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Differential Effects of Radiotherapy on Growth and Endocrine Function Among Acute Leukemia Survivors: A Childhood Cancer Survivor Study Report

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Abstract

Background—The differential effects of cranial (CRT), spinal (SRT), and total body irradiation (TBI) on growth and endocrine outcomes have rarely been examined in combination among childhood acute leukemia survivors.

Procedure—Self-reported height/weight, hypothyroidism, and pregnancy/live birth were determined among acute lymphoblastic and myeloid leukemia survivors (n=3,467) participating in the Childhood Cancer Survivor Study, an ongoing cohort study of 5-year survivors of pediatric cancers diagnosed from 1970 to 1986.

Results—Compared with no radiotherapy, risk estimates were consistent across outcomes (adult short stature, hypothyroidism, absence of pregnancy/live birth) with CRT treatment associated with 2–3 fold increased risks, TBI associated with 5–10 fold increased risks, and CRT+TBI associated with >10 fold increased risks. Exposure to any SRT further increased risk of these outcomes 2–3 fold. Changes in body composition were more nuanced as CRT only was associated with an increased risk of being overweight/obese (OR 1.6, 95% CI 1.3–1.9) whereas TBI only was associated with an increased risk of being underweight (OR 6.0, 95% CI 2.4–14.9).

Conclusions—Although patients treated with CRT+TBI were at greatest risk for short stature, hypothyroidism, and a reduced likelihood of pregnancy/live birth, those treated with either modality alone had significantly increased risks as well, including altered body composition. Any SRT exposure further increased risk in an independent fashion.

Keywords

leukemia; childhood; survivor; growth; hypothyroidism; pregnancy

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INTRODUCTION

Radiotherapy has been part of effective multimodality therapy for childhood acute leukemia since it was introduced in the late 1960s (1). However, the resulting radiation-associated late effects including disrupted growth and endocrine function are well recognized (2). In response, radiotherapy doses used to treat childhood leukemia have been systematically reduced or eliminated to avoid these late occurring adverse events. Nevertheless, most contemporary protocols continue to reserve cranial with or without spinal radiotherapy for select patient groups, such that an estimated 10–15% of contemporary patients may still be exposed (3). In addition, total body irradiation (TBI) remains a common part of the allogeneic hematopoietic cell transplantation (HCT) conditioning process (4). Given that very high risk or relapsed acute leukemias are the most common indication for allogeneic HCT in children (5), it remains important to understand the late effects associated with TBI, as well as any cumulative effect of TBI plus prior cranial and spinal radiotherapy. Most larger studies of endocrine-related outcomes among childhood acute leukemia survivors have focused primarily on conventionally treated patients or only on HCT survivors, rarely comparing the two directly. Therefore the primary goal of this study was to determine the differential effects of cranial, spinal, and total body irradiation on growth, hypothyroidism, and reproductive outcomes in the large population of acute leukemia survivors enrolled in the Childhood Cancer Survivor Study (CCSS).

METHODS

Study Population

Methodology and subject accrual for the CCSS previously have been reported in detail (6;7). Briefly, the cohort (n=14,372) was constructed from rosters of all children treated for eight common types of childhood cancer at 26 institutions in the U.S. and Canada (Supplemental Table I). Eligibility criteria included diagnosis before age 21, initial treatment at one of the collaborating institutions between January 1, 1970 and December 31, 1986, and survival for at least five years following diagnosis. The CCSS protocol was approved by the Human Subjects Committee at each participating institution.

For the current study, the analytic cohort was defined as: 1) children diagnosed with acute lymphoblastic or myeloid leukemia prior to age 18 years, 2) at least 18 years of age at time of last study assessment, and 3) had survived at least five years from initiation of conventional therapy (n=3,688) or HCT that included TBI (n=201). Participants treated with HCT without TBI were not included. Participants also were excluded if they had incomplete radiotherapy data including unclear documentation of modalities received (345 conventional therapy patients; 77 TBI patients), resulting in 3,343 and 124 individuals available for final analysis treated with conventional therapy and TBI, respectively.

Cancer Therapy Exposures

Medical records at all participating institutions were reviewed and abstracted for cancer diagnosis and treatment information including all chemotherapy, surgery, and radiotherapy. Photocopies of radiation therapy records were sent to the CCSS Radiation Dosimetry Center for central review and determination of field and organ-specific cumulative radiotherapy doses. Radiation doses to the brain, thyroid gland, ovaries, uterus, and testes were estimated for each survivor as applicable, based on individual radiotherapy treatment records. Total organ-specific absorbed doses were estimated by applying water phantom measurements to a three-dimensional mathematical phantom that can simulate a patient of any age or size (8). Six patients had complete pre-transplant radiotherapy records, confirmed receipt of TBI, but had missing TBI dose. For these individuals, the missing TBI dose was imputed based on

the mean dose given to other individuals in our cohort by the same treating institution in that calendar year. Information on other details of the conditioning regimen (aside from TBI exposure), stem cell source, and any graft-versus-host disease occurring after HCT was unavailable for all participants. The primary exposures of interest were categorized into the following mutually exclusive treatment categories: 1) no radiotherapy, 2) cranial radiotherapy (CRT) only, 3) TBI only, and 4) CRT+TBI. Exposure to any spinal radiotherapy (SRT) apart from any TBI-related spine exposure was categorized separately.

Outcome Definitions

All CCSS participants completed a baseline questionnaire including a wide range of topics such as demographic characteristics, healthcare utilization, health conditions, health-related behaviors, family cancer history, and reproductive history. Participants also received four subsequent follow-up questionnaires updating health status. The current analysis used relevant data from the baseline and the most recent follow-up questionnaires. Proxy responses from family members were used for five-year survivors who had subsequently died unless otherwise noted below.

Outcomes examined in the current analysis included adult short stature, underweight, overweight/obese, hypothyroidism, pregnancy, and live birth. Adult height and weight used the first self-reported values (proxy responses were not considered). Thyroid gland function and history of pregnancy used the most recent self-reported or proxy responses. Height, weight, and derived body mass index (BMI) were converted to z-scores based on the Centers for Disease Control and Prevention's (CDC) Year 2000 growth charts (9) for individuals age 18–19 years, and the National Health Interview Study's 1995–96 reference norms for those aged ≥20 years (10). Adult short stature was defined as height z-score less than −1.96. Adult BMI categories were classified per CDC definitions as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (≥30). Individuals 18–19 years were classified using corresponding percentiles (<5th, 5–84th, 85–94th, and ≥95th, respectively) unless they met adult BMI thresholds. Individuals reporting hypothyroidism secondary to thyroidectomy were excluded from the hypothyroidism analyses. All pregnancies and the subset that led to a live birth also were identified. Because the CCSS cohort is defined by 5-year survivorship, any pregnancy within five years following cancer diagnosis or HCT date was excluded given lack of comparable data from patients who did not survive 5 years. In contrast, thyroid outcomes that first occurred prior to cohort entry or within 5 years of HCT were included, as these would be expected to remain prevalent at the 5 year time point.

Statistical Analysis

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) associated with dichotomized outcomes of interest (adult short stature, underweight vs. normal weight, overweight/obese vs. normal weight, hypothyroidism, and ever pregnant/live birth) in relation to the previously defined radiotherapy exposure groups including SRT, all categorized as yes/no. In addition to the radiotherapy exposures, all models were adjusted for gender, race/ethnicity (White non-Hispanic vs. other), age at diagnosis (<5, 5–9, and 10 years), age at last follow-up (continuous variable), and diagnosis (ALL vs. AML). Adjustment for self-reported growth hormone supplementation was applied to the growth analyses *a priori*. In sensitivity analyses, we also examined the effect of subsequent relapse and/or second cancers following initial cancer diagnosis (non-TBI group) or following HCT (TBI group) on our outcomes, and results were generally similar. All analyses were performed using SAS 9.2 (Cary, NC, USA).

RESULTS

Compared with the 3,343 non-TBI exposed participants, the 124 members of the TBI cohort were more likely to be male (62.9% vs. 50.4%), to have been treated for AML (33.9% vs. 6.8%), to be older at cancer diagnosis (median 8.3 years vs. 4.7 years), and to have subsequently died (8.1% vs. 1.9%; Table I). The median TBI dose received was 1200 cGy (range 150–1580 cGy), with the majority of exposed patients (75%) receiving doses 1000 cGy. The proportion of TBI exposed patients who also received CRT was 41.1% compared with 64.1% among the non-TBI group. In addition, 296 (13.8%) CRT only patients and 8 (15.7%) CRT+TBI patients also received SRT.

Adult Height and Body Mass Index

Compared with survivors who did not receive any radiotherapy, those who received CRT +TBI had the lowest adult height z-scores, with the TBI only and CRT only groups having intermediate values (Table II). Similarly, risk for adult short stature was highest for the CRT +TBI group compared with no radiotherapy (OR 10.6, 95% CI 4.5–25.3), with the CRT only and TBI only groups having intermediate risk estimates (ORs ranging from 2.9–8.0; difference between CRT only vs. TBI only, $p < 0.01$). Survivors exposed to any SRT had a further increase in risk (OR 2.8, 95% CI 1.9–4.0). Female gender, other race/ethnicity, age <10 years at diagnosis/HCT, AML diagnosis, and growth hormone treatment also were at higher risk of having short stature (Table III). However, the association between AML diagnosis and short stature was not significant in analyses restricted to HCT survivors only.

Compared with survivors who did not receive any radiotherapy, those treated with TBI only were significantly more likely to report being underweight (OR 6.0, 95% CI 2.4–14.9), while those treated with CRT only were significantly more likely to report being overweight or obese (OR 1.6, 95% CI 1.3–1.9; Figure 1). Other radiotherapy groups, including any SRT, were not independently associated with changes in BMI category compared with those unexposed. Baseline characteristics independently associated with having altered BMI included: 1) age <10 years at diagnosis/HCT associated with an increased risk of being overweight/obese; 2) growth hormone supplementation associated with being underweight; and 3) female survivors being less likely than male survivors to be overweight/obese (Table III).

Hypothyroidism

Hypothyroidism was reported by 223 survivors (6.5%), of whom 23 reported becoming hypothyroid within 5 years of cancer diagnosis/HCT. Rates of hypothyroidism ranged from 4.0% among those who did not receive any radiotherapy to 29.8% among those treated with CRT+TBI (Table IV). Although survivors with hypothyroidism and those without both received a median dose of 1800 cGy to the brain, those with hypothyroidism tended to receive higher radiotherapy doses to the thyroid gland compared with those without hypothyroidism (median 100 cGy, interquartile range (IQR) 65–1200, vs. median 78 cGy, IQR 54–120). In multivariable analyses using survivors who did not receive any radiotherapy as the referent group, TBI exposure was significantly associated with risk of hypothyroidism, with the CRT+TBI group having the greatest risk (OR 10.9, 95% CI 5.3–22.3; Table IV). Both the TBI only and CRT+TBI groups had increased risks of hypothyroidism compared with the CRT only group ($p < 0.01$ for both). Exposure to any SRT further increased risk independently (OR 2.6, 95% CI 1.7–3.8). Baseline characteristics independently associated with hypothyroidism included female gender, younger age at diagnosis/HCT (<5 vs. 10 years), and AML diagnosis (Table III). The association between AML diagnosis and hypothyroidism remained significant even when the analysis was restricted to TBI exposed survivors.

Reproductive Outcomes

Overall, 38.9% of non-HCT survivors reported becoming pregnant or fathering a pregnancy 5 or more years after cancer diagnosis, with 33.4% of survivors having live offspring, compared with 8.1% and 4.0% among TBI exposed survivors 5 or more years after HCT, respectively (Table IV). Only 1 pregnancy (no live birth) was reported within 5 years of HCT among TBI exposed survivors; that individual also reported a second pregnancy (no live birth) 5 years after HCT. Among the non-TBI group, 27 survivors had 29 pregnancies (13 live births) within 5 years of cancer diagnosis; 19 (70%) of those 27 survivors also reported pregnancy 5 years after cancer diagnosis, with 18 having at least one live birth. The range of brain and reproductive organ-specific cumulative radiotherapy doses experienced by the cohort are shown in Supplemental Tables II and III. In multivariable analysis, all radiotherapy treatment groups had a decreased likelihood of ever reporting a pregnancy or live birth (ORs ≤ 0.5) compared with chemotherapy alone (Table IV). Exposure to any SRT further decreased the likelihood of reproductive outcomes by 50%. Male gender but not any other baseline characteristic also was independently associated with a decreased likelihood of pregnancy or live birth (Table III).

DISCUSSION

The current analysis was undertaken to take advantage of the large number of adult survivors of childhood acute leukemia within the CCSS cohort, with a median follow-up of over 20 years, in order to investigate the effects of different combinations of radiotherapy exposures on adult height/BMI, hypothyroidism, and reproductive outcomes. Although the long-term effects of radiation exposure on these outcomes have long been recognized, we were able to make direct comparisons of risks associated with various combinations of radiation exposures including CRT and TBI, relative to a group of survivors not treated with radiation therapy. In a recent collaborative analysis between the CCSS and the Bone Marrow Transplant Survivor Study, the endocrine system was the organ system most commonly affected among childhood HCT survivors, with upwards of 30% of HCT survivors reporting severe endocrine conditions compared with 5% of non-HCT general cancer survivors (11). However, that study did not investigate specific endocrine complications or radiotherapy exposures in detail (11). Typically, most other existing studies of these endocrine-associated outcomes (discussed in detail below) have examined patients treated with conventional therapies and HCT/TBI in isolation, and have rarely examined both groups directly.

A variety of studies have documented that children treated for leukemia may develop adverse height and BMI outcomes. Prior reports, including those from the CCSS have identified younger age at diagnosis, female gender, and increased CRT dose as factors associated with short stature, with those exposed to any spinal radiotherapy and any TBI at even greater risk (12–15). However, even those treated with chemotherapy alone may be at increased risk of short stature (13;15–17). Although growth hormone supplementation was associated with an increased rate of short stature in our analysis, we suspect that this was a surrogate for survivors who were most affected, as most studies suggest that timely supplementation among growth hormone deficient children improves final height (18–20).

Among non-HCT pediatric leukemia survivors, particularly girls and those younger at diagnosis, exposure to CRT has been an established risk factor for subsequent obesity (21–23). Although the exact mechanism remains unclear, it is postulated that radiotherapy injures the hypothalamic pituitary axis, affecting growth hormone secretion and leptin sensitivity (22). However, more contemporary therapy without CRT also has been associated with increased BMI in some but not all studies, suggesting a possible role for glucocorticoids and lifestyle factors (16;24–27). Our current results suggest that children

treated with CRT+TBI tended to have an intermediate BMI phenotype compared with CRT only (higher average BMI) and TBI only (lower average BMI). However, a more detailed examination of TBI exposed patients' body composition has typically revealed significant central adiposity and decreased lean body mass even among those with low or normal BMI (28–30). Although the mechanism by which this sarcopenic obesity develops remains unclear, central adiposity may be a more specific risk factor for cardiometabolic risk than BMI defined adiposity (31;32).

A prior report from the CCSS found a clear dose-relationship between craniospinal radiotherapy and subsequent hypothyroidism among ALL survivors, with risk differences between <2000 vs. 2000 cGy CRT doses, and increased risk with any spinal radiotherapy (33). An analysis of nearly 800 pediatric HCT survivors treated at a single US center found that approximately 30% of patients subsequently developed some form of hypothyroidism, with those treated with TBI and/or busulfan having the greatest risk compared with those receiving cyclophosphamide-based regimens only (34). Risk with busulfan exposure alone without concurrent radiotherapy also has been reported in other HCT populations (35–37). Although our study lacked complete information on survivors' HCT conditioning regimen, inclusion of only those who were treated with TBI would have excluded most individuals treated with busulfan-containing regimens. Our study also was limited by lack of hormonal data, which made it impossible for us to differentiate between primary and central hypothyroidism. Nonetheless, other studies have suggested that following HCT, compensated primary hypothyroidism is the most common type of hypothyroidism to develop (34;35;38;39).

Finally, previous CCSS studies have shown that both female leukemia survivors and female partners of male survivors in general have decreased rates of pregnancy compared with siblings (40;41). Among all childhood cancer survivors, increased radiation doses to the hypothalamus/pituitary gland (e.g., from CRT or TBI) and to the reproductive organs (e.g., from TBI, SRT-related scatter, or any testicular radiotherapy), as well as increased alkylating chemotherapy doses all have been associated with decreased fertility in a clear dose-response fashion (41;42). Larger studies of HCT survivors generally feature transplant recipients treated as adults and report very low rates of subsequent pregnancies (typically 5% prevalence) (43–45). In one study, 11 out of 196 (6%) prepubertal HCT recipients reported subsequent pregnancies (45), which is consistent with our results. Nevertheless, recovery of ovarian and testicular function has been reported to occur in small numbers of patients, even after TBI-based myeloablative HCT regimens (45;46).

Although our outcomes were self- (or proxy-) reported, self-reported heights and weights have generally been well-validated and correlate closely with measured values (47), and also were used to derive the general population adult normative values in this study (10). A study of HCT survivors that used a similar questionnaire as the current study found that the validity of self-reported hypothyroidism compared with medical records was excellent, with sensitivity, specificity, and overall agreement greater than 95% (48). The reliability of self-reported pregnancies is known to be variable, as studies from the general population suggest that nearly one-quarter of pregnancies as detected by laboratory testing are not recognized by parents (49). Nevertheless, we are not aware of evidence suggesting that such awareness would differ across our exposure groups of interest.

Additional factors that should be considered when interpreting our findings include changes in radiation therapy over the past 20 years. Although methods for delivering TBI, CRT, and SRT have changed less relative to other radiation modalities, contemporary CRT/SRT may result in less scatter to surrounding tissue than the older conventional doses experienced by our cohort, and reduced intensity or non-myeloablative TBI doses now becoming more

common were much less likely to have been used during our study period (4). Finally, it is possible select post-HCT exposures such as chronic graft versus host disease may contribute to some of the adverse outcomes examined. However, restriction of our TBI exposed cohort to those who were more than 5 years from transplant make it less likely that most transplant-related exposures would be actively present at time of outcome. Furthermore, we would not expect such exposures to necessarily differ between those treated with CRT+TBI vs. TBI alone.

In summary, our study of a very large cohort of childhood acute leukemia survivors was able to quantify and discriminate between the effects of cranial, spinal, and total body irradiation with respect to specific endocrine outcomes. Although the majority of acute leukemia survivors no longer receive cranial or craniospinal radiotherapy routinely, they remain an important part of many higher risk protocols. TBI-based HCT regimens also remain a common frontline choice for relapsed or very high risk acute leukemias in children. Therefore, these results may help clinicians better counsel patients and families with regards to these common late effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Distribution of body mass index (BMI) categories among leukemia survivors by radiotherapy category. Underweight, normal, overweight, and obese defined by BMI <18.5, 18.5–24, 25–29, and 30, respectively. No radiotherapy group as referent: (*) overweight/obese vs. normal, $p<0.05$; (†) underweight vs. normal, $p<0.05$.

TABLE I**Selected Demographic and Treatment Characteristics of the Study Population**

Characteristics, n (%)	No TBI Cohort N=3343	TBI Cohort N=124
Female sex	1657 (49.6)	46 (37.1)
White Non-Hispanic	2804 (83.9)	98 (79.0)
Histology		
ALL	3117 (93.2)	82 (66.1)
AML	226 (6.8)	42 (33.9)
Median age, years (range)		
Cancer diagnosis	4.7 (0.0, 20.8)	8.3 (0.7, 20.7)
Hematopoietic cell transplant	-	11.6 (1.6, 23.8)
Baseline questionnaire	20.8 (8.8, 45.1)	22.4 (10.7, 43.7)
Last follow-up	31.1 (18.0, 55.5)	32.0 (18.8, 50.9)
Cranial radiotherapy ^a		
None	1200 (35.9)	73 (58.9)
<2000 cGy	976 (29.2)	28 (22.6)
2000 cGy	1167 (34.9)	23 (18.5)
Median dose among exposed, cGy (interquartile range)	2390 (1800–2400)	1800 (1800–2400)
Spinal radiotherapy ^a	299 (8.9)	8 (6.5)
Median dose among exposed, cGy (interquartile range)	1600 (1200–2400)	1140 (740–1800)
Primary disease relapse	369 (11.0)	56 (45.2)
Secondary malignancy ^b	102 (3.1)	18 (14.5)
Deceased at time of baseline questionnaire	64 (1.9)	10 (8.1)

^a Apart from total body irradiation;^b Not counting non-melanoma skin cancers.

TABLE II
Height (z-score) and Risk of Short Stature (z-score < -1.96) among Leukemia Survivors

Radiotherapy	No. analyzed ^a	Mean z-score (SD)	No. short stature (%)	OR ^b	(95% CI)
CRT/TBI					
None	983	0.02 (1.16)	37 (3.8)	1.0	(ref)
CRT only	1872	-0.64 (1.12)	189 (10.1)	2.9	(2.0, 4.2)
TBI only	55	-1.00 (1.70)	13 (23.6)	8.0	(3.7, 17.4) ^c
CRT+TBI	35	-1.36 (1.30)	11 (31.4)	10.6	(4.5, 25.3) ^c
SRT					
None	2672	-0.36 (1.18)	196 (7.3)	1.0	(ref)
Any	273	-1.15 (1.15)	54 (19.8)	2.8	(1.9-4.0)

CRT, cranial radiotherapy; HCT, hematopoietic cell transplant; SRT, spinal radiotherapy; TBI, total body irradiation.

^aExcluded proxy responses;

^bAdjusted for sex, race/ethnicity, age at diagnosis/HCT and at follow-up, ALL vs. AML, growth hormone supplementation, and all radiotherapy categories simultaneously;

^cP-value <0.05 compared with CRT only group.

TABLE III

Association of Baseline Characteristics with Study Outcomes among Leukemia Survivors

Characteristic	OR (95% CI) ^a					
	Short stature	Underweight	Overweight/obese	Hypothyroidism	Ever pregnant	Live birth
Female vs. male	1.5 (1.1–2.0)	1.2 (0.8–1.7)	0.7 (0.6–0.8)	1.6 (1.2–2.1)	2.1 (1.8–2.4)	1.8 (1.5–2.1)
Others vs. White non-Hispanic	1.5 (1.1–2.1)	0.7 (0.4–1.2)	1.1 (0.9–1.3)	0.7 (0.5–1.1)	1.1 (0.9–1.3)	1.0 (0.8–1.2)
Age at diagnosis/HCT, yrs						
10	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
5–9	3.3 (1.8–6.0)	0.5 (0.3–0.9)	1.4 (1.1–1.8)	1.2 (0.8–1.9)	1.1 (0.9–1.4)	1.1 (0.9–1.4)
<5	5.4 (3.0–9.6)	0.6 (0.4–1.1)	1.9 (1.5–2.4)	1.8 (1.2–2.8)	0.9 (0.7–1.1)	0.8 (0.6–0.98)
AML vs. ALL	2.8 (1.7–4.5)	0.8 (0.4–1.7)	0.9 (0.6–1.2)	2.0 (1.2–3.2)	1.0 (0.8–1.4)	1.0 (0.8–1.4)
Growth hormone treatment vs. none ^b	2.2 (1.4–3.6)	2.2 (1.1–4.4)	0.6 (0.4–0.9)	n/a	n/a	n/a

^a Adjusted for all variables shown as well as current age and all radiotherapy categories;^b Included in models for short stature and body mass categories only.

TABLE IV
Prevalence and Odds of Hypothyroidism and Reproductive Outcomes among Leukemia Survivors

Radiotherapy	Hypothyroid				Ever pregnant				Live birth			
	No. analyzed ^a	No. affected (%)	OR ^b	(95% CI)	No. analyzed	No. affected (%)	OR ^b	(95% CI)	No. affected (%) ^c	OR ^b	(95% CI)	
CRT/TBI												
None	1198	48 (4.0)	1.0	(ref)	1200	527 (43.9)	1.0	(ref)	451 (37.6)	1.0	(ref)	
CRT only	2127	145 (6.8)	1.6	(1.1, 2.3)	2143	773 (36.1)	0.5	(0.5–0.6)	666 (31.1)	0.6	(0.5–0.7)	
TBI only	70	16 (22.9)	6.8	(3.4, 13.5) ^d	73	8 (11.0)	0.1	(0.04–0.2) ^d	5 (6.9)	0.07	(0.03–0.18) ^d	
CRT+TBI	47	14 (29.8)	10.9	(5.3, 22.3) ^d	51	2 (3.9)	0.03	(0.01–0.14) ^{d,e}	0	0	–	
SRT												
None	3148	180 (5.7)	1.0	(ref)	3160	1222 (38.7)	1.0	(ref)	1048 (33.2)	1.0	(ref)	
Any	294	43 (14.6)	2.6	(1.7–3.8)	307	88(28.7)	0.5	(0.3–0.6)	74 (24.1)	0.5	(0.3–0.6)	

CRT, cranial radiotherapy; HCT, hematopoietic cell transplant; SRT, spinal radiotherapy; TBI, total body irradiation.

^aExcludes individuals who underwent thyroidectomy prior to reporting hypothyroidism;

^bAdjusted for sex, race/ethnicity, age at diagnosis/HCT and at follow-up, ALL vs. AML, and all radiotherapy categories simultaneously;

^cSame number analyzed as ever pregnant;

^dP<0.05 compared with CRT only group;

^eP<0.05 compared with TBI only group.