

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
October 10, 2005

- 1. **STUDY TITLE:** Risk of Increased Morbidity and Mortality in Underweight Survivors
- 2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed Investigators will include:

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3. **BACKGROUND AND RATIONALE:**

When compared to normal controls, a substantial percentage of adult survivors followed in the CCSS cohort are underweight [1]. Through an analysis of BMI (kg/m²), survivors more likely to be underweight included: female and male survivors of Hodgkin's disease and Wilms' tumor, female survivors of bone cancer without amputation, and male survivors of leukemia, brain tumors, non-Hodgkin's lymphoma, neuroblastoma, and soft tissue sarcomas [2]. Of those who were underweight, 55% had moderate to extreme adverse health status, 39% reported a major medical condition and 22% were current smokers [3]. We are interested in long-term morbidity and mortality in the underweight survivors, in particular the survivors who were underweight at the baseline questionnaire with no identifiable cause (e.g. no major medical condition, adverse health status or history of being a current smoker).

In the general population, the clinical implications of being underweight are controversial. There is a debate in the literature as to whether the BMI mortality curves are J shaped, U shaped or L shaped.([4-10] Calle in the NEJM describes the nadir of the BMI mortality risk curve occurring at a BMI of 23.5-24.9 kg/m² in males and 22.0-23.4 kg/m² in females[4].The curve for the risk of death from cardiovascular disease was J shaped and the curve was U shaped for the risk of death from all other causes. The increased risk of death for the low BMI subjects was a result of cerebrovascular disease, pneumonia and central nervous system disease. Hayashi describes an increased risk of death in low BMI individuals with a HR of 2.66 95% CI (1.59-4.46 in males and HR 3.14 95% CI (1.38-7.13) in females[10]. In Hayashi's population the mortality curves for males was L shaped and females U shaped. Low BMI was associated with risk of death from cancer but not cardiovascular disease. The data was analyzed for smoking status in male subjects. The hazard ratio for mortality with low BMI subjects who had never smoked was 3.74 95% CI (1.71-8.17) vs current smokers HR=1.88 95% CI(1.08-3.26) Singh et all reported increased risk of death in low BMI females due to cerebrovascular disease and respiratory disease[11]. Rexrode et all examined the risk of stroke and BMI in women[8]. They found a nonsignificant inverse relationship between BMI and risk of hemorrhagic stroke with the highest risk in the leanest women (p for trend=.20) Lastly Bigaard further subdivides the U shaped curve that describes the relation between mortality and BMI in a J shaped curve due to the effect of body fat mass index on mortality that can be combined with a reverse J shaped curve that describes the relation of fat free mass index and mortality[7]

The purpose of this analysis is to determine whether the clinical state of being underweight predicts an increased risk of mortality, subsequent diagnosis of major medical conditions, or the development of moderate to extreme adverse health status. A finding of poor outcomes in underweight survivors would strengthen the rationale for nutritional support and close surveillance [12, 13].

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Question Are underweighted survivors without a known underlying condition more likely to have poor health outcomes as they age than normal weighted, overweighted or obese survivors?

Aim 1 Determine long-term risk associated with being an underweight adult survivor.

Hypothesis 1 Adult survivor without a major medical condition who were underweight (BMI < 18.5 kg/m²) at baseline enrollment will have a higher mortality rate, higher rates of second malignancies and/or be more likely to have adverse health status at FU2 in comparison with adult survivors without medical condition who were normal weight (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²) and obese (>30 kg/m²).

Hypothesis 2 Adult survivors who were underweight (BMI < 18.5) and with a major medical condition at baseline enrollment will have a higher mortality rate, higher rates of second malignancies and/or be more likely to have adverse health status at FU2 in comparison with adult survivors who were normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9 kg/m²) or obese (>30 kg/m²) with and without major medical conditions and with underweight individuals without a major medical condition.

Aim 2 Identify socio-demographic and cancer/cancer treatment related factors associated with an increased risk of mortality, second malignant neoplasms and adverse health status in underweight adult survivors.

Hypothesis 1 Underweight survivors without a major medical condition at baseline enrollment have underlying undetected conditions that predisposed them to low BMI that are identifiable as death, second malignancy or adverse health status at FU2.

Aim 3 Determine if BMI categories remain stable

Hypothesis 1 Survivors remain in the same BMI category from baseline to FU2

5. ANALYSIS FRAMEWORK:

a. Subject population: adult (\geq 18 yrs of age) survivors at baseline enrollment

Six subpopulations:

- underweight without a major medical condition at baseline
- underweight with a major medical condition at baseline

- overweight without a major medical condition at baseline
- overweight with a major medical condition at baseline
- obese without a major medical condition at baseline
- obese with a major medical condition at baseline

Major medical condition [3]: reported current use of a selected medication (anticonvulsants, cardiovascular medications or chemotherapy/immune suppressants) or the presence of selected medical conditions (complete deafness, renal failure requiring dialysis, congestive heart failure, myocardial infarction, stroke or cerebrovascular accident, current use of oxygen, cirrhosis of the liver, coronary artery bypass surgery, angioplasty, heart transplant, lung transplant, kidney transplant, repeated seizures, convulsions or blackouts, confirmed new malignancy excluding basal cell carcinoma or relapse, amputation, or a joint replacement).

- b. Comparison group: Normal weight (BMI: 18.5-24.9) and adult (≥ 18 yrs of age) survivors at baseline enrollment with and without a major medical condition
- c. Outcomes of interest: mortality, second malignancy and adverse health status at FU2.
 1. Mortality: mortality since baseline enrollment
 2. Second malignant neoplasms: SMN since baseline enrollment.
 3. Stroke
 4. New Major medical condition identified at FU2.
 5. Adverse health status (AHS): any of the 6 HS domains (general health, mental health, activity limitations, functional impairment, pain following cancer, anxiety following cancer) determined at FU2.
- d. Independent variables of interest:
 - socio-demographics (age, gender, race/ethnicity, household income)
 - cancer diagnosis
 - cancer treatment
 - interval from cancer diagnosis
 - change in BMI status
 - health status at baseline and FU2
 - tobacco use at baseline and FU2
 - alcohol intake at baseline and FU2
 - physical activity at baseline and FU2

e. Statistical analysis

To compare socio-demographic and cancer treatment variables between these four groups (underweight without major medical condition, underweight with major medical condition, and the reference group of normal weight with and without major medical condition), linear regression models will be used for continuous variables and chi-square tests performed for categorical variables. The number of deaths will be determined for the three groups, stratified by gender. Poisson regression models will be used to compare the incidence of death in the three groups. Relative risk for

mortality will be determined for the two underweight groups in comparison with the normal weighted population, stratified by gender, and adjusted for age and cancer diagnosis. The same data will be used to construct Kaplan-Meier survival curves.

Poisson regression models will be used to compare SMN incidence among the three groups, stratified by age and gender. The number of person-years at risk for the cohort will be calculated using the 5-year anniversary of the first cancer diagnosis as the start point, and the date of SMN diagnosis, death, or questionnaire completion as the end point. The observed number of SMNs in each group will be compared with the expected number which will be, computed using data from the Surveillance, Epidemiology and End Results (SEER) database.

The prevalence of adverse outcomes in each of the health status domains will be determined. Logistic regression models with adverse health status as the dependent variables will be used to compare the two underweight groups to the referent normal weighted population. To estimate odds ratios (OR) with 95% confidence intervals (95% CI) for these outcomes, subjects will be stratified by gender and adjusted for age and cancer diagnosis. Analyses were performed with and without adjustment for the following SES variables: health insurance, household income, and level of education.

Statistical analysis will be performed by the FHCRC group.

6. TABLES/FIGURES:

Figure 1 – Mortality rates for survivors with and without recognized major medical conditions across all 4 BMI categories (underweight, normal, overweight and obese) X axis years post diagnosis and Y axis mortality. .

Figure 2 – Cumulative incidence of secondary malignant neoplasm for survivors with and without major medical conditions across all 4 BMI categories (underweight, normal, overweight and obese) . X axis is years post diagnosis and y axis is cumulative incidence second malignant neoplasms.

Table 1. Demographics of Participants

	Under Weight No MMC	Under Weight With MMC	Normal Weight No MMC	Normal Weight with MMC	Over Weight No MMC	Over Weight with MMC	Obese No MMC	Obese with MMC
Histology								
<i>ALL</i>								
<i>Other Leukemia</i>								
<i>Brain Tumors</i>								
<i>Hodgkin's disease</i>								
<i>NHL</i>								
<i>Wilms' tumor</i>								
<i>Neuroblastoma</i>								
<i>Soft Tissue Sarcomas</i>								
<i>Bone Malignancies</i>								
Amputation								
No amputation								
Race/ethnicity								
White, non-Hispanic								
Black, non-Hispanic								
Hispanic								
Other- not specified								
Radiation therapy								
Brain								
Spine								
Abdomen								
Pelvis								
TBI								
Chest								
Head								
Unspecified RT								
Radiation unknown								
No Radiation								
Chemotherapy								
Anthracycline								
Alkylating agent								
Anthracycline								

and alkylating agents								
Other Chemotherapy								
No Chemotherapy								
Age at diagnosis Mean, SD Median, range								
Age at study Mean, SD Median, range								
Interval from cancer Mean, SD Median, range								

Table 2. Odds ratio (OR) and 95% Confidence Intervals (CI) of the likelihood of adverse health status (HS) in underweight survivors at baseline enrollment compared with normal weight survivors. MMC-Major Medical Condition, AHS – Adverse Health Status

	MMC FU2	AHS Any FU2	AHS General health	AHS Mental health	AHS Activity limitations	AHS Functional impairment	AHS Pain post cancer	AHS Anxiety post cancer
Underweight BMI with MMC								
Underweight BMI Without MMC								
Normal BMI with MMC								
Normal BMI Without MMC	1.0 Ref							
Overweight BMI With MMC								
Overweight BMI Without MMC								
Obese BMI With MMC								
Obese BMI Without MMC								

Table 3. Change in BMI status from baseline to FU2.

	Underweight at baseline <18.5 kg/m²	Normal weight at baseline 18.5-24.9 kg/m²	Overweight at baseline 25-29.9 kg/m²	Obese at Baseline >30 kg/m²
Underweight at FU2 <18.5 kg/m²				
Normal weight at FU2 18.5-24.9 kg/m²				
Overweight at FU2 25-29.9 kg/m²				
Obese at FU2 >30 kg/m²				

7. REFERENCES:

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