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Cardiovascular Risk Factors in Survivors of Childhood Hematopoietic Cell Transplantation Treated with Total Body Irradiation: A Longitudinal Analysis

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Abstract

Hematopoietic cell transplantation (HCT) survivors treated with total body irradiation (TBI) are known to be at increased risk for the development of cardiovascular risk factors (CVRF). We sought to characterize the incidence of CVRF in a TBI-exposed survivor cohort and describe prognostic indicators of their development. Retrospective analysis of CVRF in 1-year survivors of leukemia or lymphoma treated with TBI at Memorial Sloan Kettering from April 1987–May 2011. Eligible participants were≤ 21 years of age at TBI and were not on glucocorticoids at the time of entry to Long-Term Follow-Up. Survivors were assessed for obesity (body mass index [BMI]≥ 95th% for ages≤ 20; ≥30 kg/m^2 for ages >20 years), elevated blood pressure, dyslipidemia (elevated triglycerides [TG], low high-density lipoprotein [HDL]), and glucose intolerance (fasting glucose ≥100 mg/dl); those with ≥3 risk factors were deemed to have a CVRF cluster, a surrogate for metabolic syndrome. Cox regression models were used to estimate hazard ratios (HRs) evaluating factors associated with each CVRF. In order to compare prevalence of CVRF in HCT survivors and the general population, survivors were compared to age-, sex-, and race-matched controls from the National Health and Nutrition Examination Survey (NHANES). 123 survivors were evaluated (62.6% male). Median age at TBI was 11.8 years (range 1.6–21.9); median followup was 8.0 years (1.01–24.6); median age at last followup 20.1 years (4.0–41.3). Five-year cumulative incidence of elevated blood pressure, elevated glucose, low HDL, hypertriglyceridemia, and obesity was 14.7%, 10.5%, 26.8%, 39.2%, and 16.0%, respectively,

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while 10-year cumulative incidence was 28.8%, 33.1%, 52.0%, 65.0%, and 18.6%, respectively. The cumulative incidence of CVRF cluster rose from 10.6% (5.6–17.5) at 5 years to 28.4% (18.8–38.7) at 10 years. In multivariate analysis, growth hormone (GH) deficiency (HR 8.6; 95% CI, 2.1–34.4, p=0.002), history of cranial radiation (HR 4.0; 95% CI, 1.7–9.6, p=0.002), and grade II-IV acute GVHD (HR 4.2; 95% CI, 1.5–12.2, p=0.008) were associated with risk of developing CVRF cluster. HCT survivors had an increased prevalence of hypertriglyceridemia and low HDL, but not glucose intolerance, elevated blood pressure, or CVRF cluster, when compared to a random sample of matched population controls. Given the young age of this HCT survivor cohort, these data highlight the importance of routine screening for CVRF starting in childhood among those exposed to TBI.

Keywords

survivors; transplant; cardiovascular risk factors; metabolic syndrome; total body irradiation

Introduction

Advances in hematopoietic cell transplantation (HCT) and supportive care have resulted in improved survival rates for patients with high-risk hematologic malignancies.[1-3] Long-term survivors, however, remain at increased risk for treatment-related morbidity, [4-6] including multiple cardiovascular risk factors (CVRF), such as obesity, elevated blood pressure, glucose intolerance, and dyslipidemia.[7-10] Taken together, these factors constitute the so-called metabolic syndrome, a constellation of abnormalities associated with increased all-cause and cardiovascular mortality.[11, 12]

Prior studies have demonstrated an increased prevalence of metabolic syndrome and its components in HCT survivors.[8, 9, 13-22] Exposure to total body irradiation (TBI) has been identified as an independent risk factor for the development of CVRF.[8, 14, 23-25] In a large single-institution study of 1885 one-year HCT survivors (median age at HCT: 44.4 years; 30.5% treated prior to age 35; 52.7% treated with TBI), the prevalence of CVRF was significantly higher among HCT survivors when compared to the general population. Additionally when compared to HCT survivors not exposed to TBI-based conditioning regimens, those treated with TBI were at 1.5fold increased risk for the development of diabetes mellitus and 1.4-fold increased risk of dyslipidemia.[8] Others have similarly demonstrated an increased risk of metabolic derangements in individuals exposed to TBI.[13, 14, 17, 18, 26, 27]

For those exposed to TBI during childhood, however, data are lacking on longitudinal changes in CVRF and the contribution of demographic and other therapeutic exposures to risk. The current report seeks to fill this gap by using a single-institutional cohort of long-term HCT survivors treated with TBI during childhood to: (1) determine the longitudinal changes in CVRF as this survivor population ages; (2) identify demographic and treatment factors associated with the development of metabolic derangements in this population; and (3) compare the prevalence of CVRF to age-, race- and sex-matched population controls.

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Methods

We performed a retrospective analysis of CVRF in one-year HCT survivors treated with TBI at Memorial Sloan Kettering (MSK) between April 1987 and May 2011. All data were obtained from review of the MSK medical record, which includes internal documentation as well as outside correspondence with survivors' local physicians. The protocol was approved by the MSK Institutional Review Board/Privacy Board.

Subjects

Eligible participants had a primary diagnosis of leukemia or lymphoma, were ≤ 21 years of age at the time of TBI, and survived at least one year relapse-free from the date of HCT. All participants had been seen at least once in one of the long-term follow-up (LTFU) clinics at MSK, which provide risk-based comprehensive follow-up care to individuals who have survived at least one year after completion of cancer-directed therapy. All patients underwent serial assessments of height, weight, blood pressure, fasting glucose, and fasting lipid panel, as would be recommended by the Children's Oncology Group LTFU guidelines.[28]

Patients were censored at the date of relapse. Any survivor who was transplanted more than once was excluded. Additionally, in an effort to exclude those with active graft-versus-host disease (GVHD) and avoid potential confounding associated with glucocorticoid use, individuals taking glucocorticoids at the time of their first LTFU visit for at least three months were excluded as well (n=11). Indications for glucocorticoid use among excluded individuals were: chronic graft versus host disease (n=7); post-transplant autoimmune hemolytic anemia (n=1); nonspecific arthritis (n=1); rejection prophylaxis after renal transplant for post-HCT renal failure (n=1); recurrent bronchiolitis obliterans organizing pneumonia (n=1).

Exposure data

Demographic information was abstracted from the medical record (see Table 1). Race/ethnicity was self-reported by the patient and/or family. Post-treatment complications including thyroid dysfunction, sex hormone deficiency, and documented growth hormone (GH) deficiency, as well as dates of treatment when relevant, were recorded.

Treatment exposures included pre-HCT chemotherapy, high-dose chemotherapy related to the conditioning regimen, and sites and doses of radiation therapy were abstracted from the medical record. Details related to transplant-related exposures, including donor type, stem cell source, and TBI-based conditioning regimen, were obtained from the MSK medical record and transplant database. Presence and severity of acute (aGVHD) and/or chronic GVHD (cGVHD) were recorded as well.[29, 30]

Outcome measurements

For this analysis, CVRFs of interest included: elevated blood pressure, elevated triglycerides (TG), low high-density lipoprotein (HDL) cholesterol, elevated fasting glucose, and obesity. Waist circumference was not routinely recorded in the medical record.

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Individual CVRF were defined according to current adult International Diabetes Foundation Consensus criteria, as well as pediatric-adapted values when indicated,[31] which have been previously used in other analyses of CVRF in childhood cancer survivors.[32] Table 2 summarizes pediatric- and adult-specific criteria used to define each CVRF in the present analysis.

For each participant, serial measurements of height, weight, and blood pressure were abstracted from the medical record. Normative pediatric data were used to calculate age- and gender-specific body mass index (BMI) [33] for those between the ages of 2-20 years, and age-, gender, and height-specific blood pressure percentiles for those between the ages of 2-17 years.[34] Fasting glucose, triglyceride, and HDL cholesterol levels at each time point were recorded as well. The onset of elevated blood pressure or hypertension, glucose intolerance, or dyslipidemia was defined as an abnormal value in the medical record according to the predefined criteria (Table 2) or the start of drug therapy for the associated outcome of interest. However, any individual receiving antihypertensive medication for non-hypertensive conditions (renal dysfunction, cardiac dysfunction) was considered inevaluable for the elevated blood pressure outcome; similarly those taking statins or other lipid-lowering medications (except omega-3-acid ethyl esters) were considered inevaluable for the high triglyceride/low HDL outcome. The term CVRF cluster, a surrogate for metabolic syndrome, was used to characterize the occurrence of three or more of the five pre-defined CVRFs.[32]

Statistical considerations

We estimated the cumulative incidence function for each CVRF with a nonparametric estimate[35] treating death as a competing risk and using the time since TBI as the time scale. Patients were considered at risk for this analysis beginning at one year after TBI.

Cause-specific Cox proportional hazards regression models were used to evaluate the association between risk factors and each CVRF, stratifying by treatment year (≤ 2000, >2000), and using time since treatment as the scale. Patients were considered at risk of a CVRF beginning at one year after TBI until development of a CVRF, death, relapse, or the date of their last clinic visit without a CVRF. GH deficiency was included as a time-dependent covariate in all models. Multivariate models were constructed using a forward selection procedure which considered all univariate risk factors having p-values < 0.1 as candidates and retaining those with an adjusted p-value < 0.05 in the final multivariate models. All multivariate models were adjusted for age at TBI.

In order to compare prevalence of CVRF in HCT survivors and the general population we used a random sample of controls from the National Health and Nutrition Examination Survey (NHANES). For each visit an HCT survivor contributed to the data, three controls from NHANES were selected and matched on sex, age at assessment (10-year group), and race/ethnicity. Differences in prevalence of CVRFs between the HCT and NHANES cohort were evaluated using generalized estimating equations with an independent working correlation matrix and adjusted for era of assessment (1991-2000, 2001-2006, and 2007-2013).

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Results

Description of the cohort

Baseline demographic characteristics of the cohort are summarized in Table 1. Among 123 childhood HCT survivors treated with TBI, 62.6% were male (n=77). TBI exposure occurred at a median age of 11.8 years (range, 1.6–21.9). Median age at last follow-up was 20.1 years (range, 4.0–41.3 years) and the duration of follow-up ranged from 1.01–24.6 years (median: 8.0). The number of visits recorded per patient ranged from one to 18.

During the post-transplant period, 27 survivors (22.0%) developed documented GH deficiency; 18 of the 27 (66.7%) elected to receive treatment with GH. Gonadal function could be assessed in 42 females and 72 males, all of whom were 10 years of age or older. One hundred percent of females (n=42) and 25.0% of males (n=18) had evidence of sex hormone deficiency, as defined by elevated FSH values (> 15 mU/ml) in females and elevated LH levels (> 15 mU/ml) with low testosterone levels (<250 ng/dl) in sexually mature males, or use of hormone replacement therapy in either gender. Thirty-eight individuals had evidence of primary hypothyroidism and 36 (94.7%) were on levothyroxine replacement therapy.

Cumulative incidence of CVRF and CVRF cluster

Five- and ten-year cumulative incidence estimates of CVRF and CVRF cluster are listed in Table 3.

Among 123 HCT survivors treated with TBI, the estimated cumulative incidence of low HDL rose 1.9-fold from 26.8% (95% CI, 18.8–35.5) at 5-years to 52.0% (95% CI, 40.7–62.2) at 10-years [Figure 1a]. Similarly, the cumulative incidence of hypertriglyceridemia increased 1.7-fold from 39.2% (95% CI, 29.8–48.4) at 5-years to 65.0% (95% CI, 53.8–74.2) at 10-years [Figure 1a]. The cumulative incidence of elevated fasting glucose levels increased 3.2-fold from 10.5% at 5-years (95% CI, 5.5–17.3) to 33.1% (95% CI, 22.4–44.1) at 10-years [Figure 1b]. The estimated cumulative incidence of elevated blood pressure doubled from 14.7% (95% CI, 8.6–22.4) at 5-years to 28.8% (95% CI, 19.2–39.2) at 10-years [Figure 1c]. Only obesity remained relatively stable over time, with 5-year cumulative incidence estimated at 16.0% (95% CI, 9.9–23.4) and 10-year cumulative incidence estimated at 18.6% (95% CI, 11.7–26.7) [Figure 1c].

Overall, the cumulative incidence of CVRF cluster increased 2.7-fold from 10.6% (95% CI, 5.6– 17.5) at 5 years to 28.4% (95% CI, 18.8–38.7) at 10 years [Figure 1d].

Factors associated with CVRF and CVRF cluster after TBI-based HCT

Results of the multivariate analysis are presented in Table 4. None of the covariates of interest were significantly associated with hypertriglyceridemia, obesity, or glucose intolerance after adjusting for age at TBI (HR 0.8; 95% CI, 0.8–0.9, p<0.001). Higher grade of aGVHD (HR 4.3; 95% CI, 1.5–12.3, p=0.007) and documented GH deficiency (HR 3.9; 95% CI, 1.3–12.3, p=0.02) were associated with elevated blood pressure Higher dose of doxorubicin was associated with low HDL (HR 2.0; 95% CI, 1.04–3.9, p=0.04). Exposure to

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CRT (HR 4.0; 95% CI, 1.7–9.6, p=0.002), GH deficiency (HR 8.6; 95% CI, 2.1–34.4, p=0.002), and history of grade II-IV aGVHD (HR 4.3; 95% CI, 1.5–12.2, p=0.008) were associated with risk of developing CVRF cluster.

Prevalence of CVRF in HCT survivors and the general US population

Overall, the prevalence of low HDL and hypertriglyceridemia was significantly higher among HCT survivors exposed to TBI during childhood when compared to sex-, age-, and race/ethnicity-matched controls from the general population (Table 5). Matched controls were more likely to be obese than TBI-exposed HCT survivors. There was no difference in the prevalence of glucose intolerance, elevated blood pressure, or CVRF cluster between the TBI-exposed survivor cohort and controls.

Discussion

We found that the risk of elevated blood pressure, low HDL, hypertriglyceridemia, glucose intolerance, and CVRF cluster increases over time in childhood HCT survivors treated with TBI. For all CVRF, except obesity, the cumulative incidence increased 1.7 to 3.2-fold from five to ten years post-TBI. However, when compared to a random sample of matched population controls, survivors were at increased risk for hypertriglyceridemia and low HDL, but not for the other outcomes of interest.

Prior studies have demonstrated that CVRF are associated with an increased risk of cardiovascular disease in HCT survivors[8, 36] as well as in the general population.[12, 37] Survivors with persistent CVRF at two or more years post- HCT have been shown to have an increased risk for several adverse cardiovascular outcomes, including ischemic heart disease, cardiomyopathy, and all-cause cardiovascular death, when compared to HCT survivors without these risk factors.[38] Additionally, prior data have demonstrated that the risk of major cardiac events is potentiated beyond what would be expected in a simple additive model among childhood cancer survivors exposed to chest-directed radiotherapy who also have hypertension, one CVRF of interest.[39] In our population of HCT survivors treated with TBI during childhood, the concern for long-term cardiovascular health is especially pronounced given that all individuals received chest-directed radiotherapy and the vast majority received anthracycline chemotherapy as well.

Earlier analyses of metabolic risk in adult survivors of childhood leukemia have demonstrated that those exposed to TBI are more likely to develop CVRF[8, 32] and metabolic syndrome [40] when compared to survivors not so treated. In the pediatric age group, however, data are limited. Two cross-sectional analyses have demonstrated that those exposed to TBI during childhood are more likely to manifest multiple cardiometabolic traits, including central adiposity, elevated blood pressure, insulin resistance, and dyslipidemia,[23] and/or abnormal glucose tolerance,[17] at an early age. Similarly, 17 very young patients treated with HCT at less than three years of age (n=11 treated with TBI) showed that more than half developed dyslipidemia,[41] which may be associated with early development of metabolic syndrome.[9] In this analysis, we present novel longitudinal follow-up data on the risk of individual CVRF, and CVRF cluster, among a large cohort of childhood HCT survivors uniformly treated with TBI at a single cancer center.

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We found a number of treatment factors to be associated with the development of CVRF cluster, and its individual components. Those treated with CRT, in addition to TBI, were at fourfold risk for development of CVRF cluster. Some have theorized that radiation-induced neuroendocrine dysregulation of the hypothalamic-pituitary axis may be linked to metabolic derangements after radiation impacting the brain, either via leptin insensitivity[42] or increased expression of hypothalamic inflammatory pathways.[43-45] These derangements may explain some of the excess metabolic risk found among those exposed to CRT, in addition to TBI, in our cohort, but the mechanism underlying this association warrants further study.

GH deficiency was also significantly associated with both elevated blood pressure and development of CVRF cluster in our cohort. Both of these associations have been previously documented in the literature.[46-49] In addition to its effect on linear growth, GH deficiency is associated with changes in body composition,[50] including reduced lean body mass and increased visceral adiposity,[51] a phenotype that has been closely linked, in both healthy individuals and childhood cancer survivors, to insulin resistance and glucose intolerance.[52-54] While it is plausible that this phenotype, which has also been consistently noted in TBI-exposed childhood cancer survivors,[55, 56] is associated with early onset of CVRF and CVRF cluster, it is noteworthy that GH deficiency was not associated with glucose intolerance in the current stud.

Irrespective of GH status, TBI-treated individuals are more likely to be underweight than unexposed individuals,[57] despite their adverse cardiometabolic profiles. It is thus not surprising that HCT survivors in our cohort, uniformly exposed to TBI, were less likely to be obese than matched NHANES population-based controls (p=0.009). As noted above, TBI-exposed HCT survivors have been shown to demonstrate a pattern of visceral adiposity and muscle deficits consistent with sarcopenic obesity,[56] which has also been demonstrated in the general HCT survivor population.[58] Survivors exposed to TBI have also been shown to have increased C– reactive protein and leptin levels, and decreased adiponectin, suggesting increased inflammation in the presence of visceral fat deposition.[23] Dysfunctional adipose tissue, rather than obesity *per se*, may play an important role in the pathogenesis of metabolic syndrome in TBI-exposed HCT survivors.[59]

Interestingly, exposure to higher doses of doxorubicin was associated with low HDL in our cohort. Prior preclinical studies have demonstrated that doxorubicin administration is associated with glucose intolerance and hyperlipidemia[60, 61] through the inhibition of peroxisomal proliferator activated receptor γ (PPARγ), a ligand-activated transcription factor that plays a key role in fat cell differentiation and insulin sensitization.[62] One small study of breast cancer patients also found an association between doxorubin and lower HDL with downregulation of PPARγ noted after doxorubicin administration.[63] To our knowledge this association has not been noted in childhood transplant survivors and thus requires replication and additional study in the future.

Allogeneic HCT recipients with grades II-IV aGVHD were also at 4.3-fold increased risk for elevated blood pressure, and 4.2-fold increased risk for CVRF cluster, in multivariate analysis. While this risk may have resulted from prolonged and intensified use of

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immunosuppressive agents, it is noteworthy that 65.3% of our allogeneic HCT recipients received T cell-depleted HCTs, and thus had reduced exposure to GVHD medications. Additionally, none of the subjects in the current study was on glucocorticoids at the time of their first long-term follow-up appointment, which coincides with the time at which monitoring for CVRF would have commenced. The precise relationship between GVHD prophylactic medication and subsequent risk for cardiometabolic derangements warrants further study.

In our cohort of HCT survivors exposed to TBI during childhood, individuals were more likely to have hypertriglyceridemia and low HDL but not glucose intolerance, elevated blood pressure, or CVRF cluster, when compared to matched population controls. The similar prevalence of glucose intolerance among HCT survivors and population controls is of particular interest given the well-established link between TBI exposure and diabetes mellitus.[15, 53, 64] It is possible that these derangements were not yet apparent in our relatively young cohort (median age: 20.3) and will become manifest with longer follow-up. In conventionally treated childhood cancer survivors exposed to abdominal radiation, for instance, there appears to be a minimum latency of 20 years between radiation therapy and onset of diabetes mellitus;[65] a similarly prolonged clinically silent period may precede the onset of CVRF, including glucose intolerance, in HCT survivors exposed to TBI during childhood.

A number of limitations must be considered when interpreting the results of this study. Importantly, given the retrospective nature of this analysis, waist circumferences were not routinely collected and we thus relied on BMI as an indicator of obesity, which is known to correlate poorly with true adiposity in childhood cancer survivors,[66] and in the TBI-exposed population in particular.[23] Additionally, formal GH stimulation testing was only performed in those with evidence of poor linear growth, so the true prevalence of GH deficiency in this cohort may have been under-estimated. Reliable data on lifestyle behaviors or family history were also lacking. Nevertheless, this analysis has a number of related strengths, including comprehensive exposure data and follow-up details on a large number of patients who were treated on protocol-driven studies with intensive TBI-based therapy at a young age, and then followed over time in specialized survivorship clinics.

In summary, individuals exposed to TBI during childhood were more likely than population controls to develop hypertriglyceridemia and low HDL at a young age. These data emphasize the importance of routine screening for CVRF in this high risk population starting in childhood and adolescence. Future studies are needed to clarify the mechanisms underlying these derangements and the impact of primary and secondary prevention on ultimate cardiovascular morbidity and mortality in childhood HCT survivors.

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Highlights

- Risk for cardiovascular risk factors (CVRF) increases over time after TBI exposure (84 characters)
- Survivors have an increased risk of high triglycerides and low HDL versus controls (84 characters)
- Data highlight the importance of CVRF screening starting in childhood after TBI (82 characters)

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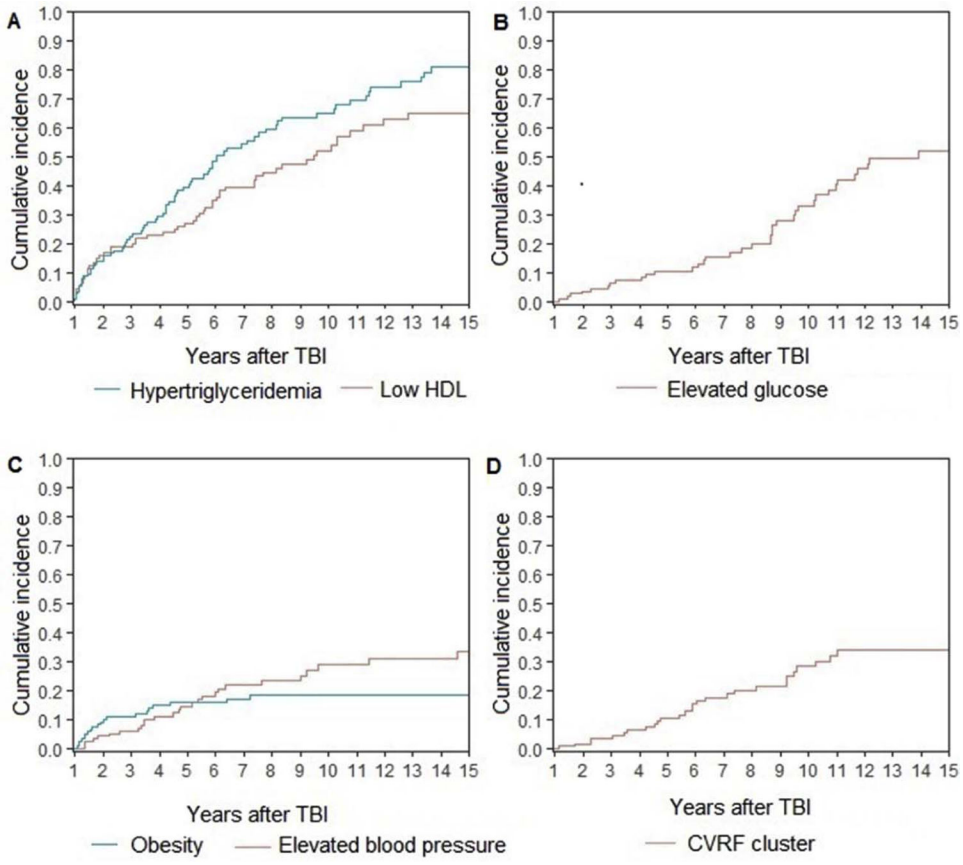

Figure 1.

Cumulative incidence of (a) hypertriglyceridemia [blue] and low HDL [red]; (b) glucose intolerance [red]; (c) obesity [blue] and elevated blood pressure [red]; and (d) cardiovascular risk factor cluster [red] among 123 childhood transplant survivors treated with total body irradiation

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Table 1
Characteristics of the study participants

Characteristic	All survivors (n=123)
Age at TBI, y, median (range)	11.8 (1.6, 21.9)
Age at last followup, y, median (range)	20.1 (4.0, 41.3)
Follow-up since TBI, y, median (range)	8.0 (1.01, 24.6)
Sex, no. (%)	
Male	77 (62.6)
Female	46 (37.3)
Race, no. (%)	
White, non-Hispanic	96 (78.0)
Other	23 (18.6)
No response	4 (0.03)
TBI dose (cGy), no. (%)	
Range	12–15 Gy
≤ 1410	54 (43.9)
> 1410	69 (56.1)
Primary diagnosis, no. (%)	
ALL/NHL	77 (62.6)
AML/CML	46 (37.4)
Pre-transplant therapy, no. (%)	
Anthracyclines	115 (93.5)
*Glucocorticoids**	100 (81.3)
Cranial radiotherapy	38 (30.9)
Pre-transplant BMI, no. (%)	
Obese	20 (16.3)
Non-obese	103 (83.7)
HCT type, no. (%)	
Autologous	5 (4.1)
Allogeneic	118 (95.9)
Graft source, no. (%)	
Bone marrow (BM)	86 (69.9)
Peripheral blood stem cells (PBSC)	27 (21.9)
Cord blood	8 (6.5)
BM + Cord	1 (0.8)
BM + PBSC	1 (0.8)
Donor source, allogeneic transplants only, no. (%)	
Related	59 (50.0)
Unrelated	59 (50.0)

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Characteristic	All survivors (n=123)
GVHD Prophylaxis**, allogeneic transplants only, no. (%)	
T-cell depletion	77 (65.3)
Cyclosporine	35 (29.7)
Methotrexate	28 (23.7)
Mycophenolate mofetil	8 (6.7)
Corticosteroids	6 (5.2)
Tacrolimus	5 (4.3)
Sirolimus	1 (0.9)
Acute GVHD, allogeneic transplants only, no. (%)	
Grade I or none	104 (88.1)
Grade II-IV	14 (11.8)
Chronic GVHD, allogeneic transplants only, no. (%)	
No	107 (90.7)
Yes	11 (9.3)

Abbreviations: y indicates years; HCT, hematopoietic stem cell transplant; TBI, total body irradiation; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; and GVHD, graft-versus-host disease.

*Refers to glucocorticoids used for upfront chemotherapy;

**Numbers do not sum to 100 percent since most allogeneic HCT recipients received more than one agent for GVHD prophylaxis

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Table 2

Definitions of cardiovascular risk factors (CVRF) in adult and pediatric individuals

	Consensus criteria	
	Adult[31]	**Pediatric[23]**
Obesity	BMI ≥ 30 kg/m^2	BMI ≥ 95th percentile for age and sex
Elevated blood pressure	≥ 130/85 mmHg	≥ 90th percentile for age, sex, and height
Elevated glucose	Fasting glucose≥ 100 mg/dl	Fasting glucose≥ 100 mg/dl
Low HDL-cholesterol	Males < 40 mg/dl Females < 50 mg/dl	≤ 40 mg/dl
Hypertriglyceridemia	≥ 150 mg/dl	≥ 110 mg/dl

HDL indicates high density lipoprotein; any individual taking drugs for hypertension and/or diabetes was classified as fulfilling the associated criterion

*Consensus criteria for obesity suggest that if BMI is greater than 30 kg/m^2, then waist circumference does not need to be measured, as over 95% of these individuals will have a waist circumference above gender- and ethnic-specific threshold values for obesity

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Table 3

Cumulative incidence estimates of cardiovascular risk factors (CVRF) in childhood HCT survivors treated with TBI (n=123)

Outcome	N	Events	5-year cumulative incidence* (95% CI)	10-year cumulative incidence* (95% CI)
Elevated blood pressure	118	34	14.7 (8.6, 22.4)	28.8 (19.2, 39.2)
Elevated glucose	121	47	10.5 (5.5, 17.3)	33.1 (22.4, 44.1)
Low HDL-cholesterol	116	58	26.8 (18.8, 35.5)	52.0 (40.7, 62.2)
Hypertriglyceridemia	117	77	39.2 (29.8, 48.4)	65.0 (53.8, 74.2)
Obesity	123	21	16.0 (9.9, 23.4)	18.6 (11.7, 26.7)
CVRF cluster[1]	123	35	10.6 (5.6, 17.5)	28.4 (18.8, 38.7)

HCT indicates hematopoietic cell transplantation; TBI, total body irradiation; CI, confidence interval; and HDL, high-density lipoprotein.

*Cumulative incidence estimates reflect the time since TBI with time zero defined as one year after the date of TBI;

[1]Defined as having 3 or more of the following CVRF: obesity, elevated blood pressure, elevated fasting glucose, low HDL, and elevated triglycerides.

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Table 4

Predictors of individual cardiovascular risk factors (CVRF) and CVRF cluster in multivariate analysis

	Elevated blood pressure		Elevated glucose		Low HDL		CVRF cluster*	
	HR (95% CI)	**P**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age at TBI	1.0 (0.9, 1.2)	0.64	0.8 (0.8, 0.9)	<0.001	1.1 (0.98,1.3)	0.09	0.9 (0.8, 1.0)	0.16
Sex								
Male								
Female								
Race								
White, non-Hispanic								
Other								
Cranial RT								0.002
No							Reference	
Yes							4.0 (1.7, 9.6)	
Anthracycline dose (mg/m^2)						0.04		
≤ 300 mg/m2					Reference			
>300 mg/m2					2.0 (1.04, 3.9)			
Glucocorticoids								
No								
Yes								
HCT type								
T-cell depleted								
Unmodified								
aGVHD grade		0.007						0.008
Grade 0-1	Reference						Reference	
Grade 2-4	4.3 (1.5,12.3)						4.2 (1.5, 12.2)	
GH deficiency**		0.02						0.002
No	Reference						Reference	
Yes	3.9 (1.3,12.3)						8.6 (2.1, 34.4)	

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Note: All analyses are stratified by treatment year ≤ 2000 vs > 2000 with time zero defined as age at TBI + 1 year; multivariate models constructed via forward selection with age at TBI in the initial model and considering all univariate covariates with p<0.1 as candidate predictors; full results for each model are shown. No significant predictors at 0.05 level for obesity or hypertriglyceridemia, thus omitted from the table above

*CVRF cluster defined as having 3 or more of the following CVRF: obesity, elevated glucose, elevated blood pressure, low HDL, high triglycerides

**Time dependent covariate;

Abbreviations: TBI, indicates total body irradiation; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease; GH, growth hormone; HDL, high density lipoprotein

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Table 5

Prevalence of cardiovascular risk factors among TBI-exposed HCT survivors and the general population by era

Prevalence	NHANES (%)	HCT survivors (%)	p-value
Elevated blood pressure			0.63
1991-2000	11.9	11.1	
2001-2006	13.4	11.9	
2007-2013	14.0	12.9	
Elevated glucose			0.07
1991-2000	12.0	7.7	
2001-2006	14.4	17.8	
2007-2013	22.4	31.0	
Low HDL cholesterol			0.02
1991-2000	27.5	52.4	
2001-2006	19.1	29.4	
2007-2013	25.1	32.9	
Hypertriglyceridemia			< 0.001
1991-2000	22.6	52.6	
2001-2006	29.3	55.8	
2007-2013	28.5	46.9	
Obesity			0.009
1991-2000	13.9	20.9	
2001-2006	18.4	9.5	
2007-2013	25.7	12.5	
CVRF cluster[1]			0.70
1991-2000	5.5	5.9	
2001-2006	8.0	6.3	
2007-2013	12.1	14.4	

TBI indicates total body irradiation; HCT, hematopoietic cell transplantation; NHANES, National Health and Nutrition Examination Survey; HDL, high density lipoprotein; CVRF, cardiovascular risk factor

[1]Defined as having 3 or more of the following CVRF: obesity, elevated blood pressure, elevated fasting glucose, low HDL cholesterol, and elevated triglycerides.