CONCEPT PROPOSAL

STUDY TITLE: Cardiometabolic Risk after Total Body Irradiation during Childhood: A Report from CCSS and CIBMTR

WORKING GROUP: This report will be written within the Chronic Disease Working Group. Proposed investigators include:

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BACKGROUND AND STUDY RATIONALE

Epidemiology of hematopoietic cell transplantation survivorship: Hematopoietic cell transplantation (HCT) has emerged as an important curative treatment for children with high-risk hematologic malignancies and solid tumors. By 2030, it is estimated that there will be 502,000 HCT survivors in the United States of whom 64,000 will have been transplanted prior to age 18[1,2]. As more children survive HCT, however, it has become increasingly clear that survivors face a lifelong risk of multiple treatment-related adverse sequelae and reduced life expectancy compared to the general population[3-5].

Cardiovascular disease and metabolic dysfunction after HCT: Cardiovascular disease (CVD) is an important contributor to treatment-related morbidity, mortality, and reduced life expectancy in this cohort[6-11]; when compared to the general population, HCT survivors have a four-fold risk of CVD[3,6,7], which includes heart failure, myocardial infarction, and stroke. Survivors of HCT are also known to be

at increased risk for CVD comorbidities, including diabetes, dyslipidemia, hypertension, and the metabolic syndrome[12-15], a clustering of cardiovascular risk factors associated with CVD and all-cause mortality[16,17].

The association between total body irradiation (TBI) and cardiometabolic dysfunction: TBI has been an important component of the preparative regimen for high-risk patients undergoing HCT, but it is also associated with a wide range of late toxicities[18,19]. With respect to cardiometabolic disease, prior work within the original cohort of CCSS demonstrated that TBI is a key independent risk factor for diabetes[20]; the cardiovascular risk factor cluster[21], a surrogate for metabolic syndrome; and risk of underweight in females[22]. Other cohort studies, which have either included individuals who have undergone HCT during adulthood or been limited by single-institutional design, similarly demonstrated an association between TBI, cardiovascular risk factors, and cardiometabolic disease[19,23-25]. For those exposed to TBI during childhood, however, updated data are lacking on how the prevalence of cardiometabolic comorbidities changes as this population ages, when compared to conventionally treated survivors and healthy controls. Phenotypically, TBI-exposed survivors have been noted to develop a unique body habitus with abdominal adiposity in the absence of clinical obesity (based on measures of body mass index)[26]. This has led to the characterization of the thin yet "metabolically obese" cancer survivor who typically presents with multiple difficult-to-control CVD comorbidities, including insulin resistance/diabetes, hypertension, dyslipidemia, and metabolic syndrome[8,24,27,28].

An extensive body of clinical work has demonstrated an association between TBI exposure, overt CVD[6,8,11,29-31], and individual CVD comorbidities[6,7,12,24,27,28,32,33], including diabetes, hypertension, dyslipidemia, and changes in body composition. Additionally, risk seems to increase with time since treatment. A single-institution, retrospective review of 123 TBI-exposed survivors found that the risk of elevated blood pressure, low HDL, hypertriglyceridemia, glucose intolerance, and the cardiovascular risk factor cluster, a surrogate for metabolic syndrome, increased over time; the cumulative incidence of all cardiovascular risk factors, except obesity, increased 1.7 to 3.2-fold from five to ten years post-TBI[25]. Similarly, cross-sectional analyses have shown that TBI-exposed HCT survivors are more likely than non-HCT survivors to manifest *multiple* adverse cardiometabolic traits, including central adiposity, hypertension, insulin resistance, and dyslipidemia, as well as increased CRP and leptin levels with decreased adiponectin levels[14]. TBI exposure among childhood cancer survivors has also been associated with higher percent fat mass, lower lean body mass, and a pro-inflammatory state with significantly elevated levels of IL-6 when compared to sibling controls[34]. These data strongly support the presence of a post-TBI inflammatory milieu in the context of adipokine derangements and visceral adiposity. Furthermore, adult HCT survivors have been noted to have an increased prevalence of sarcopenia, or low skeletal muscle mass, which has been linked to physiologic frailty in older adults without a cancer history[35] and has been hypothesized to play a role in premature aging in adult survivors of childhood cancer [36,37].

Notably, TBI-exposed survivors' risk for hypothalamic-pituitary dysfunction, including growth hormone deficiency, may be causally related to the development of this phenotype. In both non-cancer cohorts and childhood cancer survivors, growth hormone deficiency is associated with reduced lean body mass and increased visceral adiposity[38-41]. Consistent with the latter, recent studies have demonstrated that TBI-exposed childhood survivors exhibit a sarcopenic and lipodystrophic phenotype based on imaging characteristics and anthropometrics[26,42]. These findings, however, are not seen in other patients treated with radiation impacting the brain, who are also at similar risk for endocrinopathies, suggesting that other explanatory factors must also be at play in mediating cardiometabolic risk after TBI.

The Center for International Blood and Marrow Transplant Research (CIBMTR) registry recently conducted an analysis of late cardiovascular morbidity and mortality among allogenic childhood HCT survivors[43]. In this study of 661 relatively young HCT survivors (median age: 18.5 years; median follow-up: 8.1 years), the prevalence of dyslipidemia was 18%; diabetes was 8%; and obesity was

52% at most recent evaluation. There was no association between TBI exposure and adverse cardiovascular outcomes. However, the very young age of this cohort with relatively short follow-up may have limited the ascertainment of these adverse outcomes and therapeutic associations.

The current study will provide novel data not only on risk over time, but also about sociodemographic and lifestyle contributors to cardiometabolic risk after TBI exposure in aging childhood cancer survivors. We will focus specifically on the TBI-exposed cohort but will compare outcomes and risk factors to individuals treated with either non-TBI based HCT or conventional chemotherapy, as well as to siblings. Data from this work will clarify which survivors are at highest risk for CVD comorbidities, including diabetes, dyslipidemia, and hypertension, based on age at treatment, attained age, sex, race/ethnicity, socioeconomic status, and lifestyle factors. These findings will inform the design of future intervention studies. Possibilities for interventions in this cohort include targeted measures to increase physical activity, modify diet, implement smoking cessations strategies, or a combination thereof, and will largely depend on what we learn from this analysis.

Linkage of CCSS and CIBMTR: While HCT-specific data are incomplete within CCSS, particularly in individuals enrolled in the original CCSS cohort, we will overcome this limitation by linking CCSS data with CIBMTR. This linkage will allow us to confirm the following HCT-specific data among CCSS survivors: (a) HCT status, including autologous; (b) Conditioning/preparative regimen; (c) Donor type, matching; (d) Cell source; (e) Acute toxicities, including acute graft versus host disease [GVHD]; (f) Chronic GVHD. *We will also explore whether it is possible to compare adverse outcomes captured in CCSS (patient-reported) and CIBMTR (center-reported) for future studies; in this analysis, we will only explore CCSS-reported outcomes.*

CCSS has had prior successful linkages with the Organ Procure & Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) and Society for Assisted Reproductive Technology (SART); we will follow procedures successfully employed in those efforts in the current linkage.

RESEARCH DESIGN AND METHODS

Study Overview: This study is an assessment of the relationship between TBI; sociodemographic characteristics, treatment exposures, and lifestyle factors; and cardiometabolic risk in childhood cancer survivors diagnosed between 1970 – 1999 and enrolled in CCSS. Using data from participants in the original and expansion cohorts, we plan to describe the risk of CVD comorbidities in CCSS survivors treated with TBI, and identify potential modifying risk factors. The potential modifying effects of age at irradiation, time since irradiation, lifestyle factors, and BMI will be evaluated. We will then explore the association between CVD comorbidities in this cohort and serious adverse cardiovascular outcomes, including ischemic heart disease, cardiomyopathy/congestive heart failure, stroke, and death due to a cardiovascular condition. By linking CCSS and CIBMTR databases, we will achieve this through the following aims:

Aim 1: Using CCSS-CIBMTR data, determine the relative risk and absolute excess risk of developing CVD comorbidities, including diabetes mellitus, hypertension, and dyslipidemia, in childhood cancer survivors treated with TBI between 1970-1999 (n=571), when compared with: (a) survivors treated with non-TBI based HCT; (b) survivors treated with conventional chemotherapy without radiation; and (c) the sibling comparison group (n=5,059).

Hypothesis: CCSS survivors treated with TBI will exhibit an increased relative and absolute excess risk of diabetes, hypertension, and dyslipidemia, when compared with: (a) survivors treated with non-TBI based HCT and (b) survivors treated with conventional chemotherapy. We expect survivors treated with non-TBI based HCT to have a higher risk than both individuals treated with conventional chemotherapy and siblings. Risk will increase with duration of time since therapy.

Aim 2: Identify additional *non-modifiable* risk factors such as primary treatment exposures, primary disease, and demographic characteristics that modify risk of CVD comorbidities, specifically diabetes, hypertension, and dyslipidemia, in survivors treated with TBI when compared to the other three groups listed in Aim 1.

Hypothesis: Survivors treated with TBI at an early age will have a greater risk of developing CVD comorbidities (diabetes, hypertension, and dyslipidemia) independent of BMI. This hypothesis is based on prior data showing that individuals treated with TBI are at risk for developing CVD comorbidities in the absence of overweight/obesity.

Aim 3: Assess whether *modifiable* lifestyle factors, including physical activity, smoking, and alcohol use, are associated with altered risk of diabetes, hypertension, and dyslipidemia in survivors exposed to TBI when compared to the other three groups listed in Aim 1.

Hypothesis: Risk of diabetes, hypertension, and dyslipidemia will be associated with sedentary lifestyle and smoking in survivors exposed to TBI.

Aim 4: Explore the impact of CVD comorbidities (diabetes, dyslipidemia, hypertension) on the subsequent development of grade 3-5 adverse cardiovascular outcomes (ischemic heart disease, cardiomyopathy/congestive heart failure, stroke, death due to a cardiovascular condition) in the population of childhood cancer survivors and siblings described in Aim 1.

Hypothesis: The presence of CVD comorbidities will be associated with increased risk of grade 3-5 adverse cardiovascular conditions among childhood cancer survivors.

Study Population: The study population of interest includes any patient in the original (diagnosed 1970-1986) or expansion (diagnosed 1987-1999) CCSS survivor cohorts treated with: TBI-based HCT; (2) non-TBI based HCT; or (3) conventional chemotherapy; as well as the sibling comparison group. Analyses will be limited to individuals treated with TBI within five-years of primary cancer diagnosis. Treatment analyses will be limited to survivors who consented to medical record abstraction. Linkages will be performed with CIBMTR to ascertain HCT status and treatment exposures for individuals enrolled in CCSS.

Explanatory (independent) variables to be analyzed: The following variables will be collected from surveys completed at baseline and as many follow-up surveys as available.

General variables (CCSS):

A. Primary cancer diagnosis
B. Age at primary cancer diagnosis
C. Attained age at assessment (DOB – assessment)
D. Length of follow-up
E. Sex (Baseline A2, Baseline – expanded A2)
F. Race/ethnicity (Baseline A4, A4.a, Baseline – expanded A5, A5.a)
G. BMI (Calculated from Height/Weight on: Baseline A10, A11; FU 2003 7-8; FU 2007 A1-A2; Expansion A3-A4); we will classify weight status as obese, overweight, normal weight, or underweight, using standard criteria set forth by the Centers for Disease Control and Prevention[44,45]
H. Household Income (Baseline <18 Q8; Baseline Q8, Q9; FU 2003 S1-S3; FU 2007 A6-A8; Expansion T1-T3)
I. Insurance (Baseline Q2, Q3, Q3.a, Q3.b; FU 2000 16; FU 2003 M1; FU 2007 B9; Expansion U2, U3, U3.a, U3.b)
J. Education level (Baseline O1; FU 2000 1; FU 2003 1; FU 2007 A3; Expansion R1)

K. Employment (Baseline <18 O6, O7; Baseline O5-O11; FU 2000 3; FU 2003 4-5; FU 2007 A4, A5; Expansion S1-S2)
L. Physical activity (meets CDC criteria for moderate or vigorous activity per week)
M. Smoking status [never/past/current]: (Baseline N1.a, N1.b, N1.c, N1.d; Expansion O1-O3)
N. Heavy alcohol consumption [7+/week female, 14+ week/male] (Baseline)
O. Growth hormone deficiency (yes/no); if yes, dates of treatment
P. Hypogonadal (yes/no); if yes, treated with testosterone or estrogen
Q. If treated with hormone replacement therapy, type of estrogen administered (transdermal vs oral)
R Vital status
S. SMN [type; date of diagnosis]
T. Late recurrence after cohort entry [date]

Treatment variables (CCSS):
We will also include data about specific radiation fields and all administered chemotherapeutic agents in those so exposed. We anticipate that key therapeutic exposures will include:

A. History of chemotherapy [yes/no]; if yes:
Doxorubicin equivalent dose (yes/no; cumulative dose; DED score; Alkylating agents; Cyclophosphamide equivalent dose (CED cumulative dose); Epipodophyllotoxin (yes/no; cumulative dose; Platinum agents (yes/no; cumulative dose); Corticosteroids (yes/no)
B. Surgery [yes/no]
C. History of transplant [yes/no]
D. TBI [yes/no; if yes, dose of TBI (cGy)]
E. Age at TBI
F. Additional sites of radiation
G. Additional doses of radiation (cGy)

HCT Variables (CIBMTR):
A. Type of transplant (allogeneic vs autologous)
B. Conditioning/preparative regimen
C. Donor type, matching
D. Cell source
E. Graft versus host disease (GVHD) prophylaxis
F. Acute toxicities, including acute GVHD, grade
G. Chronic GVHD, grade

Primary outcome variables *(CCSS)*:
Eligible cases will be defined in accord with prior CCSS analyses[20], which utilize the CCSS chronic condition matrix as follows:

A. Diabetes, grade 2-4
B. Hypertension, grade 2-4
C. Dyslipidemia, grade 2-4

Secondary outcome variables *(CCSS)*:
In accord with prior CCSS analyses[10], we will define grade 3-5 adverse cardiovascular outcomes as follows:

A. Grade 3: coronary artery disease (on medication), CHF (on medication), atrial fibrillation or flutter, supraventricular dysrhythmia.
B. Grade 4: myocardial infarction (MI), heart transplant for cardiomyopathy, cerebrovascular accident, endocarditis, cardiac arrest, arterial embolism.
C. Cardiac surgery: coronary artery bypass, pericardectomy, heart catheterization, angioplasty, surgery for heart valve replacement, surgery for pacemaker, other heart surgery.

D. Death due to Disease of the Circulatory System (ICD 390-459)

ANALYSIS PLAN

Statistical analysis:
Summary statistics and graphical methods will be used to explore the data and understand the distributions of the variables, any trends over time, and the correlations between the different variables. Prevalence of the primary outcomes of interest (diabetes, dyslipidemia, hypertension) will be estimated and compared between groups using a regression framework.

Aims 1-3:
The age-specific prevalence of each outcome of interest (diabetes, dyslipidemia, hypertension) will be calculated by assessing reported events from each questionnaire and tabulating according to age at questionnaire completion. Rates of each outcomes among survivors in each group of interest [(1) TBI-based HCT; (2) non-TBI based HCT; (3) conventional chemotherapy] will be compared to rates for the sibling population.

In separate models for each outcome of interest (diabetes, dyslipidemia, hypertension), the outcomes will be used as dependent variables and modeled as functions of independent variables using Poisson models with robust standard errors. Independent variables will include (1) HCT-related factors: type of HCT, graft source, acute GVHD, chronic GVHD; (2) chemotherapy-related risk factors: anthracycline exposure, alkylating agent exposure (CED score), and corticosteroid exposure; (3) sociodemographic risk factors: household income, insurance status, education level, employment status, physical activity, smoking status, alcohol use; (4) possible effect modifiers: age at survey completion (attained age), race/ethnicity, sex; and (5) an indicator of group membership, where the groups are: childhood cancer survivors treated with TBI; childhood cancer survivors treated with non-TBI based HCT; survivors treated with conventional chemotherapy; and siblings. The associations between each treatment-related or sociodemographic factor and the different outcomes will be evaluated in separate models that include the group membership indicator and are adjusted for the possible effect modifiers.

A multivariable model will then be developed. When deciding which variables to include in the multivariable model, we will carefully consider the correlations and overlap in information captured by different variables. We will also test interactions between variables, such as between sex and race/ethnicity, and may consider building diagnosis-specific models. By carefully considering the correlations and relationships between the different variables in the CCSS data, we expect to be able to construct adjusted models that account for different factors and potential confounders which may be highly correlated.

Model diagnostics will be used to evaluate the model assumptions of all the models described above, including the overall goodness of fit of the models and whether the functional forms of the different variables in the model are appropriate. Different functional forms for the covariates (e.g. using a logarithmic transformation or a squared term) may be used if the linear term does not appear to be the best fit. For a sensitivity analysis, we may also compare the results of these models to log-binomial models.

Aim 4:
We will then assess the association of grade 3-5 adverse cardiac events (coronary artery disease, heart failure, valvular disease, and arrhythmia) with the presence of cardiovascular risk factors in the three groups of childhood cancer survivors enumerated above (siblings will not be included in this analysis). Multivariable Poisson regression analysis will be performed to calculate the rate ratio (RR) and 95% CI according to the number of CVD comorbidities present for each of the four types of adverse cardiac events, conditioned on the exposure group (TBI; non-TBI based HCT; conventional

chemotherapy). Conditions will be evaluated as time-dependent risk factors. Time at risk for cardiac events will end at the first cardiac event of interest, date of diagnosis of second malignant neoplasm or late recurrence, death, or completion of the last questionnaire. Additionally, the relative excess risk due to interaction (RERI) will be used to determine whether the interaction effects of treatment with CVD comorbidities of interest will be more than additive when present together[10].

TABLES/FIGURES

Table 1. Characteristics of Childhood Cancer Survivors and Siblings

Characteristic	Survivors Treated with TBI- based HCT	Survivors Treated with non-TBI based HCT †	Survivors treated with conventional chemotherapy	Siblings	p[1]*	p[2]**	p[3]***
Sex Male Female							
Race/ethnicity White, NH Black Other Unknown							
Age at Treatment, y Median (Range)							
Age at Interview, years Mean (SD) Median (Range)							
Cancer Diagnosis Leukemia Lymphoma Wilms tumor Hodgkin lymphoma Neuroblastoma Other							
BMI at interview <18.5 18.5-24.9 25.0-29.9 ≥ 30							
HCT Type Allogeneic Autologous							
Donor Type							
Stem Cell Source							
Chemotherapy Alkylating agents Anthracyclines Corticosteroids							
Conditioning regimen TBI-based regimen Non-TBI based regimen							
Acute GVHD							
Chronic GVHD							
Median age at last follow up, years (Range)							
Median duration of							

follow-up, years (Range)							
Vital Status Alive Deceased							

Abbreviations: *p^1 comparison between CCSS survivors treated with TBI and CCSS Survivors treated with non-TBI based HCT; ** p^2 comparison between CCSS survivors treated with TBI and CCSS survivors treated with conventional chemotherapy; *** p^3 comparison between CCSS survivors treated with TBI and siblings

Table 2. Non-modifiable risk factors for hypertension, diabetes, and dyslipidemia among CCSS survivors treated with TBI-based and non-TBI based HCT in multivariable analysis
(Non-modifiable risk factors: primary treatment exposures, primary disease, demographic characteristics)

Table 3. Modifiable risk factors for hypertension, diabetes, and dyslipidemia among CCSS survivors treated with TBI-based and non-TBI based HCT in multivariable analysis
(Modifiable risk factors: smoking, physical activity, alcohol consumption)

Table 4. Treatment-specific relative risks for grade 3-5 cardiac events according to presence of CVD comorbidities
(Treatments: TBI-based HCT; non-TBI based HCT; conventional chemotherapy; CVD comorbidities: diabetes, hypertension; dyslipidemia; 2+ factors)

Figure 1. Prevalence of (a) diabetes; (b) hypertension; and (c) dyslipidemia in childhood cancer survivors exposed to TBI when compared to CCS treated with non-TBI based HCT; CCS treated with conventional chemotherapy; and siblings

Figure 2. Risk of CVD comorbidities among HCT survivors before and after adjustment for lifestyle factors (smoking, alcohol use, physical activity)
*Model one adjusted for sex, nonwhite race/ethnicity, current age, and body mass index;
**Model two includes additional adjustment for current smoking, alcohol use, and level of physical activity

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