Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2019 June 01; 104(2): 415–424. doi:10.1016/j.ijrobp.2019.02.009.

Hyperthyroidism Following Radiation Therapy for Childhood Cancer: A Report from the Childhood Cancer Survivor Study

Peter D. Inskip, ScD^{a,b}, Lene H.S. Veiga, PhD^a, Alina V. Brenner, MD^{a,c}, Alice J. Sigurdson, PhD^{a,b}, Evgenia Ostroumova, MD^{a,d}, Eric J. Chow, MD^e, Marilyn Stovall, PhD^{f,b}, Susan A. Smith, MPH^f, Wendy Leisenring, ScD^e, Leslie L. Robison, PhD^g, Gregory T. Armstrong, MD^g, Charles A. Sklar, MD^h, Jay H. Lubin, PhDⁱ

^aRadiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

^bRetired

^cRadiation Effects Research Foundation, Hiroshima, Japan

^dInternational Agency for Research on Cancer, Lyon, France

^eClinical Research and Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

^fDepartment of Radiation Physics, The University of Texas MD Anderson Cancer Center; Houston, TX, USA

^gDepartment of Epidemiology and Cancer Control, St. Jude Children's Research Hospital; Memphis, TN, USA

^hDepartment of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

ⁱBiostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

Abstract

Background.—The association of hyperthyroidism with exposure to ionizing radiation is poorly understood. This study addresses the risk of hyperthyroidism in relation to incidental therapeutic radiation dose to the thyroid and pituitary glands in a large cohort of survivors of childhood cancer.

Methods.—Utilizing the Childhood Cancer Survivor Study, a cohort of five-year survivors of childhood cancer diagnosed at hospitals in the United States and Canada between 1970 and 1986, the occurrence of hyperthyroidism through 2009 was ascertained among 12,183 survivors based on serial questionnaires. Radiation doses to the thyroid and pituitary glands were estimated from

Corresponding author: Dr. Peter D. Inskip; 5421 Marlin St., Rockville, MD 20853-3607; inskipeter@gmail.com.

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Conflicts of Interest: No conflicts

radiotherapy records, and chemotherapy exposures were abstracted from medical records. Binary outcome regression was used to estimate prevalence odds ratios (ORs) for hyperthyroidism at five years from diagnosis of childhood cancer and Poisson regression to estimate incidence rate ratios (RRs) after the first five years.

Results.—Survivors reported 179 cases of hyperthyroidism, of which 148 were diagnosed five or more years after their cancer diagnosis. The cumulative proportion of survivors diagnosed with hyperthyroidism by 30 years after the cancer diagnosis was 2.5% (95% CI: 2.0-2.9) among those who received radiotherapy. A linear relation adequately described the thyroid radiation dose-response for prevalence of self-reported hyperthyroidism five years after cancer diagnosis (excess OR/Gy=0.24; 95% CI: 0.06-0.95) and incidence rate thereafter (excess RR/Gy = 0.06; 95% CI: 0.03-0.14) over the dose range of 0-63 Gy. Neither radiation dose to the pituitary gland nor chemotherapy was associated significantly with hyperthyroidism. Radiation-associated risk remained elevated > 25 years after exposure.

Conclusions.—Risk of hyperthyroidism following radiotherapy during childhood is positively associated with external radiation dose to the thyroid gland, with radiation-related excess risks persisting for > 25 years. Neither radiation dose to the pituitary gland nor chemotherapy exposures were associated with hyperthyroidism among childhood cancer survivors through early adulthood.

Keywords

Hyperthyroidism; ionizing radiation; radiotherapy; childhood cancer; thyroid disorders; epidemiology

Introduction

The thyroid gland is well-established as a radiosensitive site, particularly following radiation exposures early in life (1, 2). Exposure to ionizing radiation during childhood is linked to increased risks of subsequent thyroid cancer, hypothyroidism and thyroid nodules, with clear evidence of a dose-response; however, the literature concerning hyperthyroidism is sparse and inconsistent (3-13). The mechanism through which radiation might cause hyperthyroidism is unknown but could involve an autoimmune reaction to thyroid antigens released by radiation-induced damage to the thyroid (13). Hyperthyroidism usually can be treated effectively by anti-thyroid drugs, radioactive iodine or thyroidectomy (14); however, if not treated, it may cause a variety of adverse health outcomes later in life, including cardiovascular complications (15). The early identification and treatment of overt hyperthyroidism in children and adolescents is important because of the deleterious effects of excess thyroid hormones on normal growth and development (16, 17).

The strongest evidence that exposure to radiation causes hyperthyroidism comes from studies of therapeutically-irradiated childhood cancer survivors. Hyperthyroidism was associated with radiation treatment among survivors of childhood Hodgkin lymphoma (HL) (5) and acute lymphoblastic leukemia (ALL) (18) but not among survivors of the atomic bomb explosions in Japan who were exposed during childhood (mean dose, 0.2 Gy) (8) nor among children exposed to ¹³¹I from atmospheric releases due to the Chernobyl accident (mean thyroid dose, 0.5 Gy) (19, 20) or from the Hanford nuclear site (21). Among HL

survivors, an increased occurrence of hyperthyroidism was seen for those with thyroid doses 35 Gy (5). Among ALL survivors, increased occurrence of hyperthyroidism was observed only among those with radiation doses 15 Gy to the thyroid and 20 Gy to the pituitary; however, the possible effect of radiation on the pituitary could not be distinguished from that on the thyroid, as subjects had been exposed to craniospinal irradiation, and both organs would have been in the radiation field(s) (18). It is not clear how irradiation of the hypothalamic-pituitary axis would increase the risk of hyperthyroidism. Findings for atomic bomb survivors are based on hormonal analysis of serum samples collected > 60 years after exposure (8); the absence of a detectable radiation-related risk among long-term survivors of the explosions does not preclude an effect at earlier times. Risk due to irradiation from internally-deposited ^{131}I from nuclear fallout may differ from that associated with external radiation and would not address pituitary radiation exposure. Here, we evaluate the risk of hyperthyroidism in relation to wide ranges of external radiation dose to the thyroid and pituitary glands in a large cohort of childhood cancer survivors with long-term, continuous follow-up beginning five years after exposure.

Methods

The study was conducted within the Childhood Cancer Survivor Study (CCSS) cohort of five-year survivors of childhood cancer [leukemia, central nervous system (CNS) cancer, HL, non-Hodgkin lymphoma (NHL), kidney cancer, neuroblastoma, soft tissue sarcoma, bone sarcoma] diagnosed at age < 21 years at 26 centers in the United States and Canada during 1970-86 (22, 23). The study was approved by institutional review boards at each participating hospital.

From the CCSS study population of 14,364 survivors, we excluded those patients who had not signed medical release forms allowing for review and abstraction of cancer treatment information (n=1608), had not completed a baseline or 2007 follow-up questionnaire (see below) (n=3), had missing or incomplete radiation treatment information (n=487), reported thyroid gland removal before the first cancer treatment (n=17), reported hyperthyroidism before the cancer diagnosis (n=18) or did not report age at diagnosis of hyperthyroidism (n=48), leaving 12,183 eligible survivors and 179 hyperthyroidism cases. For incidence rate analyses only, we excluded an additional 31 survivors who reported hyperthyroidism diagnosed within the first five years after first cancer treatment and 544 patients who reported thyroid removal, hypothyroidism or a second primary cancer (exclusive of non-melanoma skin cancer) within the first five years, leaving 11,608 survivors and 148 hyperthyroidism cases for incidence rate analysis.

Survivors were asked to complete a questionnaire at time of entry to the study (1992-1994) and a 2007 follow-up questionnaire administered in 2007-2009. The two questionnaires obtained information on a variety of health-related outcomes and practices, including physician-diagnosed thyroid disorders, prescription thyroid medication use, thyroid surgery and new primary cancers. Information about treatment with radioiodine was not collected. With regards to hyperthyroidism, questions included "Have you ever been told by a doctor or other health care professional that you have or have had an overactive thyroid gland

(hyperthyroid)?" and, if yes, "Age at first occurrence?" Of 12,183 survivors who completed the baseline questionnaire, 7,216 (59%) also completed the 2007 questionnaire.

Trained abstractors reviewed medical records at hospitals where participants were treated for their cancer according to a standardized protocol. Radiotherapy records for individual patients were photocopied and sent to collaborating medical physicists where radiation field details for each patient were abstracted onto standardized forms by dosimetry staff. Abstracted details included dates of radiotherapy, beam energy, dose delivered, and field parameters (field location, field size, field borders, configuration, and blocking). Data were abstracted for all chemotherapy drugs. Medical record abstraction forms are available at <http://ccss.stjude.org/ccss>.

Nearly all irradiated patients in the present study were treated with high energy photons, and fractionation schedules were highly standardized. Two percent of survivors received total body irradiation (TBI) as part of hematopoietic stem cell transplantation. External radiation doses to the thyroid and pituitary gland were estimated for each individual. The abstracted radiotherapy details were used to reconstruct the fields for each patient on a mathematical phantom, which matched the age of patient at the time of first cancer treatment (24). The depth and distance of the points in the organs from the field were calculated from the age-appropriate phantom, and then dose was estimated using measured water phantom data by energy. Dose estimations accounted for typical beam shielding or blocking. Pituitary dose was used as a proxy for dose to the hypothalamic-pituitary axis. With the possible exception of partial-brain radiotherapy, doses to the pituitary and hypothalamus would have been very similar. Radiation treatments up to 10 years after the cancer diagnosis were included.

Because cohort eligibility required survival five or more years after the cancer diagnosis, we calculated prevalence of hyperthyroidism at five years after cancer diagnosis, incidence rate for five or more years after cancer diagnosis, and a cumulative measure ("cumulative proportion affected"), combining prevalence at five years with cumulative incidence from five to 30 years post-cancer diagnosis. The cumulative incidence after five years was calculated according to a method described by Gooley et al. (25) using Stata (Stata, release 13.1, College Station, TX). The cumulative proportion affected measure was not adjusted for other covariates. We computed prevalence odds ratios (ORs) using unconditional binary regression models with baseline adjusted for sex, attained age, type of cancer and calendar year of follow-up using the GMBO module of the EPICURE statistical program (Risk Sciences International, Ottawa, Canada).

Follow-up for incidence rate analyses began five years after the date of cancer diagnosis and was truncated at the earliest of the following events: a) diagnosis of hyperthyroidism or hypothyroidism b) thyroid removal, c) second cancer (exclusive of non-melanoma skin cancer), d) death; or e) date of last contact.

Case counts and person-years of follow-up (PYR) were summarized in a multidimensional cross-tabulation based on categorized demographic, diagnostic and treatment-related variables as described in detail in a previous report concerning hypothyroidism (12). These included sex, year of birth, age at cancer diagnosis, type of cancer, time since cancer

diagnosis, attained age, thyroid and pituitary gland radiation dose and indicator variables (yes/no/unknown) for any chemotherapy and treatment with various classes of chemotherapeutic agents (alkylating agents, anthracyclines, epipodophyllotoxins, platinum-based compounds) and bleomycin. The DATAB module of EPICURE was used to construct the events/PYR table.

We modeled the incidence rate for hyperthyroidism as a function of a vector of explanatory variables, which included sex, attained age, calendar year of follow-up, type of cancer, thyroid radiation dose, pituitary radiation dose and chemotherapy exposure. For thyroid and pituitary radiation effects, we modeled the excess rate ratio (or excess relative risk) (ERR). For prevalence analyses, we substituted the excess odds ratio (EOR). Radiation dose-response models were variants of the general model:

$$\text{ERR} = (\beta_1 D + \beta_2 D^2) \exp(\beta_3 D + \beta_4 D^2),$$

where D is organ dose and β_1 - β_4 are regression coefficients. The model $\text{ERR} = \beta_1 D$ corresponds to a linear dose-response relation, and β_1 represents ERR/Gy. Possible effect modifiers, such as sex, age at exposure, time since exposure, attained age, calendar year of follow-up, type of cancer, pituitary dose and chemotherapy, were evaluated by including them in the exponential term. We used the AMFIT module of EPICURE for all incidence rate analyses.

Results

Leukemia was the most common type of childhood cancer (34%), followed by HL (13%) and CNS cancer (13%) (Table 1). More of the study population was male (53%) than female. The average age at cancer diagnosis was eight years (range, 0-20 years), and the average follow-up for incidence analyses, beginning five years after cancer diagnosis, was 16.3 years (total: 189,182 PYR). The average age at the end of follow-up was 29.4 years, and 93% of the study population was still alive. Two-thirds of the population was treated with radiation. The average dose to the thyroid gland among irradiated survivors was 10.8 Gy (range, 0.005- 63 Gy), and the average dose to the pituitary gland was 15.2 Gy (range, 0.01-109 Gy). Thyroid dose was highest among HL survivors (median, 36.4 Gy), and pituitary dose was highest among survivors of CNS cancer (median, 39.9 Gy) and leukemia (median, 22.1 Gy). Eighty percent of survivors received chemotherapy for their cancer, most often including alkylating agents (53%) and/or anthracyclines (41%).

We identified 179 self-reported cases of hyperthyroidism, 31 of which were diagnosed within the first five years after cancer diagnosis. The average age at diagnosis of hyperthyroidism among incident cases was 24 years (range, 8-53). The average interval between cancer diagnosis and diagnosis of hyperthyroidism for prevalent and incident cases combined was 15.1 years (median 14.9 years). The cumulative proportion of survivors diagnosed with hyperthyroidism by 30 years after diagnosis of the cancer was 2.1% (95% CI: 1.8-2.5). It was 2.7% (95% CI: 2.2-3.4) among females and 1.5% (95% CI: 1.2-2.0) among males and was higher among those who received radiotherapy (2.5%; 95% CI:

2.0-2.9) than among those who did not (1.4%; 95% CI: 0.9-2.0). The proportion was highest among survivors of HL (6.6%; 95% CI: 4.9-8.7). Six cases occurred among persons treated with TBI, one within the first five years after cancer diagnosis. During the same time period, we identified 1,193 cases of hypothyroidism (as first functional thyroid disorder) among all survivors, including prevalent cases five years post-cancer diagnosis (12). The average interval between cancer and hypothyroidism diagnoses was 10.5 years (median, 8.7 years).

The adjusted incidence rate of hyperthyroidism was significantly higher among females than males and increased with calendar year of follow-up but was not associated significantly with age at cancer diagnosis, calendar year of cancer diagnosis, time since cancer diagnosis or attained age (Table 2). The incidence rate (adjusted for thyroid radiation dose) varied significantly by type of cancer, with higher rates among survivors of HL, CNS cancer or leukemia. Incidence was significantly higher among survivors who received radiation than among those who did not (RR=2.2; 95% CI: 1.2-4.0). Incidence was not associated significantly with chemotherapy, neither overall (RR=1.1; 95% CI: 0.7-1.7) nor for specific classes of agents (Table 2).

The incidence rate of hyperthyroidism was associated significantly with radiation dose to the thyroid [$P(\text{trend}) < 0.01$] but not the pituitary [$P(\text{trend})=0.35$] (Table 2; Figure 1). A linear thyroid dose-response model was consistent with the incidence data, with an ERR/Gy of 0.06 (95% CI 0.03-0.14). Tests of departure from linearity were not significant for linear-quadratic ($P=0.68$), linear-exponential ($P=0.75$) or linear-quadratic-exponential ($P=0.20$) models (Supplementary Table S1). There was no significant modification of the linear thyroid radiation dose-response term by sex, age at radiation exposure, time since exposure, attained age, calendar year of follow-up, type of cancer, pituitary radiation dose or chemotherapy (Table 3). The prevalence of hyperthyroidism five years after diagnosis of the childhood cancer also was significantly associated with radiation dose to the thyroid gland, based on 31 cases [$P(\text{trend}) < 0.01$]; EOR/Gy=0.24 95% CI: 0.06-0.95] (Table 4). The thyroid dose-response relationships for incidence and prevalence did not change appreciably when patients treated with TBI were excluded (data not shown). The estimated ERR/Gy for the linear thyroid dose-response also was essentially unchanged (0.05 versus 0.06), and with similar 95% CIs, when survivors of HL, the type of cancer with the highest thyroid doses, were excluded.

Because of concern that some cases of hypothyroidism might be erroneously reported as hyperthyroidism, we conducted a sensitivity analysis in which we identified questionable incident cases of hyperthyroidism. These included 61 survivors who reported only hyperthyroidism (i.e., did not report hypothyroidism), but who did report taking hypothyroidism medications. This would be legitimate if, for example, the survivor developed hyperthyroidism and went on to develop hypothyroidism due to treatment for hyperthyroidism. It also could reflect erroneous reporting of hypothyroidism as hyperthyroidism. Major findings identified above were similar whether based on this case series or the total case series (N=148); that is, there was a significant radiation dose-response for the thyroid but not the pituitary, no association with chemotherapy, and no indication of radiation effect modification by the factors listed in Table 3.

Discussion

We observed evidence of a radiation-related increased risk for hyperthyroidism, and data were consistent with a linear thyroid radiation dose-response. We did not observe evidence of an effect of pituitary (or hypothalamic) irradiation or chemotherapy. The previous finding of an increased incidence of hyperthyroidism among survivors of ALL in the CCSS who received high radiation doses to both the thyroid and pituitary (18) probably is attributable to an effect of radiation on the thyroid, as was noted by the authors. The present study has the advantages of larger sample size (including multiple types of childhood cancer), coupled with more formal dose-response analysis based on individual-level, and mutually adjusted, dose estimates for the thyroid and pituitary. The association of hyperthyroidism incidence with thyroid radiation dose was not modified significantly by sex, age at exposure, time since exposure, attained age, calendar year of follow-up, type of cancer or chemotherapy. The radiation-related excess of hyperthyroidism was apparent early, within the first five years after irradiation, and the slope of the thyroid dose-response was greater for prevalence five years after exposure than for incidence in later years; however, there was no indication of a decreasing relative effect of radiation between five and 25 years following exposure.

The estimated thyroid dose-response relation for incidence of hyperthyroidism was consistent with a linear association ($ERR=0.06/Gy$), corresponding to an estimated RR of 1.06 at 1 Gy. Most previous studies of hyperthyroidism in relation to childhood exposure to radiation for reasons other than cancer treatment have involved populations mostly exposed to < 1 Gy to the thyroid (18-21). Based on results from the present study, it is not surprising that these studies have not found evidence of an association.

The elevated risk of hyperthyroidism among survivors of HL, CNS cancer and leukemia in the present study, even after adjustment for thyroid radiation dose, might be due, in part, to closer surveillance for thyroid abnormalities following radiation treatment for these cancers, particularly HL survivors (3, 4, 26). Similarly, increases in the RR (but not the ERR/Gy) for hyperthyroidism with calendar year of follow-up might reflect enhanced ascertainment related to increased surveillance and/or improved sensitivity of laboratory tests. Associations with type of cancer also could result from errors in estimated thyroid radiation doses, such that type of cancer effects were conflated with dose effects, or due to a failure to account for important cancer treatment effects other than radiation dose to the thyroid. The latter might include irradiation of the thymus, spleen or gonads, though we do not have reason to believe that such effects are large. Aberrations in immune function among persons who develop HL also could have a bearing on thyroid autoimmunity. To our knowledge, shared susceptibility factors linking spontaneous hyperthyroidism with HL, CNS cancer or ALL have not been established.

Current understanding of the etiology of autoimmune thyroid disorders, whether manifesting as hyperthyroidism related to Graves' disease or hypothyroidism related to Hashimoto's thyroiditis, is that they arise due to a loss of tolerance to thyroid antigens among genetically susceptible persons, triggered or exacerbated by environmental factors (6, 16, 27-29). The immediate cause of Graves' disease, the most common cause of hyperthyroidism (14, 30), is autoantibodies to the thyroid stimulating hormone receptor (TSHR) (29, 31). The TSHR has

multiple epitopes, and anti-thyroid antibodies can bind to the TSHR both agonistically and antagonistically, with effects ranging from thyroid cell stimulation and proliferation to apoptosis (32-34). Whereas stimulatory antibodies can cause hyperthyroidism, blocking antibodies can cause hypothyroidism (31, 33, 35). Damage to the thyroid caused by radiation could, in principle, induce or enhance the expression of either or both types of antibodies. Indeed, TSHR stimulatory and blocking antibodies have been found in the same individuals (31, 35, 36), though, to our knowledge, such observations have not been linked to radiation exposure. In an experimental study with mice, a single whole-body exposure to 0.5 Gy was sufficient to exacerbate thyroiditis and increase anti-thyroglobulin titers; however, this exposure did not influence titers of anti-TSHR antibodies or the incidence of hyperthyroidism (37). It is unclear whether radiation-related hyperthyroidism and radiation-related primary hypothyroidism develop through overlapping or distinct pathways, or some combination. Radiation-related primary hypothyroidism also could develop as a result of direct radiation-induced damage to the thyroid that does not involve an immune component.

Children treated with allogeneic hematopoietic stem cell transplantation sometimes develop hyperthyroidism (thyrotoxicosis) after transplantation (38-41). This is seen among patients not receiving TBI as part of their conditioning regimen as well as those who received TBI, suggesting a role of non-radiation factors. Adoptive transfer from donor to recipient of immune-related factors, possibly including TSHR antibodies, may play a role (38). In the present study, only a small fraction of patients received TBI, and the estimated thyroid radiation dose-response relationship was insensitive to their inclusion or exclusion in the analysis.

Strengths of this study include its large size, long follow-up, longitudinal ascertainment of hyperthyroidism at two widely separated time points following treatment for childhood cancer, systematic and detailed ascertainment of treatments for the childhood cancer, estimation of radiation doses to the thyroid and pituitary glands for individual cancer survivors based on radiotherapy records, multivariate radiation dose-response analyses mutually-adjusted for thyroid and pituitary doses, and evaluation of potential modifiers of the thyroid radiation dose-response relationship.

The most important limitation is reliance on self-reported information about the occurrence of hyperthyroidism in the absence of supporting serological measurements, specifically, for thyroid stimulating hormone, free thyroxine and anti-thyroid antibodies. Possible misreporting of hypothyroidism as hyperthyroidism is a concern, particularly because hypothyroidism was so much more common (6.7-fold) than hyperthyroidism. Results of a sensitivity analysis, in which we analyzed questionable cases of hyperthyroidism (i.e., those who reported only hyperthyroidism but also taking hypothyroidism medications) separately, provide reassurance that this was not a major source of bias in the present study.

We also note several differences between findings reported here for hyperthyroidism and those we reported previously for hypothyroidism in the CCSS cohort (12): (a) the occurrence of hypothyroidism, but not hyperthyroidism, was associated significantly with radiation dose to the pituitary as well as the thyroid; (b) the thyroid dose-response for hypothyroidism at low pituitary doses was much steeper than that for hyperthyroidism

regardless of pituitary dose; (c) for hypothyroidism, there was evidence of radiation effect modification by sex, age at exposure and time since exposure, none of which were observed here for hyperthyroidism; (d) risk of hypothyroidism, but not hyperthyroidism, was associated with chemotherapy; (e) the median interval from cancer diagnosis to diagnosis of thyroid disorder was longer for hyperthyroidism. Together, these differences suggest specificity of detection of these two functional thyroid disorders by our questionnaire instrument.

Although the CCSS study population is large compared to most other childhood cancer survivor cohorts, the number of hyperthyroidism cases was small, which limited our ability to distinguish between possible underlying linear or curvilinear thyroid radiation dose-response relationships, let alone address the possibility of a threshold dose. Our analysis centered on a linear dose-response model, both for a summary estimate of the effect of radiation (ERR/Gy) and for consideration of possible radiation effect modifiers, because it provided an adequate, parsimonious, summary of the dose-response data.

The present study has several other, lesser limitations. Radiotherapy given at another institution for a recurrence of the childhood cancer or a new malignancy may have been under-ascertained, though, for the latter, it would only be relevant if the cancer was not known to us, as we truncated follow-up at the time of diagnosis of a second primary cancer. We cannot distinguish among different possible underlying causes of hyperthyroidism, such as Graves' disease or toxic nodular goiter (14), nor can we address subclinical hyperthyroidism, the ultimate clinical importance of which is unclear (42). We do not have information about other risk factors for hyperthyroidism, including genetic susceptibility and iodine intake (16, 28).

Results support a radiation etiology for hyperthyroidism among childhood cancer survivors and point to a radiation dose-dependent effect on the thyroid gland but not the hypothalamic/pituitary axis. We did not observe evidence of an effect of chemotherapy. Irradiated childhood cancer survivors are at increased risk for hyperthyroidism within five years after exposure and remain at elevated risk for at least 25 years. While our results are consistent with a linear thyroid dose-response relationship with no threshold, the radiation-related risk appears to be relatively small except at therapeutic doses. Radiation-related risk appears to be less than that for hypothyroidism (12) or thyroid cancer (43, 44).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This study was supported by the Intramural Research Program of the U.S. National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. The Childhood Cancer Survivor Study is supported by the National Cancer Institute (CA55727, G.T. Armstrong, Principal Investigator). Support to St. Jude Children's Research Hospital is also provided by the Cancer Center Support (CORE) grant (CA21765, C. Roberts, Principal Investigator) and the American Lebanese-Syrian Associated Charities (ALSAC).

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Summary

The association of hyperthyroidism with exposure to ionizing radiation is poorly understood. We evaluated the occurrence of hyperthyroidism in relation to incidental therapeutic radiation dose to the thyroid and pituitary glands among 12,183 childhood cancer survivors based on individualized radiation dosimetry and serial questionnaires to ascertain hyperthyroidism. Risk of hyperthyroidism was positively associated with radiation dose to the thyroid gland, but not the pituitary gland, with radiation-related excess risk persisting for > 25 years.

Figure 1.

Incidence rate ratio (RR) for hyperthyroidism and 95% confidence intervals for categories of thyroid radiation dose (left panel) and pituitary radiation dose (right panel) together with fitted relation based on straight-line dose-response model (solid line). Baseline is adjusted for sex, attained age, attained calendar year, type of cancer and thyroid radiation dose (for pituitary dose-response). Horizontal dashed line denotes reference level corresponding to $RR=1.0$.

Table 1.

General characteristics of study subjects in the Childhood Cancer Survivor Study cohort evaluated for risk of hyperthyroidism.

Number of patients	12,183
Person-years of follow-up ^a	189,182
Mean age at cancer diagnosis, years (range)	8 (0-20)
Mean age at end of follow-up, years (range)	29.4 (5-58)
Number of females (%)	5,727 (47)
Mean dose to thyroid gland, Gy (range) ^b	10.8 (>0-63.4)
Mean dose to pituitary gland, Gy (range) ^b	15.2 (>0-109)
Type of childhood cancer (%)	
Leukemia	4,129 (34)
Central nervous system cancer	1,546 (13)
Hodgkin lymphoma	1,580 (13)
Non-Hodgkin lymphoma	899 (7)
Kidney cancer (Wilms)	1,059 (9)
Neuroblastoma	822 (7)
Soft tissue sarcoma	1,058 (9)
Bone cancer	1,022 (8)
Radiotherapy (%)	
No	3,990 (33)
Yes	9,125 (67)
Chemotherapy (%)	
No	2,278 (19)
Yes	9,672 (79)
Missing information	165 (1)
Chemotherapy drugs (%)	
Any alkylating agents	6,415 (53)
Any anthracyclines	4,934 (41)
Any bleomycin	720 (6)
Any platinum-based compounds	735 (6)
Any epipodophyllotoxins	1,139 (9)

^aFrom the incidence analysis (11,608 patients)

^bAmong those treated with radiation

Table 2.

Incidence rate ratio (RR) for hyperthyroidism by selected demographic, clinical and treatment-related factors among five-year cancer survivors in the Childhood Cancer Survivor Study cohort.

Characteristic	Cases	PYR/10,000	RR ^a (95% CI)
Sex			
Male	60	9.9	1.0
Female	88	9.0	1.7 (1.2-2.4)
			P ^b <0.01
Age at cancer diagnosis, years			
< 5	48	7.2	1.0
5-9	33	4.6	0.9 (0.5-1.4)
10-14	34	3.7	0.8 (0.5-1.4)
15-20	33	3.4	0.6 (0.4-1.2)
			P ^b > 0.50
			P ^c =0.20
Calendar year of cancer diagnosis			
1970-74	39	4.7	1.0
1975-79	47	6.2	1.0 (0.7-1.6)
1980-86	62	8.0	1.0 (0.7-1.6)
			P ^b >0.50
			P ^c =0.81
Time since cancer diagnosis, years			
5-9	30	5.5	1.0
10-14	30	4.6	1.2 (0.7-2.0)
15-19	29	3.8	1.1 (0.6-2.0)
20	59	5.0	1.1 (0.6-2.2)
			P ^b >0.50
			P ^c =0.47
Attained age, years			
<25	66	11.2	1.0
25-29	30	3.3	0.9 (0.6-1.5)
30-34	23	2.2	0.9 (0.5-1.5)
35-39	15	1.3	0.8 (0.4-1.5)
40	14	0.9	0.8 (0.4-1.6)
			P ^b >0.50
			P ^c =0.20
Calendar year of follow-up			
<1985	11	2.1	1.0
1985-1989	24	3.4	1.7 (0.8-3.5)

Characteristic	Cases	PYR/10,000	RR ^a (95% CI)
1990-1999	48	8.5	1.7 (0.8-3.4)
2000-2004	36	3.0	4.4 (1.9-10.0)
2005	29	1.9	6.2 (2.6-14.8)
			P ^b <0.01
			P ^c <0.01
Type of cancer			
Other cancers	33	8.2	1.0
Leukemia	46	6.6	1.7 (1.0-2.6)
Central nervous system cancer	20	2.1	2.0 (1.1-3.5)
Hodgkin lymphoma	49	1.9	3.1 (1.6-5.9)
			P ^b <0.01
Radiation treatment			
No	31	6.7	1.0
Yes	117	12.2	2.2 (1.2-4.0)
			P ^b =0.03
Chemotherapy			
No	35	3.6	1.0
Yes	110	15.1	1.1 (0.7-1.7)
			P ^b >0.50
Any alkylating agents			
No	71	9.3	1.0
Yes	73	9.3	0.9 (0.6-1.4)
			P ^b >0.50
Any anthracyclines			
No	100	11.5	1.0
Yes	44	7.2	0.9 (0.6-1.4)
			P ^b >0.50
Bleomycin			
No	132	17.8	1.0
Yes	12	0.9	1.4 (0.7-2.8)
			P ^b 0.29
Platinum-based compounds			
No	140	17.9	1
Yes	4	0.7	1.0 (0.3-2.8)
			P ^b >0.50
Epipodophyllotoxins			
No	134	17.4	1.0
Yes	10	1.3	1.1 (0.6-2.2)
			P ^b >0.50

Characteristic	Cases	PYR/10,000	RR ^a (95% CI)
Radiation dose to thyroid, Gy (mean)			
0	31	6.7	1.0
> 0 - < 1.0 (0.4)	37	6.5	1.2 (0.8-2.0)
1.0 - < 2.0 (1.4)	9	1.3	1.4 (0.6-3.0)
2.0 - < 15.0 (7.7)	10	1.4	1.7 (0.8-3.4)
15.0 - < 25.0 (19.6)	10	1.0	1.8 (0.8-3.8)
25.0 - < 30.0 (27.2)	8	0.4	3.1 (1.3-7.2)
30.0 - < 35.0 (32.5)	8	0.3	4.3 (1.8-10.4)
35.0 - < 40.0 (37.5)	20	0.4	6.7 (3.1-14.6)
40.0 (45.9)	15	0.7	3.1 (1.3-7.1)
			P ^b <0.01
			P ^c <0.01
Radiation dose to pituitary, Gy (mean)			
0	31	6.8	1.0
> 0 - < 1.0 (0.27)	29	4.0	1.4 (0.7-2.6)
1 - < 10 (2.8)	37	1.6	1.4 (0.6-2.9)
10 - < 30 (20.9)	36	4.9	1.2 (0.7-2.1)
30 (44.3)	15	1.5	1.3 (0.6-3.0)
			P ^b =0.82
			P ^c =0.35

^aRRs computed using Poisson regression analysis with multiplicative adjustment for, sex, attained age, type of cancer, calendar year of follow-up, and thyroid radiation dose categories. (0, >0-<1.0, 1.0-<2.0, 2.0-<15.0, 15-<25.0, 25-<30, 30-<35, 35-<40, 40 Gy). Model was fitted excluding the respective risk factor according to the analysis for comparison with the full model and then computing the likelihood ratio test of homogeneity of risk across categories (nested models).

^bP-value for likelihood ratio test of homogeneity of risk across categories

^cP-value for trend

^dPatients with missing information on chemotherapy or classes of chemotherapy agents were excluded. Abbreviations: CI=confidence interval; PYR=person-years; ref=reference category; RR=relative risk (rate ratio)

Table 3.

Estimates of modification to the linear component (β_1) of the thyroid radiation dose-response relationship^a for incidence of hyperthyroidism among five-year survivors of childhood cancer: Childhood Cancer Survivor Study.

Effect Modifier	Cases	Linear term (ERR/Gy) (95% CI)
None	148	0.06 (0.03-0.14)
Sex		
Male	60	0.10 (0.03-0.28)
Female	88	0.03 (0.01-0.13)
		P ^b =0.19
Age at radiation exposure, years (mean)		
<5 (2.5)	49	0.11 (0.04-0.29)
5-9 (6.7)	32	0.07 (0.02-0.19)
10-14 (12.1)	34	0.04 (0.01-0.13)
15-21 (17.2)	33	0.05 (0.01-0.15)
		P ^b >0.50
		P ^c =0.35
Attained age, years (mean)		
20-24 (17.1)	66	0.11 (0.04-0.28)
25-29 (27.4)	30	0.002 (0.00-14.51)
30-34 (32.3)	23	0.03 (0.01-0.44)
35-57 (39.9)	29	0.07 (0.01-0.36)
		P ^b =0.36
		P ^c =0.52
Time since exposure, years (mean)		
5-9 (7.4)	30	0.07 (0.02-0.20)
10-14 (12.4)	29	0.07 (0.02-0.20)
15-19 (17.4)	31	0.06 (0.02-0.19)
20-24 (22.3)	32	0.07 (0.02-0.21)
25-38 (28.8)	26	0.05 (0.01-0.20)
		P ^b >0.50
		P ^c =0.94
Calendar year of follow-up		
<1985	11	0.05 (0.006-0.41)
1985-1989	24	0.09 (0.02-0.35)
1990-1999	48	0.05 (0.01-0.16)
2000-2004	36	0.08 (0.02-0.24)
2005-2009	29	0.07 (0.02-0.26)
		P ^b >0.50

Effect Modifier	Cases	Linear term (ERR/Gy) (95% CI)
		$P^c > 0.50$
Type of cancer		
Leukemia	46	0.08 (0.02-0.33)
Central nervous system	20	0.04 (0.007-0.26)
Hodgkin lymphoma	49	0.15 (0.02-0.90)
Other cancers	33	0.04 (0.01-0.30)
		$P^b = 0.72$
Chemotherapy ^c		
No	35	0.08 (0.03-0.25)
Yes	110	0.05 (0.02-0.14)
		$P^b = 0.48$
Pituitary dose (Gy) (mean)		
<1 (0.22)	60	0.11 (0.04-0.31)
1-<10 (2.6)	37	0.10 (0.04-0.26)
10-<30 (20.4)	36	0.06 (0.02-0.20)
30 (44.1)	15	0.04 (0.01-0.19)
		$P^b = 0.62$
		$P^c = 0.18$

Abbreviations: CI=confidence interval; ERR=excess rate ratio (excess relative risk)

^aModel for radiation dose-response: $1 + \beta_1 d$; Baseline adjusted for sex, attained age, type of cancer and calendar year of follow-up. For modifiers, β_d was replaced by $(\sum_j \beta_j Z_{jd})$ where z_j was a zero/one indicator variable for the j_{th} category and β_j represented the linear parameter within the j_{th} category.

^bP-value for likelihood ratio test of homogeneity of risk across categories.

^cP-value for trend

Table 4.

Prevalence odds ratios for hyperthyroidism at five years after diagnosis of childhood cancer, by radiation dose to the thyroid gland in the Childhood Cancer Survivor Study cohort.

Radiation dose to thyroid, Gy (mean)	Cases	OR (95% CI) ^a
< 2 (0.32)	9	1.0
2-<30 (15.5)	9	3.5 (1.3-9.4)
30 (40.8)	13	5.9 (1.6-22.6)
		P ^b =0.01
		P ^c <0.01
EOR/Gy=0.24 (95% CI: 0.06-0.95)		

Abbreviations: CI=confidence interval; EOR=excess odds ratio; OR=odds ratio

^aORs computed using binary outcome regression, adjusting for sex, attained age, type of first cancer, and calendar year of follow-up.

^bP-value for likelihood ratio test of homogeneity across categories.

^cP-value for trend