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Endocrine Abnormalities in Aging Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
The development of endocrinopathies in survivors of childhood cancer as they age remains understudied. We characterized endocrine outcomes in aging survivors from the Childhood Cancer Survivor Study on the basis of therapeutic exposures.

Patients and Methods
We analyzed self-reported conditions in 14,290 5-year survivors from the Childhood Cancer Survivor Study, with a median age 6 years (range, < 1 to 20 years) at diagnosis and 32 years (range, 5 to 58 years) at last follow-up. Identification of high-risk therapeutic exposures was adopted from the Children's Oncology Group Long-Term Follow-Up Guidelines. Cumulative incidence curves and prevalence estimates quantified and regression models compared risks of primary hypothyroidism, hyperthyroidism, thyroid neoplasms, hypopituitarism, obesity, diabetes mellitus, or gonadal dysfunction between survivors and siblings.

Results
The cumulative incidence and prevalence of endocrine abnormalities increased across the lifespan of survivors ($P < .01$ for all). Risk was significantly higher in survivors exposed to high-risk therapies compared with survivors not so exposed for primary hypothyroidism (hazard ratio [HR], 6.6; 95% CI, 5.6 to 7.8), hyperthyroidism (HR, 1.8; 95% CI, 1.2 to 2.8), thyroid nodules (HR, 6.3; 95% CI, 5.2 to 7.5), thyroid cancer (HR, 9.2; 95% CI, 6.2 to 13.7), growth hormone deficiency (HR, 5.3; 95% CI, 4.3 to 6.4), obesity (relative risk, 1.8; 95% CI, 1.7 to 2.0), and diabetes mellitus (relative risk, 1.9; 95% CI, 1.6 to 2.4). Women exposed to high-risk therapies had six-fold increased risk for premature ovarian insufficiency ($P < .001$), and men demonstrated higher prevalence of testosterone replacement ($P < .001$) after cyclophosphamide equivalent dose of 20 g/m^2 or greater or testicular irradiation with 20 Gy or greater. Survivors demonstrated an increased risk for all thyroid disorders and diabetes mellitus regardless of treatment exposures compared with siblings ($P < .001$ for all).

Conclusion
Endocrinopathies in survivors increased substantially over time, underscoring the need for lifelong subspecialty follow-up of those at risk.

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INTRODUCTION

As a result of remarkable improvements in the treatments for childhood cancer, the current 5-year survival exceeds 80%.[1] Presently, there are an estimated 420,000 childhood cancer survivors in the United States.[2] Survivors are at increased risk for a broad range of serious health conditions, including disorders of the endocrine system.[3-5] Risk factors differ by endocrine outcome but include both host (eg, sex or age at diagnosis) and cancer treatment (eg, irradiation).[3,6] Endocrine late effects frequently occur many years after cancer treatment,[7,8] and although an increase in the occurrence of endocrinopathies in aging survivors is expected, currently, there are few long-term follow-up data with respect to endocrinopathies in childhood cancer survivors as they age beyond young adulthood. Our analysis was undertaken to determine the prevalence and cumulative incidence of endocrine abnormalities in childhood cancer survivors over an extended period of follow-up according to therapeutic exposures to determine how the magnitude of

risk changes over time. We were especially interested in understanding these changes in survivors exposed to treatments known to place them at highest risk. This study used participants from the Childhood Cancer Survivor Study (CCSS), a multi-institutional cohort of long-term survivors of various childhood cancers.

PATIENTS AND METHODS

Patients

The CCSS is a multi-institutional retrospective cohort study, with longitudinal follow-up of survivors of childhood cancer diagnosed and treated at 26 institutions in the United States and Canada. A total of 14,290 survivors were eligible for study participation and included those diagnosed with cancer before age 21 years, treated between January 1, 1970, and December 31, 1986, and alive at 5 years after diagnosis of leukemia, CNS malignancy, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, sarcoma, or bone malignancy. The cohort methodology and study design have been previously described in detail.[9,10] The CCSS was approved by each institutional review board, and participants provided informed consent.

Participants completed a baseline survey (administered between 1994 and 1999) that included demographics, personal and family medical histories, and assessment of second malignant neoplasms and chronic health conditions, such as endocrine abnormalities. A surrogate (parent, spouse, or next of kin) completed the baseline survey for survivors who had died more than 5 years after diagnosis, were age younger than 18 years, or were unable to complete the survey. Sex and race/ethnicity characteristics were available from surveys. Subsequently, there were four follow-up surveys. The data for our study were obtained from baseline and follow-up questionnaires administered in 2000, 2003, and 2007. Sixty-eight survivors with underlying diagnoses of trisomy 21 or Turner syndrome were excluded, given that endocrine abnormalities can be associated with these conditions. Siblings of CCSS participants were selected by simple random sampling of survivors. Four thousand thirty-one siblings with no history of a cancer diagnosis were enrolled.

Endocrine Outcomes

At baseline and subsequent follow-up evaluations, participants completed a multi-item survey, which included participant age at the onset of endocrine conditions. Endocrine-related outcomes of interest included underactive or overactive thyroid, thyroid nodule, thyroid cancer, hypopituitarism, osteoporosis, obesity, diabetes mellitus (DM), male gonadal dysfunction, premature ovarian insufficiency (POI), and diabetes insipidus. Outcomes were determined on the basis of patient responses to questionnaires, as listed in Appendix Table A1 (online only). Body mass index (BMI; kg/m^2) was calculated from self-reported height (cm) and weight (kg). Obesity was defined as BMI of 30 kg/m^2 or greater or BMI higher than the 95th percentile per age and sex for participants age younger than 18 years. Cancer diagnosis and treatment data were abstracted from medical records at the treatment institutions for the 12,593 patients who provided medical release.[11,12]

Treatment exposures classified as high risk for development of a subsequent endocrinopathy were adapted from the Children's Oncology Group Long-Term Follow-Up (COG-LTFU) Guidelines.[13] The likelihood of developing a specific endocrine disorder was stratified on the following therapeutic exposures: (1) underactive thyroid: thyroid irradiation with 20 Gy or greater, hypothalamic pituitary (HP) irradiation with 40 Gy or greater, or both exposures or neither; (2) overactive thyroid: thyroid irradiation with 40 Gy or greater versus 0 to less than 40 Gy; (3) thyroid nodule: thyroid irradiation with 25 Gy or greater versus 0 to less than 25 Gy; (4) thyroid cancer: thyroid irradiation with more than 30 Gy, more than 5 to 30 Gy or less, or 0 to 5 Gy; (5) growth hormone (GH) deficiency: HP irradiation with 18 Gy or greater versus 0 to more than 18 Gy; (6) osteoporosis: exposure to methotrexate, glucocorticoids, and/or total-body irradiation (TBI); (7) obesity: cranial irradiation with 18 Gy or greater versus 0 to less than 18 Gy; (8) DM: TBI and/or abdominal irradiation versus neither; (9) adrenocorticotropic hormone (ACTH) deficiency: HP irradiation with 30 Gy or greater versus 0 to less than 30 Gy; (10) male gonadal dysfunction: testicular irradiation with 20 Gy or greater or cyclophosphamide equivalent dose[14] (CED) of 20 g/m^2 or greater (primary gonadal dysfunction), HP irradiation with 30 Gy or greater (central gonadal dysfunction), high-risk exposures for both primary and central gonadal dysfunction, or no high-risk exposures; (12) POI: age younger than 12 years at cancer diagnosis and ovarian irradiation with 15 Gy or greater, age 12 years or older at cancer diagnosis and ovarian irradiation with 10 Gy or greater, CED of 8 g/m^2 or greater, or any pelvic irradiation and any CED greater than 0 g/m^2 (primary ovarian dysfunction), HP irradiation with 30 Gy or greater (central dysfunction), high-risk exposures for both primary and central ovarian dysfunction, or no high-risk exposures; and (13) diabetes insipidus: suprasellar CNS malignancy.

Statistical Analysis

For endocrine outcomes with reported age at onset, such as underactive or overactive thyroid, thyroid nodules, thyroid cancer, GH deficiency, and osteoporosis, analyses used time-to-event methods on the basis of time from cohort entry (5 years after primary cancer diagnosis) to time at the earliest event of interest or date of last follow-up survey. Cumulative incidence curves were generated for survivors overall and for specific exposure groups, treating death as a competing risk. Cox proportional hazards models were used to compare adjusted risks of endocrine outcomes among survivors stratified by exposures and reported as hazard ratios (HRs) with 95% CIs. Cox models used age as the time scale and censored at death and last follow-up, adjusting for sex and age at the time of primary cancer diagnosis.

For endocrine outcomes where age of onset was not reported, including obesity, DM, and male or female gonadal dysfunction, point estimates of prevalence with 95% CIs were calculated for cross-sectional observations with repeated measurements across follow-up surveys. Generalized linear models with generalized estimating equations used a log-link function and Poisson error distribution with robust variance estimates to compare survivors on the basis of treatment exposures, adjusting for sex and age at survey, and were reported as relative risks (RRs) with 95% CIs.[15] Predicted age-specific prevalence and 95% CIs of outcomes were calculated from these models and displayed in figures. Because the lack of hormone data prevented differentiation between central versus end organ dysfunction for certain endocrine outcomes (eg, thyroid-stimulating hormone deficiency *v* primary hypothyroidism or central *v* primary gonadal dysfunction), we structured the model such that survivors only with high-risk exposures for central dysfunction were compared with survivors without any high-risk exposures. Similarly, survivors with only high-risk exposures for end organ dysfunction were compared with survivors without any high-risk exposures. The analyses also included a separate group for survivors exposed to therapies resulting in both primary and central organ dysfunction (eg, craniospinal irradiation for underactive thyroid).

For endocrine outcomes that are common in the general population, including obesity, DM, and all thyroid disorders, we examined risk estimates in all survivors versus siblings and reported HRs or RRs with 95% CIs. To determine if exposure to any cancer therapy affected these outcomes, we compared risks between survivors exposed to non–high-risk therapies versus siblings. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC) and STATA/SE software (version 14.0; STATA, College Station, TX). A P value of less than .05 was considered statistically significant, and two-sided tests of hypotheses were used throughout. Continuous variables were expressed as mean (± standard deviation) or median (range) for skewed distributions.

Table 1. Demographic and Treatment Characteristics of Survivors and Siblings

Characteristic	Survivors (n = 14,290) No.	%	Siblings (n = 4,031) No.	%
Sex				
Female	6,615	46	2,088	52
Male	7,675	54	1,943	48
Race/ethnicity				
White (non-Hispanic)	11,885	83	3,509	87
Black (non-Hispanic)	665	5	112	3
Hispanic	749	5	149	4
Other or mixed	434	3	111	3
Missing or incomplete data	557	4	150	4
Age at cancer diagnosis, years				
< 5	5,711	40		
5-9	3,187	22		
10-14	2,908	20		
15-20	2,484	17		
Median	6			
Range	< 1-20			
Age at most recent survey, years				
< 20	1,531	11	267	7
20-29.9	4,483	31	1,136	28
30-39.9	5,208	36	1,396	35
40-49.9	2,714	19	979	24
≥ 50	354	2	253	6
Median	32		34	
Range	5-58		5-62	
Interval between cancer diagnosis and most recent survey, years				
Median	24			
Range	5-39			
Cancer diagnosis				
Leukemia	4,774	33		
Hodgkin lymphoma	1,927	13		
CNS tumor	1,873	13		
Wilms tumor	1,254	9		
Soft tissue sarcoma	1,245	9		
Bone cancer	1,187	8		
Non-Hodgkin lymphoma	1,078	8		
Neuroblastoma	952	7		
Cancer treatment				
Chemotherapy				
Any	10,082	80		
Alkylating agent dose, CED g/m^2				
0 to < 8	8,510	75		
≥ 8 to < 20	2,288	20		
≥ 20	564	5		
RT exposure, Gy				
Any	8,502	67		
Brain				
None	4,101	33		
> 0 to < 18	4,063	33		
≥ 18 to < 30	2,580	21		
≥ 30	1,520	12		
Neck				
None	4,101	33		
> 0 to < 20	5,673	46		
≥ 20 to < 30	762	6		
≥ 30	1,730	14		
Abdominal				
None	4,101	33		
> 0 to < 10	5,046	41		
≥ 10 to < 20	631	5		
≥ 20	2,485	20		
Pelvic				
None	4,101	33		
> 0 to < 10	5,630	46		
≥ 10 to < 20	527	4		
≥ 20	2,008	16		
TBI	199	2		
Combined chemotherapy and RT				
Alkylator plus TBI	178	1		
Alkylator plus pelvic RT ≥ 10 Gy	1,361	11		

Abbreviations: CED, cyclophosphamide equivalent dose; RT, radiotherapy; TBI, total-body irradiation.

RESULTS

Demographic and treatment characteristics for the 14,290 eligible survivors and 4,031 siblings are summarized in Table 1. For survivors, median age at diagnosis was 6 years (range, < 1 to 20 years), and median age at last follow-up was 32 years (range, 5 to 58 years). Median age at last follow-up for siblings was 34 years (range, 5 to 62 years).

Overall, 44% of survivors in this study demonstrated at least one, 16.7% at least two, and 6.6% three or more endocrinopathies. Survivors of HL had the highest frequency of an endocrine abnormality (60.1%), followed by survivors of CNS tumor (54%), leukemia (45.6%), sarcoma (41.3%), non-Hodgkin lymphoma (39.7%), neuroblastoma (31.9%), Wilms tumor (28.5%), and bone cancer (27.8%).

Thyroid Disorders

Survivors experienced steadily increasing cumulative incidence with increasing age for all thyroid disorders (Fig 1). Multivariable analysis confirmed an increased risk for an underactive or overactive thyroid, thyroid nodules, and thyroid cancer in survivors overall as well as for survivors exposed to thyroid and/or HP irradiation compared with siblings ($P < .001$ for all; Fig 2; Appendix Table A2, online only). Importantly, even among survivors exposed to non–high-risk exposures, thyroid disorders were more frequent than among siblings: underactive thyroid (HR, 2.2; 95% CI, 1.8 to 2.7), overactive thyroid (HR, 2.4; 95% CI, 1.7 to 3.3), thyroid nodules (HR, 3.9; 95% CI, 2.9 to 5.4), and thyroid cancer (HR, 2.5; 95% CI, 1.2 to 5.3; Fig 2; Appendix Table A2). Among survivors, those exposed to high-risk therapies were at greater risk of developing an underactive thyroid (primary hypothyroidism: HR, 6.6; 95% CI, 5.6 to 7.8; central hypothyroidism: HR, 3.9; 95% CI, 2.9 to 5.2), an overactive thyroid (HR, 1.8; 95% CI, 1.2 to 2.8), thyroid nodules (HR, 6.3; 95% CI, 5.2 to 7.5), and thyroid cancer (HR, 9.2; 95% CI, 6.2 to 13.7) when compared with survivors not so exposed (Figs 1 and 2; Appendix Table A2).

Obesity and DM

Survivors showed a similar risk of becoming obese compared with siblings (RR, 1.0; 95% CI, 0.9 to 1.1), and the risk of developing DM was significantly higher in survivors compared with siblings (RR, 1.8; 95% CI, 1.4 to 2.3) and increased over time (Figs

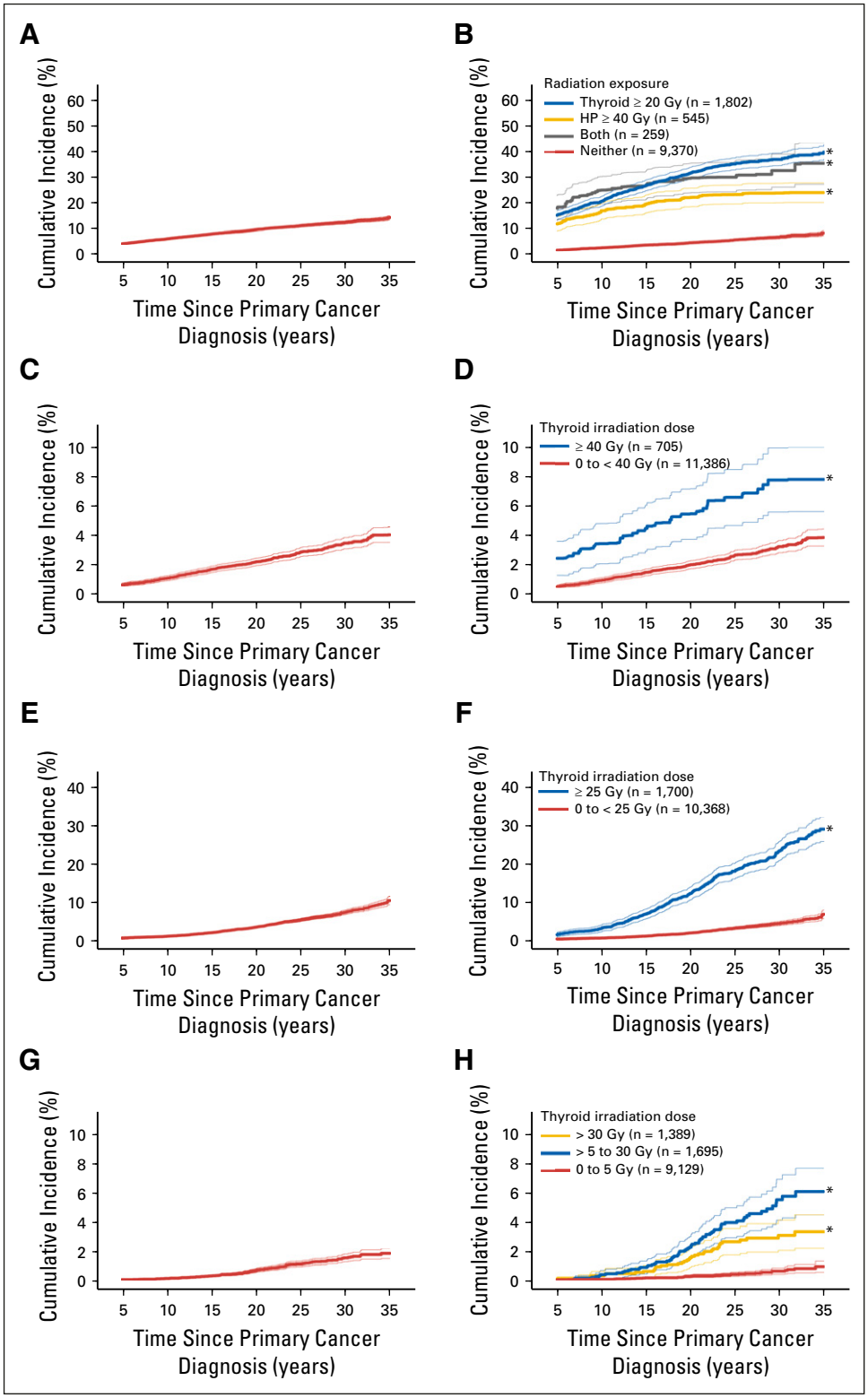

Fig 1. Cumulative incidence of thyroid disorders: (A, B) underactive thyroid, (C, D) overactive thyroid, (E, F) thyroid nodules, and (G, H) thyroid cancer in (A, C, E, G) survivors overall and (B, D, F, H) survivors stratified by treatment exposure. Thin lines represent 95% CIs. HP, hypothalamic pituitary. (*) $P < .01$ for comparison versus the non–high-risk exposure group.

2 and 3; Appendix Table A2). Among survivors with DM, at least 70% seemed to have adult-onset or type 2 DM on the basis of the type of diabetes medication they were receiving. Furthermore, compared with siblings, survivors treated with cranial irradiation with 18 Gy or greater had greater risk of developing obesity (RR, 1.4; 95% CI, 1.3 to 1.5), and those exposed to abdominal irradiation or TBI had a greater risk of developing DM (RR, 2.7; 95% CI, 2.1 to 3.6; Appendix Table A2). In multivariable regression models adjusted for sex and age, survivors exposed to cranial irradiation with 0 to less than 18 Gy had a lower risk of obesity

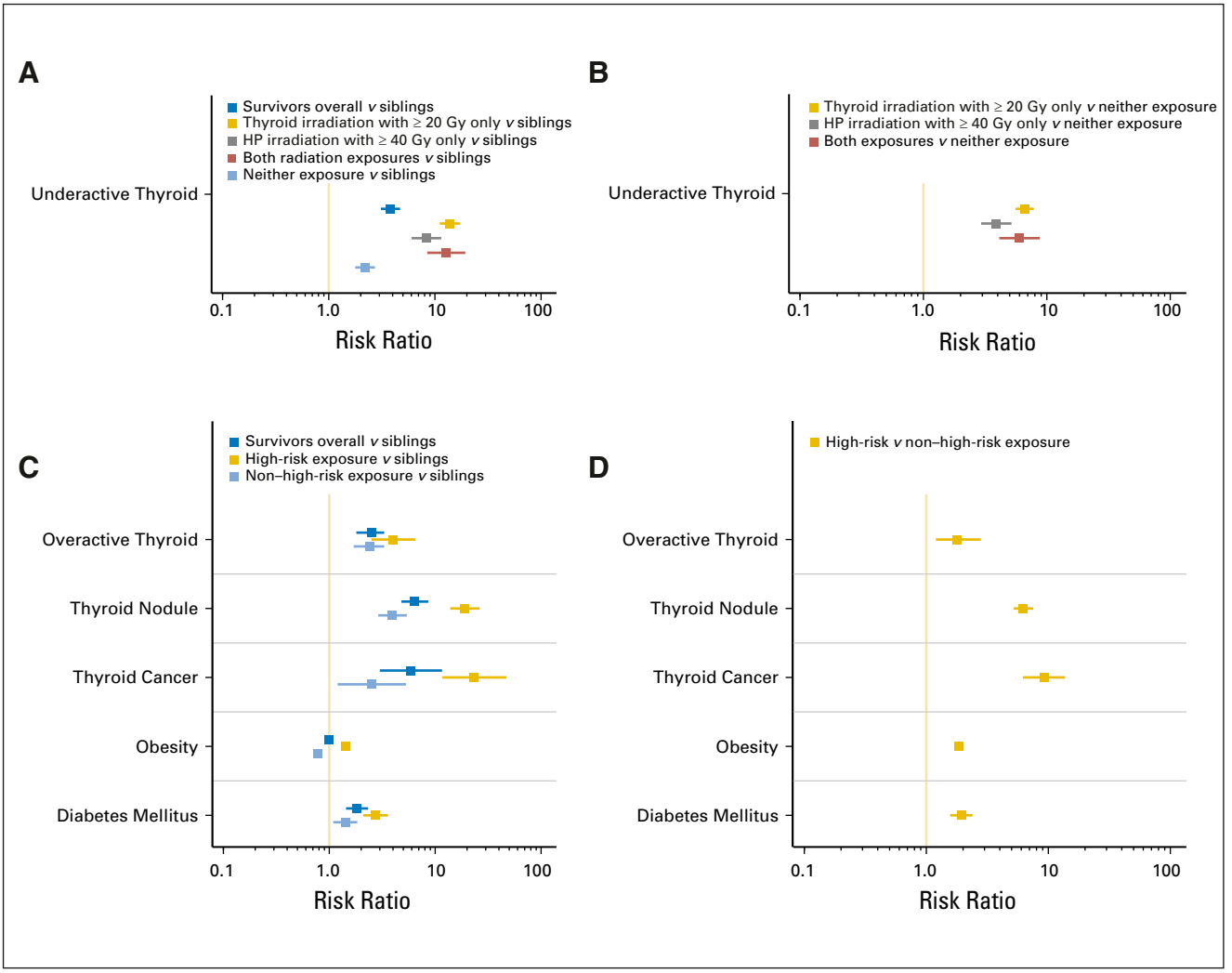

Fig 2. Risk for (A, B) underactive thyroid and (C, D) other thyroid disorders, obesity, and diabetes mellitus in (A, C) survivors compared with siblings and (B, D) survivors according to treatment exposure. Bars represent 95% CIs. For obesity outcome, the 95% CIs are narrower than the width of the square plotting symbol. High-risk exposure for thyroid cancer includes thyroid irradiation with > 5 to 30 Gy, and non–high-risk exposure includes thyroid irradiation with 0 to ≤ 5 Gy or > 30 Gy. HP, hypothalamic pituitary.

compared with siblings (RR, 0.8; 95% CI, 0.7 to 0.8). In contrast, survivors not exposed to abdominal irradiation or TBI demonstrated a significantly greater risk of developing DM compared with siblings (RR, 1.4; 95% CI, 1.1 to 1.8; Figs 2 and 3; Appendix Table A2). Survivors treated with cranial irradiation with 18 Gy or greater or abdominal irradiation or TBI had an almost two-fold greater risk of obesity (RR, 1.8; 95% CI, 1.7 to 2.0) and DM (RR, 1.9; 95% CI, 1.6 to 2.4), respectively, compared with survivors not so exposed (Figs 2 and 3; Appendix Table A2).

Gonadal Dysfunction

Female survivors exposed to high-risk therapies for primary ovarian dysfunction had a six-fold increased risk of developing POI (RR, 6.3; 95% CI, 5.0 to 8.0) when compared with survivors who did not receive such therapies. Risk of POI was also increased after HP irradiation with 30 Gy or greater (RR, 6.0; 95% CI, 4.2 to 8.5; high risk for central gonadal dysfunction) compared with survivors without high-risk exposure for central gonadal dysfunction (Fig 4). In men, treatment with testicular irradiation with 20 Gy or greater or chemotherapy CED of 20 g/m^2 or greater (high risk for primary gonadal dysfunction) resulted in an increased need for testosterone replacement (RR, 10.8; 95% CI, 8.2 to 14.2) compared with men not so treated. Similarly, men also demonstrated an increased need for testosterone treatment after HP irradiation with 30 Gy or greater (RR, 5.7; 95% CI, 4.2 to 7.7) compared with survivors treated with non–high-risk exposures. Surprisingly, we noted a decline in the prevalence of testosterone treatment in older survivors. This decline was related not to an increased risk of death among those exposed to high-risk therapies but rather to an effect of diagnosis era, with survivors diagnosed in an earlier era less likely to receive testosterone therapy despite treatments associated with the development of gonadal dysfunction (Appendix Table A3, online only).

Other HP Deficits

Among survivors, deficits of GH and ACTH occurred significantly more often after high-risk exposures compared with survivors without high-risk exposures: GH deficiency (HR, 5.3; 95% CI, 4.3 to 6.4) and ACTH deficiency (HR, 4.5; 95% CI, 3.7 to

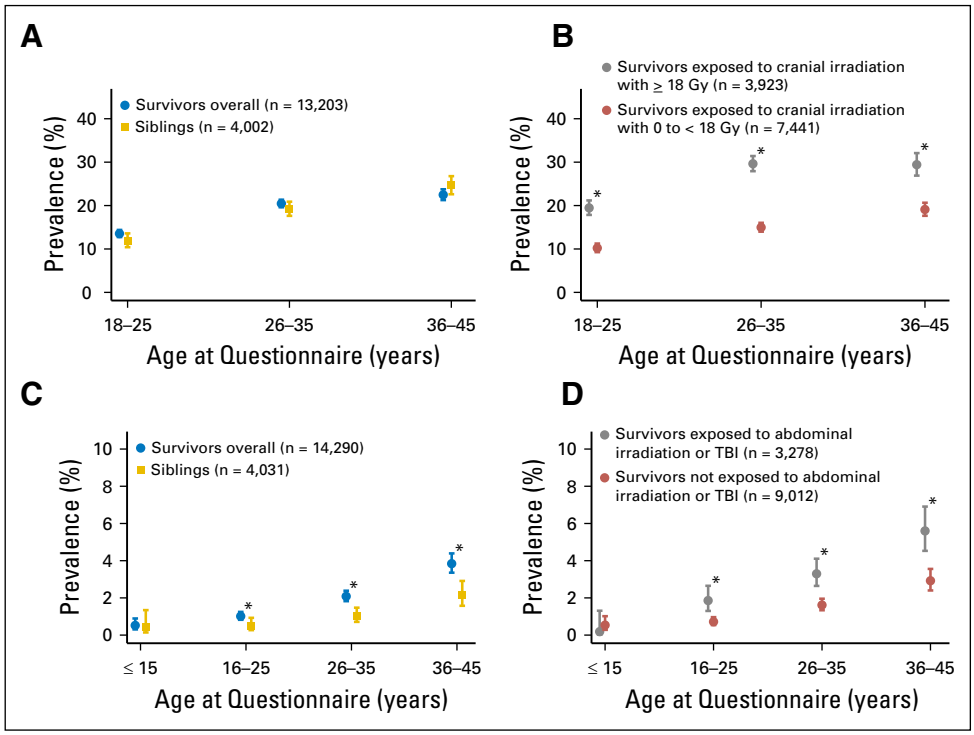

Fig 3. Prevalence of (A, B) obesity and (C, D) diabetes mellitus in (A, C) survivors overall compared with siblings and (B, D) survivors according to treatment exposure. Bars represent 95% CIs. TBI, total-body irradiation. (*) $P < .05$.

5.5). The cumulative incidence of GH deficiency plateaued at 15 years after primary cancer diagnosis in survivors exposed to HP irradiation with 18 Gy or greater (Fig 5; Appendix Fig A1, online only). Prevalence of diabetes insipidus in survivors was 0.8% (95% CI, 0.5 to 1.2) and remained unchanged with increasing age.

Osteoporosis

Risk for osteoporosis in survivors treated with methotrexate, glucocorticoids, and/or TBI was greater (HR, 1.2; 95% CI, 1.0 to 1.4) compared with survivors who were not exposed to these therapies.

DISCUSSION

In the largest study to date to our knowledge, we examined the evolution of endocrine outcomes in aging survivors of childhood cancer in the context of prior treatment exposures. Our findings indicate that the cumulative risk of developing endocrine disorders

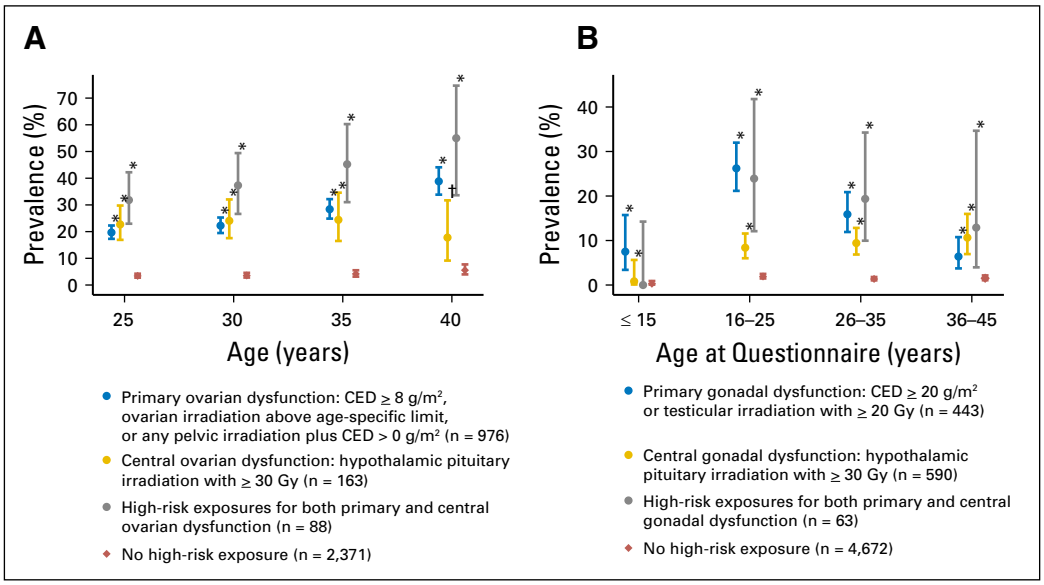

Fig 4. Prevalence of (A) premature ovarian insufficiency in female survivors and (B) testosterone medication use in male survivors by age according to treatment exposure. Bars represent 95% CIs. CED, cyclophosphamide equivalent dose. (*) $P < .001$. (†) $P < .01$.

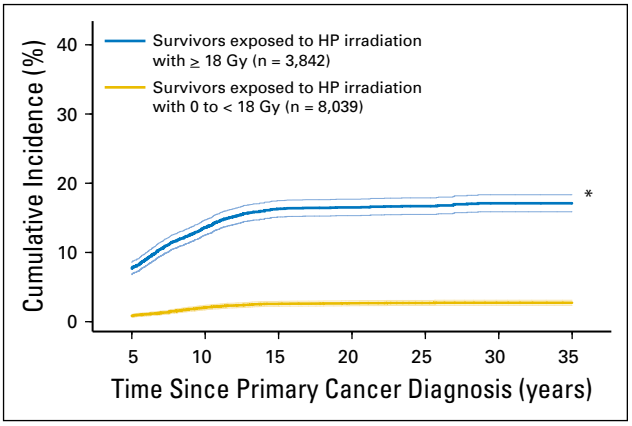

Fig 5. Cumulative incidence of self-reported growth hormone deficiency in survivors by treatment exposure. Thin lines represent 95% CIs. HP, hypothalamic pituitary. (*) $P < .001$.

steadily increases over time for most outcomes. These risks are particularly great for survivors previously treated with specific high-risk exposures, such as high-dose irradiation of the head, neck, or pelvis, and after exposure to high doses of alkylating agents. For many outcomes, even survivors exposed to non–high-risk therapies were significantly more likely to develop an endocrine disorder compared with siblings.

The magnitude and burden of endocrine abnormalities in childhood cancer survivors, particularly after high-risk cancer therapies, are striking.[7,8,16,17] In a study of 310 adult survivors, Brignardello et al[7] reported at least one endocrine disorder in more than half of survivors, 16 years after the diagnosis of childhood cancer. Patterson et al[16] described a wide range of endocrine health conditions in 519 pediatric-age survivors observed in a survivor program, with many of the identified endocrinopathies associated with radiotherapy or stem-cell transplantation; however, their study did not include survivors of brain tumors, a group typically affected by endocrinopathies. In our study, nearly half of childhood cancer survivors experienced at least one endocrine abnormality, 16.7% at least two, and 6.6% three or more.

Among aging survivors, particularly after cranial irradiation, endocrine conditions with vague or minimal clinical symptoms, such as HP deficits, frequently remain undiagnosed or undertreated because of a lack of formal assessment. In this study, cumulative incidence of GH deficiency in CCSS participants after HP irradiation with 18 Gy or greater reached 17.3% within 15 years of primary cancer diagnosis and subsequently plateaued (Fig 5). These findings reflect an underascertainment of GH-deficient adult CCSS participants without a prior diagnosis of GH deficiency during childhood, resulting from a lack of systematic clinical follow-up. In contrast, Chemaitilly et al[8] demonstrated an increasing prevalence of unrecognized adult GH deficiency in a cohort of childhood cancer survivors exposed to cranial irradiation when risk-based screening was applied. Furthermore, they reported a frailty phenotype of 13.1% in their survivors with untreated pituitary deficits at a median age of 33.6 years, a rate observed in the general population among individuals age 65 years or older. These findings underscore the long-term morbidity associated with unrecognized and untreated endocrinopathies in adult childhood cancer survivors.

Similarly, male survivors born in the 1950s were less likely to receive testosterone replacement, despite treatment exposures associated with the development of primary gonadal dysfunction, compared with survivors born after the 1980s. This likely reflects both underdiagnosis and undertreatment of this outcome. Because untreated gonadal insufficiency in men is associated with abdominal obesity, hypertension, dyslipidemia, low bone mineral density, sarcopenia, and frailty,[8] timely diagnosis and treatment of gonadal dysfunction in aging male survivors is critical.

The COG-LTFU Guidelines provide consensus-based, exposure-specific recommendations for screening and management of late effects of pediatric cancer therapy and are intended for survivors 2 or more years after completion of therapy.[13] Both our data and those from the recent St Jude Life studies[8,18] validate the utility of the COG-LTFU Guidelines for identifying survivors with exposures that place them at high risk for late adverse endocrine outcomes.[19] Nevertheless, as noted in our study, even childhood cancer survivors treated with non–high-risk therapies demonstrated an increased risk for certain endocrine outcomes compared with siblings, highlighting the need for long-term surveillance and individualized screening practices in childhood cancer survivors even in the absence of high-risk treatment exposures.

The CCSS has many unique strengths, including longitudinal characterization of overall health conditions in a large, geographically diverse population of aging childhood cancer survivors, with detailed treatment information through middle adulthood, along with a sibling comparison population. Despite these strengths, a number of limitations must be considered when interpreting our findings. First, the outcomes are self-reported, with external validation only for thyroid malignancies, which could lead to both over- and under-reporting of certain outcomes; however, we used strict criteria, such as reported use of hormone replacement for endocrine outcomes of interest, to overcome some of these limitations. Second, given the lack of hormone data to differentiate between primary versus central endocrine dysfunction in some instances, our findings may have resulted in some misclassification of these outcomes. Third, the role of selection and surveillance bias should be considered when interpreting these results. The latter may explain, at least in part, the elevated risk of thyroid cancer in survivors in the non–high-risk exposure group. Finally, treatments for childhood malignancies have evolved over time, and for some cancers, such as HL and acute lymphoblastic leukemia, in which irradiation has been either eliminated or the dose fields reduced, the risks for several endocrine disorders will likely be lower than those reported in this study. However, the chemotherapy and radiotherapy treatments used in this cohort remain the backbone of therapeutic protocols for many childhood malignancies.[20,21] Lastly, our findings are based on the most recent COG-LTFU Guidelines (ie, version 4.0), which provide consensus-based definitions for high-risk exposures for endocrine outcomes of interest. As new information emerges, these definitions may change, which could affect the reported risk estimates.

In summary, the prevalence and cumulative incidence of endocrine outcomes continue to increase as survivors age, particularly after high-risk treatment exposures. These findings underscore the importance of lifelong screening of at-risk childhood cancer survivors for endocrine abnormalities. The National Cancer Policy Board of the Institute of Medicine recommends that survivors receive risk-based care[22]; thus, our findings provide a compelling rationale for continued risk-based endocrine screening throughout adulthood.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Definitions of Various Endocrine Outcomes

Outcome	Definition
Time-to-event data collection	"Have you ever been told by a doctor or other health care professional that you have or have had…"*
Primary hypothyroidism	"Underactive thyroid gland/hypothyroid?" Yes response and self-reported medication history included thyroid hormone replacement; survivors with high-risk exposures only for primary hypothyroidism (thyroid radiation exposure > 20 Gy) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central hypothyroidism (eg, craniospinal radiation) were grouped separately
Hyperthyroidism	"Overactive thyroid gland (hyperthyroid)?" Yes response
Thyroid nodules	"Thyroid nodules?" Yes response
Thyroid cancer	Participants were asked: "At any time following your original cancer diagnosis, were you diagnosed with another cancer, leukemia, tumor, or similar illness?" If yes, participants were asked to report the name of disease and institution where they were diagnosed; medical records and pathology reports were obtained from diagnosing institution and reviewed by CCSS to verify diagnosis type and date; malignant diagnoses with primary site of thyroid gland (ICD-O-3 site code C73.9) were counted as thyroid malignancy events
GH deficiency	"Deficiency of growth hormone?" Yes response
Central hypothyroidism (TSH deficiency)	"Underactive thyroid gland (hypothyroid)?" Yes response and self-reported medication history included thyroid hormone replacement; survivors with high-risk exposures only for central hypothyroidism (hypothalamic pituitary radiation exposure ≥ 40 Gy) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central hypothyroidism (eg, craniospinal irradiation) were grouped separately
Osteoporosis	"Osteoporosis or osteopenia (thin, brittle, or fragile bones)?" Yes response
Cross-sectional data collection	
Obesity	Adult BMI ≥ 30; BMI was calculated from height and weight values self-reported on CCSS questionnaires; obesity analyses restricted to those age 18 years or older
Diabetes mellitus	Participant reported regularly taking oral diabetes medications and/or insulin†
ACTH deficiency	Participant reported regularly taking steroid medications "to replace body hormones"†‡
Central gonadal dysfunction; LH/FSH deficiency (men)	Participant reported regularly taking testosterone medication†; survivors with high-risk exposures only for central gonadal dysfunction (hypothalamic pituitary radiation exposure ≥ 30 Gy) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central gonadal dysfunction (eg, craniospinal irradiation) were grouped separately
Male primary gonadal dysfunction (Leydig cell dysfunction)	Participant reported regularly taking testosterone medication; survivors with high-risk exposures only for primary gonadal dysfunction (CED ≥ 20 g/m^2 or testicular irradiation ≥ 20 Gy) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central gonadal dysfunction (eg, craniospinal irradiation) were grouped separately

(continued on following page)

Table A1. Definitions of Various Endocrine Outcomes (continued)

Outcome	Definition
Female central gonadal dysfunction; LH/FSH deficiency (premature ovarian insufficiency)	Experienced premature menopause (age < 40 years) or never experienced menarche§; survivors with high-risk exposures only for central gonadal dysfunction (hypothalamic pituitary radiation exposure ≥ 30 Gy) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central gonadal dysfunction (eg, craniospinal irradiation) were grouped separately
Female primary gonadal dysfunction (premature ovarian insufficiency)	Experienced premature menopause (age < 40 years) or never experienced menarche; survivors with high-risk exposures only for primary gonadal dysfunction (age < 12 years at cancer diagnosis and ovarian radiation dose ≥ 15 Gy, age ≥ 12 years at cancer diagnosis and ovarian radiation dose ≥ 10 Gy, CED ≥ 8 g/m^2, or any pelvic irradiation plus any CED > 0 g/m^2) were compared with survivors without any high-risk exposures; survivors exposed to therapies potentially resulting in both primary and central gonadal dysfunction (eg, craniospinal irradiation) were grouped separately
Diabetes insipidus	Participant reported regularly taking DDAVP (desmopressin; Ferring Pharmaceuticals, Saint-Prex, Switzerland)

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; CCSS, Childhood Cancer Survivor Study; CED, cyclophosphamide equivalent dose; FSH, follicle-stimulating hormone; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

*If yes response was given, respondent was asked to report his or her age at first occurrence of the condition.

†Medication use questions were preceded by instructions to report all prescription medicines or drugs taken regularly during the 2-year period leading up to the questionnaire date. Medications taken for < 30 days per year and over-the-counter drugs were excluded from reporting.

‡Steroid use specifically to replace body hormones was available only from baseline and follow-up 2000 questionnaires. The ACTH deficiency analysis was limited to observations obtained from those questionnaires.

§Observations on participants who cited a surgical reason (eg, hysterectomy, bilateral oophorectomy) for menstrual periods ceasing before age 40 years were excluded.

Table A2. HRs and RRs for Thyroid Disorders, Obesity, and Diabetes Mellitus

Outcome	Survivors Versus Siblings	Survivors by Treatment Exposure
	HR (95% CI)	HR (95% CI)
Underactive thyroid		
Overall	3.8 (3.1 to 4.7) *	—
≥ 20 Gy thyroid irradiation	13.9 (11.1 to 17.3)*	6.6 (5.6 to 7.8)*
≥ 40 Gy HP irradiation	8.3 (6.0 to 11.5)*	3.9 (2.9 to 5.2)*
Both exposures	12.8 (8.5 to 19.3)*	6.0 (4.1 to 8.8)*
Neither exposure	2.2 (1.8 to 2.7)*	Reference group
Overactive thyroid		
Overall	2.5 (1.8 to 3.3)*	—
≥ 40 Gy thyroid irradiation	4.0 (2.5 to 6.5)*	1.8 (1.2 to 2.8)†
0 to < 40 Gy thyroid irradiation	2.4 (1.7 to 3.3)*	Reference group
Thyroid nodule		
Overall	6.4 (4.8 to 8.6)*	—
≥ 25 Gy thyroid irradiation	19.1 (13.9 to 26.3)*	6.3 (5.2 to 7.5)*
0 to < 25 Gy thyroid irradiation	3.9 (2.9 to 5.4)*	Reference group
Thyroid cancer		
Overall	5.9 (3.0 to 11.6)*	—
> 30 Gy thyroid radiation	10.8 (5.2 to 22.6) *	5.7 (3.5 to 9.3) *
> 5 to ≤ 30 Gy thyroid radiation	23.5 (11.7 to 47.1)*	9.2 (6.2 to 13.7)*
0 to ≤ 5 Gy thyroid radiation	2.5 (1.2 to 5.3)†	Reference group
	RR (95% CI)	RR (95% CI)
Obesity		
Overall	1.0 (0.9 to 1.1)	—
≥18 Gy cranial irradiation	1.4 (1.3 to 1.5)*	1.8 (1.7 to 2.0)*
0 to < 18 Gy cranial irradiation	0.8 (0.7 to 0.8)*	Reference group
Diabetes mellitus		
Overall	1.8 (1.4 to 2.3)*	—
Abdominal irradiation or TBI	2.7 (2.1 to 3.6)*	1.9 (1.6 to 2.4)*
No abdominal irradiation or TBI	1.4 (1.1 to 1.8)†	Reference group

Abbreviations: HP, hypothalamic pituitary; HR, hazard ratio; RR, relative risk; TBI, total-body irradiation.
*$P < .05$.
†$P < .001$.

Table A3. Testosterone Replacement in Male Survivors by Exposure to Treatments Associated With Primary Gonadal Dysfunction According to Birth Year

	Male CCSS Survivors			
	CED < 20 g/m^2 and Testicular Irradiation 0 to 20 Gy		CED ≥ 20 g/m^2 or Testicular Irradiation ≥ 20 Gy	
Questionnaire by Birth Year	No. Taking Testosterone Medication	%	No. Taking Testosterone Medication	%
1949-1959				
Baseline (1992-1999)	325	0.6	28	0.0
Follow-up one (2000-2002)	248	1.2	16	0.0
Follow-up two (2003-2005)	220	1.4	16	0.0
Follow-up 2007	188	1.6	16	0.0
1960s				
Baseline (1992-1999)	1,461	0.3	147	4.8
Follow-up one (2000-2002)	1,118	0.7	101	6.9
Follow-up two (2003-2005)	985	1.4	98	6.1
Follow-up 2007	900	1.7	87	11.5
1970s				
Baseline (1992-1999)	2,037	1.7	213	23.9
Follow-up one (2000-2002)	1,569	1.8	128	29.7
Follow-up two (2003-2005)	1,363	2.1	117	22.2
Follow-up 2007	1,165	2.7	101	23.8
1980s				
Baseline (1992-1999)	849	0.1	55	9.1
Follow-up one (2000-2002)	668	2.7	40	25.0
Follow-up two (2003-2005)	588	1.9	25	24.0
Follow-up 2007	479	1.9	22	27.3

Abbreviations: CCSS, Childhood Cancer Survivor Study; CED, cyclophosphamide equivalent dose.

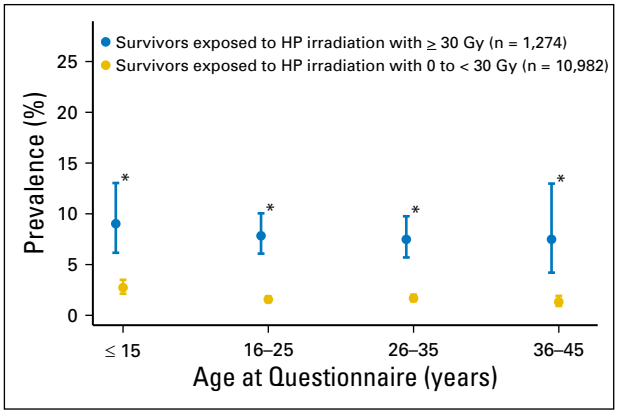

Fig A1. Prevalence of adrenocorticotropic hormone deficiency by age among survivors by treatment exposure. Bars denote 95% CIs. HP, hypothalamic pituitary. (*) $P < .05$.