possible that multiple-behavioral interventions will have a greater impact on health than a more traditional one-behavior-at-a-time approach.[22] Evidence indicates that when an intervention effects a reduction of two risky health behaviors, a savings of $2000 per year can be realized in general populations,[23] thus demonstrating the cost-effectiveness of MRHB interventions.[5,24-26]

4) SPECIFIC AIMS AND HYPOTHESES

Aim 1: To describe clusters and longitudinal patterns of risky health behaviors among childhood cancer survivors and compare these clusters (at each time point) and longitudinal patterns of risky health behaviors between survivors and a sibling comparison group.

We hypothesize that:
1a) Smoking, risky drinking and physical inactivity will cluster together at each time point.
1b) The prevalence of the smoking/risky drinking cluster will decline over time and the prevalence of physical inactivity will increase over time, particularly among continuing tobacco and alcohol users.
1c) Survivors will be less likely than siblings to exhibit the smoking/risking drinking cluster and more likely than siblings to exhibit the inactivity cluster.

Aim 2: To describe demographic, chronic disease and psychological risk factors from the baseline questionnaire for both increased and decreased risk of subsequent risky health behavior clusters.

We hypothesize that:
2a) Chronic disease burden (number of grade 3 or 4 chronic conditions) at baseline will be associated with a low or declining prevalence of risky health behavior at subsequent questionnaires

2b) Psychological distress will be associated with an increase in risky health behavior at subsequent questionnaires.

5) ANALYTIC PLAN

Descriptive statistics including means standard deviations, medians and ranges, and frequencies and percent(s) will be used to describe the demographic and treatment characteristics of the survivors and the demographic characteristics of the sibling comparison group. Demographic characteristics will be compared among participant and non-participant survivors and between survivors and siblings with two-sample t-tests or Chi-square statistics as appropriate.

Aim 1.

Step 1. Determining risky health behavior clusters: Using data from all time points among both survivors and siblings 25-40 years of age at measurement (assuming that health behaviors are likely to be most stable during adulthood), cluster analysis[27] will be used to determine whether risky health behaviors group into one or more than one broad cluster of "Risky health behaviors". The proportion of survivors and siblings in each of the determined clusters will be presented and compared at each time point in generalized linear models adjusted for age and sex and with an error term for family membership.

Step 2. Longitudinal patterns of health behavior: This portion of the analysis assumes that the clusters of risky health behavior will have some type of pattern (ordered or unordered) so persons can have health behaviors that get worse, stay the same or improve over time. Therefore, we will use latent class analysis to define distinct classes of risky health behavior in terms of how they change over time. Once class membership has been determined, we will again compare the proportions of survivors and siblings who fall into each class using either a proportional odds model or a generalized logit model, again adjusted for age and sex.

Aim 2.

Predictors of longitudinal patterns of health behavior: This portion of the analysis again assumes that the clusters of risky health behavior will have some type of pattern so persons can have health behaviors that get worse, stay the same or improve over time. The distinct classes defined in aim 1 above will be retained. We will use multivariate modeling (a proportional odds model or a generalized logits model) to evaluate associations between baseline chronic conditions and baseline emotional health and patterns of risky health behavior.

6) DATA

Sample: Survivors and siblings 25-40 years of age at baseline who responded to the 2003 and/or 2007 questionnaires.

Outcome variables: (Primary in bold text)
Smoking (reference [28]) (BL; N1, N1a-N1e, FU1; L1-L5, F2; N7-N12)
-Never smokers; never having smoked greater than or equal to 100 cigarettes (in total) in one's lifetime
-Ever smokers; ever having smoked at least 100 cigarettes
-Ever regular smokers; having ever smoked at least one cigarette per day for 6 months
-Current smoker (yes/no)

Alcohol (reference [8]) (BL; N3-N8, FU1, no questions, FU2; N1-N6)
- Current drinker; one or more drinks in the past year
- **Current Risky drinking**
       • Women; > 3 drinks per day or 7 drinks per week
       • Men; > 4 drinks per day or 14 drinks per week
- Current Heavy drinking
       • Women; ≥ 5 drinks per day at least once a month in the past year
       • Men; ≥ 6 drinks per day at least once a month in the past year

Physical Activity [15] (BL; N9, 2003; D1-D7, 2007; N15-N21)
-Active; meets the CDC guideline in the past year[29]
-Inactive; does not meet the CDC guideline[#]

CDC guideline [29];
At least 30 minutes of moderate intensity physical activity on five or more days of the week, or at least 20 minutes of vigorous intensity physical activity on three or more days per week.

Multiple RHB is defined to include any current smoking, current risky drinking, and not meeting the CDC guidelines for past year physical activity.. These can be examined as the total number of RHB or grouped, such as none vs 1 & 2 vs 3 RHB.

Combinations of RHB will be examined in specific analyses as defined from the cluster analysis described above. We hypothesize that they may be:
1) Tobacco use and risky alcohol use
2) Tobacco use and physical inactivity
3) Risky alcohol use and physical inactivity
4) Tobacco use, risky alcohol use and physical inactivity
Exploratory variables:
Chronic condition severity score [1]
Chronic conditions from baseline, based on the Commom Terminology Criteria for Adverse Events (version 3) will be used in these analyses as the number of chronic conditions Grade 3 or 4. It is possible to account for the development of chronic conditions over time (prior to any age) – we will use these as time varying covariates in our models – evaluating them etiologically as associations between chronic condition events and subsequent behaviors.

Psychological distress
Brief Symptom Inventory (BSI)[30] The BSI includes 18-items and has 3 subscales that assess depression, somatization and anxiety and allow for a T score for each sub-scale and a summary T score (for the 3 subscales) called the Global Severity Index (GSI). Depression, anxiety and the GSI will be the primary distress measure predicting outcomes. The BSI has been validated in healthy populations[31] and in CCSS participants. The BSI when used in adult childhood cancer survivors was compared to the Symptom Checklist-90-R (SCL-90-R) with high correlations (0.88-0.94) with the corresponding SCL-90-R subscales and acceptable internal consistency (alpha >0.80). The Case definition for distress is a GSI T ≥ 63 or any two subscales ≥ 63. This definition is recommended by Derogatis in the BSI=18 manual and has been used in many publications.[32] (J16-J35)

Demographics from the baseline questionnaire
•Gender (A2)

•Age at Survey (Continuous age in years, A1 and date of survey completion)
•Race/ethnicity (Non-Hispanic White, Non- Hispanic Black, Hispanic, Asian/Pacific Islander, Other, A4)
•Education (Did not graduate from high school, high school graduate, and college graduate, O1, O2)
•Annual household income (Q8)
•Marital status (L1, L2)

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Potential Tables and Figures for Paper

Table 1. Characteristics of the study population

	Survivors		Siblings		
	N	%	N	%	p-value
Sex					
Female					
Male					
Race/Ethnicity					
Asian					
Black – non-Hispanic					
Hispanic					
White – non Hispanic					
Other					
Not-reported					
Age at baseline					
Mean + SD					
Median + Range					
Age at 2003 survey					
Mean + SD					
Median + Range					
Age at 2007 survey					
Mean + SD					
Median + Range					
Educational Attainment					
< High School					
High School Graduate					
College Graduate					
Household Income					
< 20,000/year					
20-39,000/year					
40-59,000/year					
60,000_/year					
Marital Status					
Single					
Married or Living as Married					
Divorced/Separated					
Number of Grade 3 Chronic Conditions					
Mean + SD					
Median + Range					
Global Distress (63+ on Brief Symptom Inventory)					
Yes					
No					

Table 2. Number and frequencies of individual and clustered risky health behaviors over time (probably will show as a figure)

	Survivors		Siblings	
	N	%	N	%
Current Smoking				
Baseline				
2003				
2007				
Risky Drinking				
Baseline				
2003				
2007				
Inactivity				
Baseline				
2003				
2007				
Clustered Behavior Group A				
Baseline				
2003				
2007				
Clustered Behavior Group B				
Baseline				
2003				
2007				
Clustered Behavior Group C				
Baseline				
2003				
2007				
Clustered Behavior Group D				
Baseline				
2003				
2007				

Table 3. Multivariable model predicting class memberships (examples only – data driven class memberships for clusters will determine groups of behaviors) – comparing those with increasing or stable risky behavior(s) to those with no original or declining risky behavior(s)

	Increasing or stable smoking and risky drinking vs. no or decreasing smoking and risky drinking (N=XX)				Increasing or stable inactivity, smoking, risky drinking vs. no or decreasing inactivity, smoking, risky drinking (N=XX)			
	N	Row %	RR	95% CI	N	Row %	RR	95% CI
Sex								
Female								
Male								
Race/Ethnicity								
Asian								
Black – non-Hispanic								
Hispanic								
White – non Hispanic								
Other								
Age at baseline								
Educational Attainment								
< High School								
High School Graduate								
College Graduate								
Household Income								
< 20,000/year								
20-39,000/year								
40-59,000/year								
60,000_/year								
Marital Status								
Single								
Married or Living as Married								
Divorced/Separated								
Number of Grade 3 Chronic Conditions								
Mean + SD								
Median + Range								
Global Distress (63+ on Brief Symptom Inventory)								
Yes								
No								

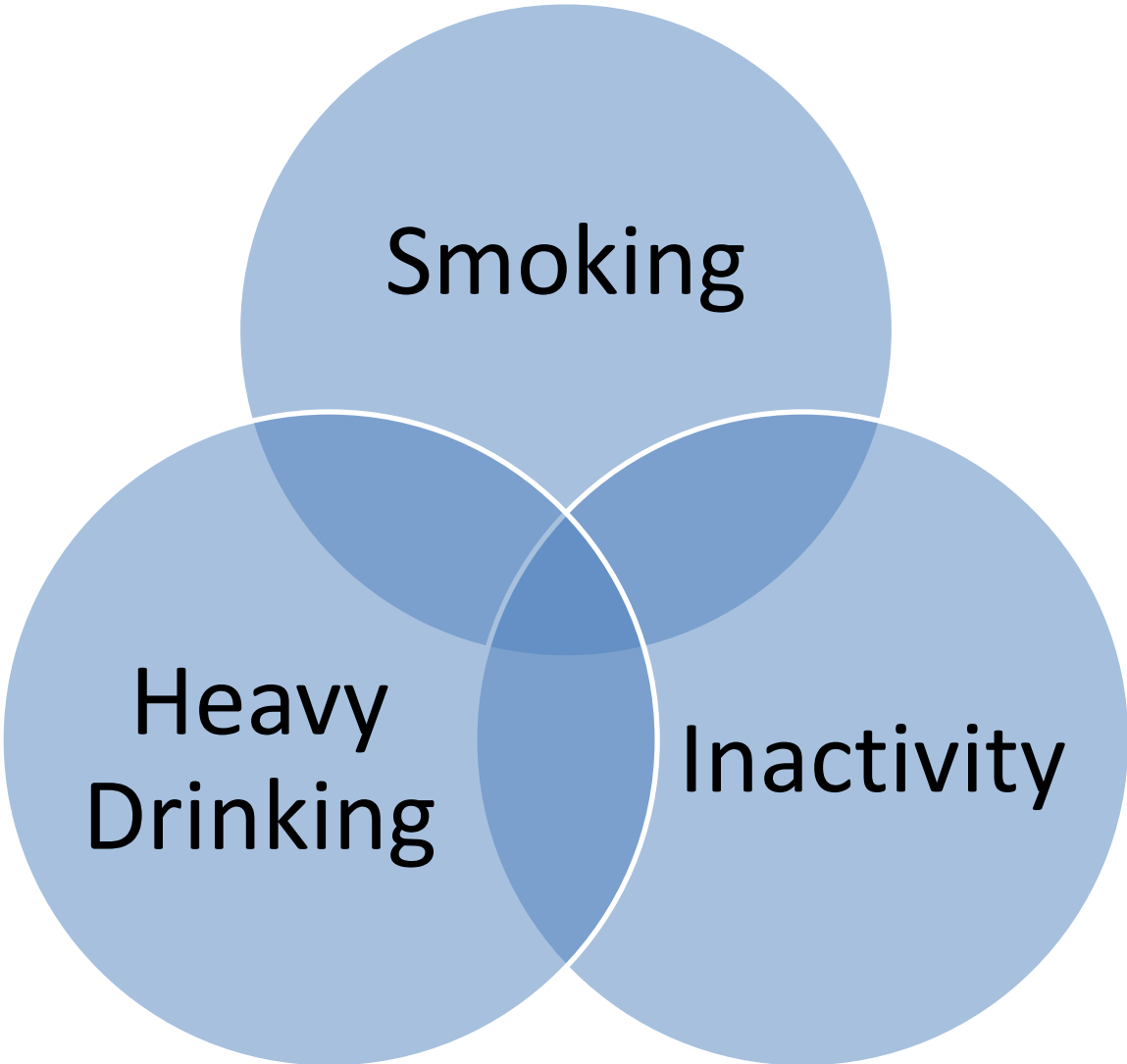**Figure 1. Potential overlap between risky health behaviors to form clusters -**

Figure 2. Longitudinal patterns of risky health behaviors (panels for the different clusters)