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Source: Radiation Research, 190(2):117-132.
Published By: Radiation Research Society
https://doi.org/10.1667/RR14888.1
URL: http://www.bioone.org/doi/full/10.1667/RR14888.1

RADIATION RESEARCH **190**, 117–132 (2018)
0033-7587/18 $15.00

DOI: 10.1667/RR14888.1

Hypothyroidism after Radiation Therapy for Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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Inskip, P. D., Veiga, L. H. S., Brenner, A. V., Sigurdson, A. J., Ostroumova, E., Chow, E. J., Stovall, M., Smith, S. A., Weathers, R. E., Leisenring, W., Robison, L. L., Armstrong, G. T., Sklar, C. A. and Lubin, J. H. Hypothyroidism after Radiation Therapy for Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *Radiat. Res.* 190, 117–132 (2018).

While thyroid cancer risks from exposure to ionizing radiation early in life are well characterized quantitatively, the association of radiation with nonmalignant, functional thyroid disorders has been less studied. Here, we report on a risk analysis study of hypothyroidism with radiation dose to the thyroid gland and the hypothalamic-pituitary axis among survivors of childhood cancer. Utilizing data from the Childhood Cancer Survivor Study, a cohort of 14,364 five-year survivors of childhood cancer diagnosed at 26 hospitals in the U.S. and Canada between 1970 and 1986 and followed through 2009, the occurrence of hypothyroidism was ascertained among 12,015 survivors through serial questionnaires. Radiation doses to the thyroid gland and pituitary gland were estimated from radiotherapy records. Binary outcome regression was used to estimate prevalence odds ratios for hypothyroidism at five years from diagnosis of childhood cancer and Poisson regression to model incidence rate ratios (RR) after the first five years. A total of 1,193 cases of hypothyroidism were observed, 777 (65%) of which occurred five or more years after cancer diagnosis. The cumulative proportion affected with hypothyroidism (prevalence at five years after cancer diagnosis plus incidence through 30 years after cancer diagnosis) was highest among five-year survivors of Hodgkin lymphoma (32.3%; 95% CI: 29.5–34.9) and cancers of the central nervous system (17.7%; 95% CI: 15.2–20.4). The incidence rate was significantly associated with radiation dose to the thyroid and pituitary. The joint association of hypothyroidism with thyroid and pituitary dose was sub-additive for pituitary doses greater than 16 Gy. In particular, a very strong thyroid radiation dose dependence at low-to-moderate pituitary/hypothalamic doses was diminished at high pituitary doses. Radiation-related risks were higher in males than females and inversely associated with age at exposure and time since exposure but remained elevated more than 25 years after exposure. Our findings indicated that hypothyroidism was significantly associated with treatment with bleomycin (RR = 3.4; 95% CI: 1.6–7.3) and the alkylating agents cyclohexyl-chloroethyl-nitrosourea (CCNU) (RR = 3.0; 95% CI: 1.5–5.3) and cyclophosphamide (RR = 1.3; 95% CI: 1.0–1.8), with a significant dose response for CCNU ($P < 0.01$). The risk of hypothyroidism among childhood cancer survivors treated with radiation depends both on direct, dose-dependent radiation-induced damage to the thyroid gland and on dose-dependent indirect effects secondary to irradiation of the hypothalamic-pituitary axis. The dose-response relationship for each site depends on dose to the other. Radiation-related risk persists for more than 25 years after treatment. Treatment with certain chemotherapy agents may increase the risk of hypothyroidism.

INTRODUCTION

The thyroid gland is a well-established radiosensitive site, particularly after radiation exposures occurring early in life (*1, 2*). Exposure to therapeutic doses of radiation during childhood has been linked to increased risks of subsequent thyroid cancer as well as benign disorders of the thyroid gland, including hypothyroidism, thyroid nodules and, less consistently, hyperthyroidism (*3–10*). Relative to thyroid cancer, the effects from irradiation during childhood on the occurrence of benign thyroid disorders have been much less studied. While there is evidence that radiation at moderate-

Editor's note. The online version of this article (DOI: 10.1667/RR14888.1) contains supplementary information that is available to all authorized users.

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to-high doses is associated with increased risk of benign thyroid conditions, the dose-response relationships for specific conditions and the factors that modify the dose-response relationships remain poorly understood (*7*). The most common of these benign disorders is hypothyroidism.

A complicating factor in quantifying radiation-related risks of hypothyroidism is that radiation effects can, potentially, be mediated through effects on the hypothalamus and anterior pituitary gland as well as the thyroid gland. Thyroid-releasing hormone (TRH) secreted by the hypothalamus promotes secretion of thyroid-stimulating hormone (TSH) by the pituitary gland, which, in turn, stimulates secretion of the hormones triiodothyronine (T3) and thyroxine (T4) by the thyroid; serum T3 and T4 levels, in turn, exert negative feedback on the hypothalamus (*11, 12*). Disruption of any of the links in this loop can lead to thyroid dysfunction (*11, 12*). For example, radiation-related hypothyroidism can develop as a result of direct damage to the thyroid gland (primary hypothyroidism) as well as by damage to the hypothalamic-pituitary axis (central or secondary hypothyroidism) (*11, 12*). While previously published studies have described the occurrence of hypothyroidism (*5, 6, 13*) and TSH deficiency (*14, 15*) after radiotherapy among childhood cancer survivors, none, to our knowledge, have addressed the joint radiation dose dependence of the thyroid gland and hypothalamic-axis in any detail.

In the current study, we evaluated the risk of self-reported hypothyroidism in relationship to radiation dose to the thyroid gland and hypothalamic-pituitary axis and the possible importance of other factors, including age at radiation exposure, time since exposure, sex, chemotherapy and type of childhood cancer, in a large cohort of childhood cancer survivors. The inclusion of different types of childhood cancer increases the range of thyroid and hypothalamic/pituitary radiation doses, which enables analysis of the specific contributions to risk from dose to the thyroid gland and to the hypothalamic-pituitary axis.

METHODS

Study Population

The Childhood Cancer Survivor Study (CCSS) is a cohort study of survivors of childhood cancer treated at 26 institutions in the U.S. and Canada. Eligibility criteria included a diagnosis of leukemia, central nervous system (CNS) cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), neuroblastoma, kidney cancer (Wilms tumor), soft tissue sarcoma or bone sarcoma, diagnosis and treatment of cancer between 1970 and 1986, age at cancer diagnosis less than 21 years and minimum survival of five years after diagnosis (*16, 17*). The study was approved by institutional review boards at each participating hospital. Informed consent was obtained directly from study participants age 18 years or older at time of contact and from parents for those younger than 18 years and those who had died or were too ill to participate directly. Of 20,276 potentially eligible survivors, 14,364 were located and agreed to participate in the study. Details about the CCSS study design and cohort characteristics have been described elsewhere (*16, 17*) and also are available online at https://ccss.stjude.org.

We excluded patients who had not signed medical release forms allowing for review and abstraction of cancer treatment information (n = 1,608), had not completed a baseline or 2007 follow-up questionnaire (n = 3), had reported thyroid gland removal before the cancer treatment (n = 17) or had missing or incomplete radiation treatment information (n = 487). We excluded an additional 234 survivors who reported hypothyroidism before the cancer diagnosis (n = 73) or who did not report age at diagnosis of hypothyroidism (n = 161). These exclusions resulted in 12,015 eligible persons. For incidence rate analyses only, we excluded an additional 416 persons who reported hypothyroidism within the first five years of cancer treatment and 96 who reported thyroid removal or hyperthyroidism within the first five years, leaving 11,503 persons and 777 hypothyroidism cases for incidence rate analysis.

Collection of Treatment, Outcome and Covariate Information

Medical records at hospitals where participants were treated for their initial cancer were reviewed by trained abstractors according to a standardized protocol. Data concerning start and stop dates of drug administration were abstracted for all chemotherapy drugs, and information about dose (mg/m^2) and route of administration was abstracted for 22 agents. Radiotherapy records were photocopied and sent to collaborating medical physicists for use in radiation dosimetry, as described below. Abstract forms are available at https://ccss.stjude.org.

Study participants were asked to complete a baseline questionnaire and follow-up resurveys (every 2–3 years), including a 2007 questionnaire containing questions similar to those administered at baseline (time at entry into the cohort). Data used in the current analysis were taken from the baseline and 2007 questionnaires, which were completed between 1992–2003 and 2007–2009, respectively. From the two questionnaires, information on a variety of health-related outcomes and practices was obtained, including physician-diagnosed thyroid disorders, prescription thyroid medication use, thyroid surgery and new primary cancers. As for hypothyroidism, questions included ''Have you ever been told by a doctor or other health care professional that you have or have had an underactive thyroid gland (hypothyroid)?'' and, ''If yes, age at first occurrence.'' Questions about hyperthyroidism were also addressed in a similar manner. Also collected from the questionnaires was information about thyroid medications ''taken consistently for more than one month or for a total of 30 days in one year'' during the two-year window prior to mailing of the questionnaire. The baseline and 2007 questionnaires are available at: https://ccss.stjude.org. Of 12,015 survivors who completed the baseline questionnaire, 7,836 (65%) also completed the 2007 questionnaire.

Radiation Treatments and Dosimetry

Nearly all radiation treatments involved exclusively external-beam high-energy photons administered in a standardized fractionation regimen.

Methods for radiation dose reconstruction have been described in detail elsewhere (*18*) and are summarized here. Radiation therapy records were reviewed at the CCSS Radiation Physics Center at The University of Texas MD Anderson Cancer Center (Houston, TX). Each patient's record was abstracted for date of radiotherapy, radiation field location, delivered dose, energy, configuration, field size, blocking and anatomic borders. For this study, doses from radiation treatments given within 10 years after the cancer were included. Doses to the thyroid gland and pituitary gland were estimated for each individual using a mathematical phantom and adjusting for the ages of patients at the time of first cancer treatment (*18*). Dose estimations accounted for typical beam blocking. Thyroid dose was estimated for each lobe of the gland, and these doses were averaged to provide a single dose for analysis. Given the close anatomic proximity of the pituitary gland and the hypothalamus, we assume that the estimated dose to the pituitary gland represents dose to the hypothalamic-

pituitary axis and use ''pituitary dose'' as shorthand for dose to both the pituitary and hypothalamus, with the caveat that doses to the pituitary and hypothalamus could differ for some patients with partial brain irradiation, such as CNS cancer patients.

Statistical Analysis

Prevalence. All CCSS cohort participants, by definition, had survived at least five years after childhood cancer diagnosis. Information about health outcomes, including hypothyroidism, was not collected for cancer patients who did not survive at least five years. Because hypothyroidism occurred frequently within the first few years after therapy, we computed the prevalence of hypothyroidism at five years after cancer diagnosis to compare with the more detailed incidence rate analysis. We computed prevalence odds ratios (ORs) using unconditional binary regression models with an additive adjustment for radiation dose and chemotherapy [see Eq. (1)] and baseline adjusted for sex, attained age and type of cancer. All parameter estimates, likelihood ratio tests (LRTs), and likelihood-based 95% confidence intervals (CIs) were computed using the GMBO module of the EPICURE statistical program (Risk Sciences International, Ottawa, Canada).

Follow-up. Follow-up for incidence rate analyses began five years after the date of childhood cancer diagnosis and was truncated at the earliest of the following events: 1. diagnosis of hypothyroidism or hyperthyroidism; 2. thyroid removal; 3. diagnosis of second cancer (exclusive of non-melanoma skin cancer); 4. death; or 5. last contact.

Incidence rate. Case counts and person-years (PYR) of follow-up were summarized in a multidimensional cross-tabulation based on categorized demographic, diagnostic and treatment-related variables. These included categories of sex, age at childhood cancer diagnosis (<1, 1–<5, 5–<10, 10–< 15, 15–<21 years), attained age (<20, 20–<25, 25–<30, …, 50–<55, ≥55 years), type of childhood cancer (leukemia, CNS cancer, HL, NHL, kidney cancer, neuroblastoma, soft tissue sarcoma, bone sarcoma), calendar year of follow-up (<1980, 1980–<1985, 1985–<1990, …, 2000–<2005, ≥2005), time since cancer diagnosis (5–<6, 6–<7, 7–<8, 8–<9, 9–<10, 10–<15, 15–<20, 20–<25, 25–<30, 30–<35, ≥35 years), thyroid and pituitary gland radiation dose (0, >0–<0.2, 0.2–<0.3, 0.3–<0.4, 0.4–<0.5, 0.5–<1.0, 1.0–<2.0, 2.0–<3.0, 3.0–<4.0, 4.0–<10.0, 10.0–<15.0, 15.0–< 20.0, 20.0–<25.0, …, ≥60 Gy), chemotherapy (yes/no/unknown) and variables (yes/no/unknown) for treatment with various classes of chemotherapeutic agents (alkylating agents, anthracyclines, bleomycin, epipodophyllotoxins, platinum-based compounds), as well as specific alkylating agents [cyclohexyl-chloroethyl-nitrosourea (CCNU); bis-chloroethyl-nitrosourea (BCNU), cyclophosphamide, mechlorethamine, procarbazine, melphalan and triethylenethiophosphoramide (Thiotepa)] plus categories based on tertiles of dose for selected alkylating agents. The DATAB module of EPICURE was used to construct the events/person-years tables.

Risk models. We modeled the incidence rate for hypothyroidism, $r(x,d_t,d_p,c)$, as a function of a vector of explanatory variables (x), which included sex, attained age, calendar year of follow-up and type of cancer, thyroid radiation dose (d_t), pituitary radiation dose (d_p) and chemotherapy exposure (c, 1 if yes and 0 if no). The model form was $r(x,d_t,d_p,c) = r_0(x) \times RR(d_t,d_p,c)$, where $r_0(x) = \exp(\alpha x)$ was the rate of hypothyroidism among non-radiation, non-chemotherapy exposed individuals with α a vector of parameters, and RR(.) was the relative risk for the joint association of radiation exposures and chemotherapy.

Preliminary analysis based on the Akaike Information Criterion (AIC) revealed that an additive RR model was the preferred form for radiation doses and chemotherapy. For I categories of thyroid radiation dose, denoted $d_{t,1}, \ldots, d_{t,I}$, where $d_{t,i}$, is zero/one indicator variable for thyroid dose in the ith category, and J categories of pituitary radiation dose, denoted $d_{p,1}, \ldots, d_{p,J}$, where $d_{p,j}$ is zero/one indicator variable for pituitary dose in the jth category, we fitted the additive model:

$$RR(d_t,d_p,c) = 1 + \left(e^{\sum_i \phi_{t,i} d_{t,i}} - 1\right) + \left(e^{\sum_j \phi_{p,j} d_{p,j}} - 1\right) + \theta c$$
$$= e^{\sum_i \phi_{t,i} d_{t,i}} + e^{\sum_j \phi_{p,j} d_{p,j}} - 1 + \theta c,$$

where $\exp(\varphi_{t,i})$ and $\exp(\varphi_{p,j})$ were RRs for the ith and jth categories of thyroid and pituitary radiation doses, respectively, with $\varphi_{t,1} = \varphi_{p,1} = 0$ for identifiability, and θ was the excess relative risk (ERR) of chemotherapy.

For continuous radiation doses, we used the general form, $RR(d_t,d_p,c) = 1 + K(d_t,d_p) + G_p(d_p) + \theta c$, where K(.) and G(.) were the radiation-associated ERRs. For K(.), we considered cross-product terms of d_t and d_p, their exponentials and logarithms. Using AIC, deviances (a measure of model fit) and likelihood ratio tests, we developed the following preferred model:

$$RR(d_t,d_p,c) = 1 + G_t(d_t) \times H(d_p) + G_p(d_p) + \theta c, \qquad (1)$$

where:

$$G_t(d_t) = \beta_t d_t e^{\gamma_1 d_t + \gamma_2 d_t^2};$$

$$G_p(d_p) = \beta_p d_p e^{\phi d_p};$$

and

$$H(d_p) = e^{\gamma_3 d_p + \gamma_4 \ln(d_p)}.$$

The ERR for thyroid radiation dose, $G_t(d_t)$ had a linear-exponential (linear-quadratic) form, while the ERR for the pituitary radiation dose, $G_p(d_p)$, had a linear-exponential(linear) form. The factor, $H(d_p)$, described departures from an additive joint association for the thyroid and pituitary radiation doses. As a function of d_p, H(.) designated a sub-additive, additive or supra-additive relationship depending on its value being less than, equal to, or greater than one, respectively.

We extended Eq. (1) to evaluate a categorical effect modifier z with J levels by replacing β_t with $\beta_t \exp\{\Sigma_j \delta_{t,j} z_j\}$ and β_p with $\beta_p \exp\{\Sigma_j \delta_{p,j} z_j\}$, where z_j, $j = 1, \ldots, J$ was an indicator variable and $\exp(\delta_{t,j})$ and $\exp(\delta_{p,j})$ represented the relative changes in the linear slope parameters for the jth category in relationship to level 1, where $\delta_{t,1} = 0$ and $\delta_{p,1} = 0$ for identifiability. We used a likelihood ratio test to evaluate sex, age at radiation exposure, attained age, time since exposure, type of cancer and use of chemotherapy as potential effect modifiers of the dose effects. We initially included 2×(J-1) distinct $\delta_{t,j}$ and $\delta_{p,j}$ parameters; however, analyses revealed that, with the exception of CCNU (see below), the relative changes in the linear parameters for each level of the modifier were statistically homogeneous for thyroid dose and for pituitary dose, i.e., $\delta_{t,j} = \delta_{p,j}$ for all j. For example, each category of age at exposure had the same relative effect on the linear parameter for thyroid dose β_t and for pituitary dose β_p.

Finally, for comparison with Eq. (1), we also fitted a multiplicative relationship for chemotherapy:

$$RR(d_t,d_p,c) = \{1 + G_t(d_t) \times H(d_p) + G_p(d_p)\} \times \{1 + \theta c\}. \qquad (2)$$

AIC values revealed a slight but consistent preference for the additive form compared to the multiplicative form. Nonetheless, our evaluation of effect modifiers under a multiplicative relationship with chemotherapy resulted in similar statistical inference.

We used the AMFIT module of the EPICURE computer program for all incidence rate analyses, including incidence rate ratio (RR) estimates, LRTs and 95% likelihood-based CIs.

Cumulative proportion affected. We also calculated a measure, ''cumulative proportion affected'', combining prevalence at five years with cumulative incidence thereafter, stratified by sex, type of cancer and radiotherapy (yes/no). This measure was not further adjusted for

TABLE 1
General Characteristics of Study Subjects in the Childhood Cancer Survivor Study Cohort Evaluated for Hypothyroidism

Characteristics	
Number of patients	12,015
Person-years of follow-up[a]	187,449
Average follow-up, years[a]	16.3
Number of hypothyroidism cases	1,193
Number of hypothyroidism cases <5 years of cancer (%)[a]	416 (35)
Number of females (%)	5,662 (47)
Mean dose to thyroid gland, Gy (range)[b]	11.0 (>0–60.4)
Mean dose to pituitary gland, Gy (range)[b]	15.2 (>0–108.7)
Mean age at first radiation exposure, years (range)[b]	8 (0–20)
Mean age at diagnosis of hypothyroidism, years (range)	20 (0–54)
Mean age at end of follow-up, years (range)[a]	22 (5–57)
Type of childhood cancer (%)	
Leukemia	4,110 (34)
Central nervous system cancer	1,516 (13)
Hodgkin lymphoma	1,550 (13)
Non-Hodgkin lymphoma	893 (7)
Kidney cancer (Wilms tumor)	1060 (9)
Neuroblastoma	819 (7)
Soft tissue sarcoma	1,049 (9)
Bone sarcoma	1,018 (8)
Radiotherapy (%)	
No	3,978 (33)
Yes	8,037 (67)
Chemotherapy (%)	
No	2,256 (19)
Yes	9,594 (80)
Missing information	165 (1)
Chemotherapy drugs (%)	
Any alkylating agents	6,347 (53)
Cyclophosphamide	5,390 (45)
Procarbazine	1,163 (10)
CCNU (Lomustine)	438 (4)
Any anthracyclines	4,899 (41)
Any bleomycin	711 (6)
Any platinum-based compounds	726 (6)
Any epipodophyllotoxins	1,124 (9)

[a] For incidence rate analysis, follow-up began five years after diagnosis of the childhood cancer. Some patients exited the cohort before follow-up started, including patients who developed hypothyroidism within the first five years. A total of 512 patients were excluded from the incidence analysis, which was based on 11,503 persons and 777 cases.

[b] Among all patients treated with radiation.

other covariates. We calculated the cumulative incidence of hypothyroidism by time since diagnosis of cancer beginning five years after date of cancer diagnosis (*19, 20*) using Stata version 13.1 (College Station, TX).

RESULTS

Characteristics of the Study Population

General characteristics of survivors are summarized in Table 1. Leukemia was the most common type of cancer, followed by HL and CNS cancer. The average age at diagnosis of the cancer was 8 years, and the average follow-up for incidence rate analyses, beginning five years after childhood cancer diagnosis, was 16.3 years. Follow-up was shortest for survivors of HL and longest for survivors of kidney cancer (Table 2). Two-thirds of the population were treated with radiation and, among irradiated five-year survivors, the average dose was 11.0 Gy to the thyroid gland and 15.2 Gy to the pituitary gland. Eighty percent of survivors received chemotherapy, which most often involved alkylating agents, anthracyclines or both. Among persons included in the incidence rate analysis, 86% were still alive at the end of follow-up, and, among survivors, the mean age at the end of follow-up was 22 years (maximum, 57 years). There were 1,193 cases of hypothyroidism, 416 (34.9%) of which were diagnosed within five years after the diagnosis of childhood cancer (prevalence at five years = 3.5%). Among these 416 cases, the median interval from diagnosis of cancer to diagnosis of hypothyroidism was two years. Based on the same questionnaires used to ascertain cases of hypothyroidism, there were 179 self-reported cases

TABLE 2
Proportion (%) of Five-Year Childhood Cancer Survivors Given Radiotherapy, Mean and Median Thyroid and Pituitary Gland Doses, Age at First Radiation Treatment and Follow-up Information According to Type of Childhood Cancer: Childhood Cancer Survivor Study

		Thyroid dose[a] (Gy)		Pituitary dose[a] (Gy)		Age at first radiation treatment[b] (years)	Age at diagnosis of hypothyroidism (years)	Time to diagnosis of hypothyroidism[c] (years)	Time to end of follow-up[c] (years)
Childhood cancer type	Radiotherapy (%)	Mean	Median (IQR)	Mean	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Leukemia	69	3.9	0.8 (0.6–1.5)	20.8	21.2 (16.8–23.4)	5 (3–9)	19 (13–28)	13.4 (7.9–20.9)	17.7 (8.6–22.5)
Central nervous system	70	10.9	1.7 (0.7–25.2)	37.6	41.3 (30.2–50.4)	7 (3–12)	12 (8–17)	5.5 (1.8–10.3)	16.1 (7.0–21.0)
Hodgkin lymphoma	94	34.8	38.0 (26.9–43.6)	3.5	1.3 (0.9–1.7)	15 (12–17)	22 (17–31)	6.4 (1.5–14.6)	14.5 (7.3–20.8)
Non-Hodgkin lymphoma	68	11.0	1.9 (0.4–20.3)	11.0	1.1 (0.1–24.0)	10 (6–14)	18 (14–29)	9.6 (3.2–18.5)	18.1 (11.3–23.6)
Kidney (Wilms)	64	1.5	0.3 (0.1–0.7)	0.2	0.1 (0.1–0.2)	3 (2–5)	21 (17–28)	16.9 (14.1–21.5)	18.9 (11.2–23.6)
Neuroblastoma	49	5.0	0.6 (0.2–5.8)	3.9	0.2 (0.1–0.6)	1 (0.6–2)	15 (9–23)	13.4 (7.7–21.9)	18.2 (10.6–23.4)
Soft tissue sarcoma	62	6.4	0.5 (0.1–3.3)	14.4	0.5 (0.1–30.5)	7 (3–13)	17 (10–28)	10.6 (3.6–15.8)	18.2 (10.2–23.7)
Bone sarcoma	36	3.8	0.7 (0.1–3.8)	3.4	0.1 (0.02–0.33)	13 (10–16)	30 (23–37)	14.7 (7.5–24.3)	17.8 (9.2–23.2)
All cancers	67	11.0	1.1 (0.5–20.4)	15.2	16.1 (0.5–23.4)	7 (3–13)	19 (13–28)	8.7 (2.9–16.4)	17.5 (8.8–22.7)

Note. IQR = interquartile range.
[a] Among patients treated with radiation.
[b] Age at first radiation treatment is nearly equal to age at diagnosis of the cancer.
[c] Beginning with date of cancer diagnosis. Includes prevalent and incident cases.

of hyperthyroidism, 31 (17.3%) of which were diagnosed within five years after the diagnosis of cancer.

Frequency of use of radiotherapy and radiation doses to the thyroid and pituitary glands varied widely by cancer type (Table 2). Radiation was used for 94% of HL survivors compared to 36% of bone cancer survivors. The median dose to the thyroid gland for HL survivors was 38 Gy, which dwarfed median thyroid doses associated with other types of cancer, although some CNS cancer and NHL survivors also received very high doses. In contrast, the median dose to the pituitary gland was highest among survivors of CNS cancer and leukemia, with some soft tissue sarcoma and NHL survivors also receiving very high doses. Leukemia and bone and soft tissue sarcoma survivors accounted for 59% of the nonirradiated group (data not shown). The median age at irradiation was youngest for survivors of neuroblastoma and kidney cancer and oldest for survivors of HL and bone cancer. The shortest median intervals from diagnosis of cancer to diagnosis of hypothyroidism were seen among survivors of CNS cancer and HL.

Incidence Rate with Respect to Patient Characteristics

Poisson regression analysis of the incidence rate of hypothyroidism beginning five years after diagnosis of childhood cancer showed the highest RRs among survivors of CNS cancer or HL (Table 3). Homogeneity of RRs by age at diagnosis of the cancer was rejected, but there was no clear trend. Incidence was significantly higher among females than males, decreased slightly for $\geq$15 years since cancer diagnosis and increased with calendar year of follow-up. There was no trend with attained age. Incidence was 2.9-fold among persons who received radiation relative to those who did not ($P < 0.01$) and 2.3-fold among those who received chemotherapy relative to those who did not ($P = 0.05$).

Cumulative Proportion Affected

Combining prevalent and incident cases through 30 years after the cancer diagnosis, the cumulative percentage of patients with hypothyroidism was 11.2% (95% CI: 10.5–11.9). The proportion was 13.8% among females (95% CI: 12.7–14.4) and 8.9% among males (95% CI: 8.1–9.7). The cumulative percentage was 32.3% for HL (95% CI: 29.5–34.9), 17.7% for CNS cancer (95% CI: 15.2–20.4), 9.2% for NHL (95% CI: 7.1–11.7), 7.3% for leukemia (95% CI: 6.2–8.3) and 5.1% for all other cancers combined (95% CI: 3.5–6.9). It was 14.5% among those who received radiotherapy (95% CI: 13.6–15.4) compared to 4.6% among those who did not (95% CI: 3.7–5.6).

Incidence Rate by Type of Chemotherapy

The chemotherapy-associated risk was greatest among CNS cancer survivors (incidence RR = 6.7; 95% CI: 3.0–14.8) (Table 4). Although homogeneity was not rejected across all types of cancer ($P = 0.14$), homogeneity was rejected for chemotherapy-associated risk with CNS cancer

TABLE 3
Relative Risk (Rate Ratio) for Incidence Rate of Hypothyroidism According to Selected Demographic and Clinical Factors in the Childhood Cancer Survivor Study Cohort

Characteristic	Cases	PYR/ 10,000	RR (95% CI)[a]
Type of cancer			
Other cancers	193	8.1	1.0
Leukemia	194	6.5	1.0 (0.5–1.9)
Central nervous system cancer	127	2.0	1.2 (0.8–1.8)
Hodgkin lymphoma	246	1.8	1.5 (1.0–2.2)
			$P^b = 0.29$
Sex			
Male	308	9.7	1.0
Female	452	8.7	1.8 (1.6–2.1)
			$P^b < 0.01$
Time since cancer diagnosis [c]			
5–<6	47	1.1	1.0
6–<10	181	4.3	1.0 (0.7–1.4)
10–<15	202	4.5	1.1 (0.7–1.5)
≥15	330	8.6	0.7 (0.5–1.1)
			$P^b = 0.05$
Attained age, years [c]			
<25	383	11.0	1.0
25–<30	133	3.2	0.8 (0.7–1.0)
30–<35	118	2.2	1.0 (0.8–1.2)
35–<40	66	1.3	0.9 (0.6–1.2)
≥40	60	0.8	1.1 (0.8–1.6)
			$P^b = 0.25$
Calendar year of follow-up [c]			
<1,990	198	5.4	1.0
1,990–<2,000	379	8.3	1.6 (1.3–1.9)
2,000–<2,005	98	2.9	1.3 (1.0–1.7)
≥2,005	85	1.9	1.9 (1.4–2.6)
			$P^b < 0.01$
Age at cancer diagnosis, years			
<5	238	7.1	1.0
5–<10	154	4.4	0.9 (0.7–1.1)
10–<15	141	3.6	0.8 (0.6–1.1)
≥15	227	3.3	1.2 (0.8–1.6)
			$P^b = 0.03$
Radiation treatment			
No	117	6.7	1.0
Yes	643	11.8	2.9 (2.1–4.0)
			$P^b < 0.01$
Any chemotherapy			
No	190	3.5	1.0
Yes	570	14.9	2.3 (1.1–4.7)
			$P^b = 0.05$

[a] Relative risks (RR)s adjusted for an additive association for categories of the cross-tabulation of radiation dose to the thyroid and pituitary, with dose categories as in Table 5, and categories of exposure to chemotherapy and type of cancer (leukemia, central nervous system cancer, Hodgkin lymphoma and other cancers). Type of first cancer included to account for possible differential surveillance and shared predisposition. Baseline adjusted for sex, attained age, type of cancer and calendar year of follow-up. Analysis excluded patients with missing information for pituitary radiation dose and chemotherapy (177 patients, including 17 cases).

[b] *P* value for likelihood ratio test of homogeneity of risk across categories.

[c] Person-years (PYR) are distributed across categories as time passes and person ages; that is, PYR, rather than persons, are classified.

compared with all other cancers ($P = 0.03$). Significant positive associations were seen for alkylating agents as a group and bleomycin, with a borderline significant association for epipodophyllotoxins. Among alkylating agents, we observed significant positive associations for CCNU and cyclophosphamide, with a significant dose response for CCNU but not cyclophosphamide. The RR for CCNU was elevated among survivors of CNS cancer (RR = 3.6; 95% CI: 1.2–7.1) and survivors of other cancers (RR = 2.6; 95% CI: 0.8–5.6). CCNU was used to treat 16.2% of CNS cancer patients, 9.7% of HL patients and 3.4% of NHL patients. Associations with CCNU and cyclophosphamide persisted when the analysis was restricted to patients with pituitary radiation doses <1 Gy, whereas that for bleomycin was attenuated (Supplementary Table S1; http://dx.doi.org/10.1667/RR14888.1.S1). Bleomycin was used most commonly in the treatment of bone cancer (25.4%) and HL (22.6%). Cyclophosphamide was widely used for all types of cancer other than CNS and kidney cancer (data not shown).

Radiation Dose Response

The joint thyroid and pituitary radiation dose response for incidence of hypothyroidism is summarized in Table 5 and Fig. 1. For pituitary doses <35 Gy, there was a strongly increasing thyroid dose response, while, at very high pituitary doses (>40–45 Gy), RRs for thyroid dose flattened. There was a significantly positive pituitary dose response for thyroid doses <10 Gy but, this association was attenuated at higher thyroid doses. The joint thyroid and pituitary radiation dose-response model included a linear-exponential(linear-quadratic) term in thyroid dose (d_t), linear-exponential (linear) term in pituitary dose (d_p) and a multiplicative factor [$H(d_p)$] accounting for pituitary dose-dependent departure from an additive joint association [Eq. (1)]. The analysis of the joint effects indicated a significant departure from an additive model ($P = 0.01$), with sub-additive effects at pituitary doses above approximately 16 Gy (Fig. 2). This crossover dose to sub-additivity of effects was estimated with considerable uncertainty and partially the consequence of the form of the interaction model.

For prevalent hypothyroidism at five years after cancer diagnosis, the fitted model for the joint thyroid and pituitary dose response was qualitatively similar to the incidence model; that is, the OR increased with thyroid dose at low-to-moderate pituitary doses and with pituitary dose at low thyroid doses, with sub-additivity at high pituitary doses (Fig. 3 and Supplementary Table S2; http://dx.doi.org/10.1667/RR14888.1.S1). The departure from additivity [i.e., $H(d_p) = 1$ in Eq. (1)] was statistically significant ($P = 0.05$). Prevalence ORs generally were higher than incidence RRs and estimated with less precision. Parameter estimates for fitted incidence and prevalence dose-response models are given in Supplementary Table S3 (http://dx.doi.org/10.1667/RR14888.1.S1).

TABLE 4
Relative Risk (Rate Ratio) for Incidence Rate of Hypothyroidism According to Type of Treatment with Chemotherapy Agents in the Childhood Cancer Survivor Study Cohort

Characteristic	Cases	PYR/ 10,000	RR (95% CI)[a]
Any chemo and childhood cancer type			
No chemotherapy[b]	190	3.5	1.0
Any chemo and leukemia	193	6.5	1.1 (0.2–7.1)
Any chemo and CNS cancer	58	0.4	6.7 (3.0–14.8)
Any chemo and HL	148	1.2	0.8 (0.0–20.4)
Any chemo and other cancers	171	6.7	1.8 (0.7–4.5)
			$P^c = 0.14$
Any alkylating agents			
No	326	9.2	1.0
Yes	433	9.2	1.8 (1.1–3.0)
			$P^c = 0.04$
Any anthracyclines			
No	522	11.3	1
Yes	237	7.1	1.1 (0.6–2.1)
			$P^c = 0.85$
Any bleomycin			
No	690	17.6	1
Yes	69	0.8	3.4 (1.6–7.3)
			$P^c = 0.03$
Any platinum-based compounds			
No	725	17.7	1
Yes	34	0.7	1.1 (0.3–4.8)
			$P^c = 0.88$
Any epipodophyllotoxins			
No	696	17.2	1
Yes	63	1.3	1.5 (1.0–2.3)
			$P^c = 0.08$
Alkylating agents			
CCNU (Lomustine)			
No	704	18.0	1.0
Yes	55	0.4	3.0 (1.5–5.3)
			$P^c < 0.01$
CCNU, mg/m^2			
0	704	18.0	1.0
>0–<411.18	13	0.1	1.0 (0.1–7.4)
411.18–<800.0	23	0.1	5.0 (2.5–9.9)
>800.0	12	0.04	8.2 (3.6–18.9)
			$P^c < 0.01$
Alkylating agents (cont'd)			
CCNU and cancer type			
No CCNU	704	18.0	1.0
CCNU and CNS cancer	35	0.2	3.6 (1.2–7.1)
CCNU and other cancers	20	0.2	2.6 (0.8–5.6)
			$P^c = 0.03$
BCNU (Carmustine)			
No	729	17.7	1.0
Yes	30	0.7	1.1 (0.5–2.0)
			$P^c > 0.50$
Cyclophosphamide			
No	450	10.3	1.0
Yes	309	8.1	1.3 (1.0–1.8)
			$P^c = 0.05$
Cyclophosphamide, mg/m^2			
0	450	10.4	1.0
>0–<5,323.1	120	3.0	1.3 (0.9–1.9)
5,323.1–<11,448.3	89	2.4	1.3 (0.9–1.9)
>11,448.3	74	2.1	1.3 (0.9–2.1)
			$P^c = 0.36$
Procarbazine			
No	598	17.1	1.0
Yes	161	1.3	1.0 (0.4–2.3)
			$P^c > 0.50$
Mechlorethamine			
No	668	17.6	1.0
Yes	91	0.9	0.7
			$P^c > 0.50$
Melphalan			
No	745	18.2	1.0
Yes	14	0.2	2.2 (0.7–5.2)
			$P^c = 0.16$
Thiotepa			
No	747	18.4	1.0
Yes	12	0.05	5.7 (0.2–15.2)
			$P^c = 0.14$

Notes. BCNU = bis-chloroethyl-nitrosourea; CCNU = cyclohexyl-chloroethyl-nitrosourea; Chemo = chemotherapy; CI = confidence interval; CNS = central nervous system; HL = Hodgkin lymphoma; PYR = person-years; RR = relative risk (rate ratio); Thiotepa = triethylenethiophosphoramide.

[a] RRs adjusted for an additive association for categories of the cross-tabulation of radiation dose to the thyroid and pituitary, with dose categories as in Table 5, and categories of exposure to classes of chemotherapy agents or chemotherapy drugs/doses. Baseline was adjusted for sex, attained age, type of cancer and calendar year of follow-up. Type of first cancer included to account for possible differential surveillance and shared predisposition. Patients with missing pituitary dose and missing information on the specific class of chemotherapy agent or chemotherapy drugs/doses were excluded from this analysis.

[b] Number of cases who did not receive chemotherapy, by cancer type: leukemia = 1; CNS = 69; HL = 98; others = 22.

[c] Likelihood ratio test of homogeneity of risk across categories.

Proportions of Radiotherapy- and Chemotherapy-Associated Hypothyroidism Cases

Among the 760 observed hypothyroidism cases with information concerning radiotherapy and chemotherapy, the fitted dose-response model estimated that 436.8 (57.5%) were due to radiation treatment, 71.4 (9.4%) were due to chemotherapy and 251.7 (33.1%) were due to causes other than radiation or chemotherapy (background) (Table 6). For the estimated 644.5 irradiated cases (165.7 + 478.8), at very low pituitary doses (<1 Gy), the estimated attributable proportion of radiation-associated cases based on the fitted dose-response model ranged from 10% for thyroid doses <2 Gy to 91% for thyroid doses ≥40 Gy (Supplementary Table S4; http://dx.doi.org/10.1667/RR14888.1.S1). For high pituitary doses (>35 Gy), the attributable proportion was approximately 70% for thyroid doses from <2–40 Gy. For thyroid doses <2 Gy, the proportion increased monotonically with pituitary dose, whereas, for thyroid doses >10 Gy, the proportion of cases attributable to radiation varied little with dose to the pituitary.

TABLE 5
Estimated Incidence Rate Ratio (RR[a]) for Hypothyroidism (95% CI) by Radiation Dose to the Thyroid Gland and Pituitary Gland: Childhood Cancer Survivor Study

	RR (95% CI)				
	Pituitary dose, Gy (mean)				
Thyroid dose, Gy (mean)	0	>0–<1 (0.2)	1–<10 (2.6)	10–<35 (21.0)	≥35 (47.0)
0	1.0[b]	-	-	-	-
>0–<2 (0.6)	-	1.3 (0.8–2.0)	2.6 (1.2–5.5)	1.4 (0.9–1.9)	5.3 (3.3–8.7)
2–<10 (4.8)	-	2.0 (0.9–4.2)	4.2 (1.9–9.3)	2.4 (1.1–5.3)	7.6 (3.9–14.7)
10–<20 (14.7)	-	3.1 (1.5–6.3)	3.9 (1.1–13.5)	3.8 (2.2–6.6)	4.7 (2.2–9.9)
20–<30 (24.1)	-	4.9 (2.8–8.9)	8.8 (4.5–16.9)	6.9 (3.7–12.6)	6.8 (3.8–12.6)
30–<40 (35.5)	-	7.8 (3.9–15.4)	9.0 (5.2–15.8)	10.1 (4.2–24.4)	9.5 (4.9–18.4)
≥40 (45.3)	-	21.0 (8.6–51.5)	12.2 (6.9–21.6)	12.4 (6.2–24.5)	8.0 (3.0–21.6)

Notes. CI = confidence interval; RR = incidence rate ratio.

[a] RRs computed using Poisson regression analysis for a joint thyroid and pituitary dose response. Fitted model includes an additive adjustment for an interaction term of chemotherapy and type of cancer (leukemia, central nervous system cancer, Hodgkin lymphoma and other cancers). Type of first cancer included to account for possible differential surveillance and shared predisposition. Baseline was adjusted for sex, attained age, type of cancer and attained calendar year.

[b] Reference category.

Modifiers of Radiation Dose Effects

We evaluated potential modifiers of the linear coefficient of the thyroid and pituitary dose-response functions and observed homogeneity of the relative changes in linear parameters for the two organs (Table 7, right-side column). Only for CCNU was the test of homogeneity of the relative change in the linear dose coefficient for thyroid dose and

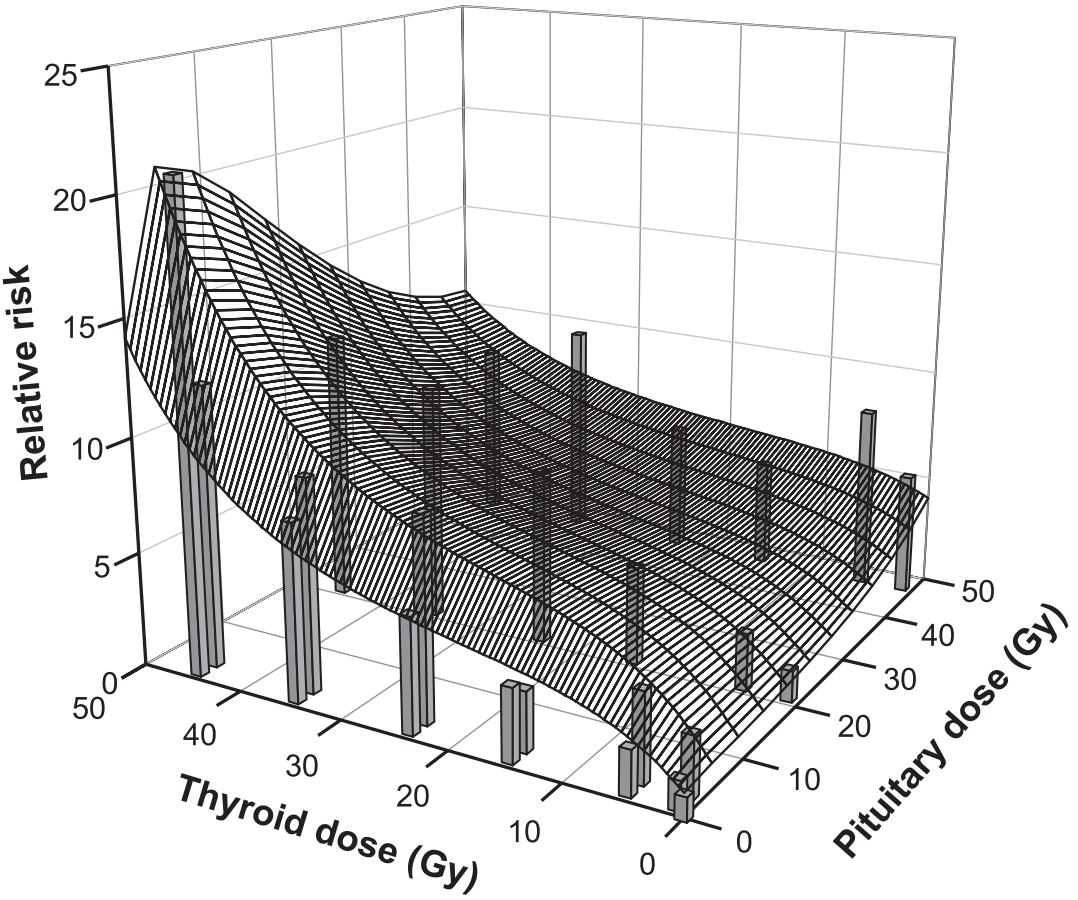

FIG. 1. Fitted joint thyroid and pituitary dose response for incidence rate of hypothyroidism among five-year survivors of childhood cancer [Eq. (1)]: Childhood Cancer Survivor Study. Vertical bars represent observed RRs by categories of radiation dose to the thyroid gland and pituitary gland from Table 5 and are centered at the category-specific, mean thyroid and pituitary doses. Width of bars is arbitrary.

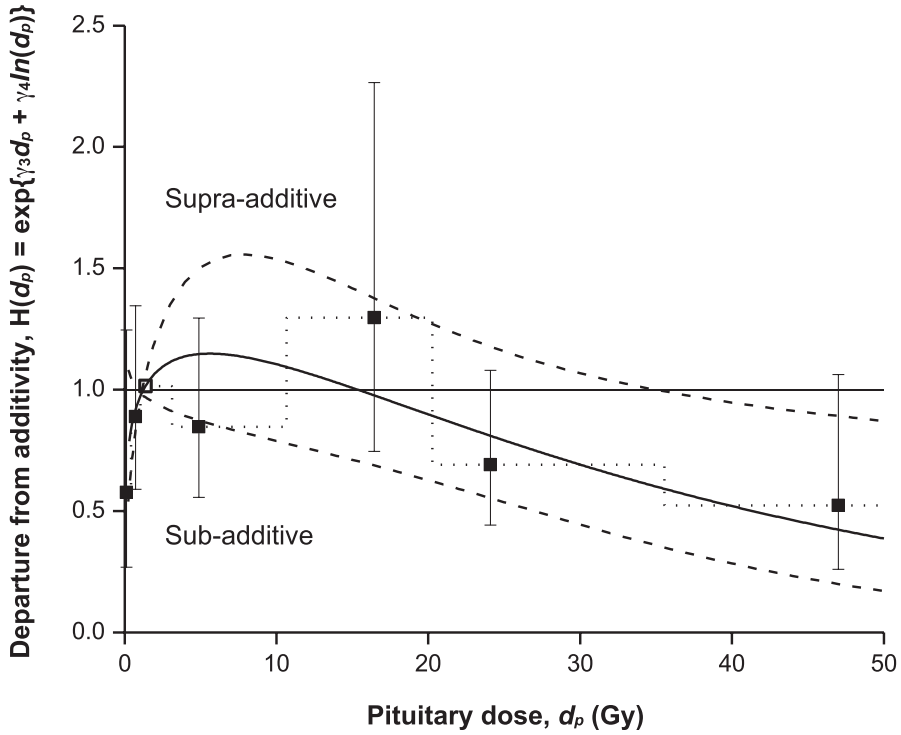

FIG. 2. Departure from additivity (deviation from horizontal line) of joint effects of thyroid dose (d_t) and pituitary dose (d_p) on risk of hypothyroidism as a function of radiation dose to the pituitary gland (solid line) and pointwise 95% CI (dashed line) [Eq. (1)]. Square symbols (and dotted line) with 95% CIs display relative effects for categories of pituitary dose on thyroid radiation dose response. Results suggest a sub-additive effect for pituitary doses $\geq$ approximately 16 Gy.

pituitary dose rejected ($P < 0.01$). The column ''exp(δ_j)'' represents the relative change in the linear slope parameter for the *j*th category relative to the referent category. Main findings were as follows.

1. Dose effects (per Gy) were greater in males than females.
2. There was a significant decrease in radiation-related risk with increasing age at exposure, time since exposure and attained age. When adjusted for time since exposure, attained age was not related significantly to the association between radiation dose and hypothyroidism. Radiation-related risk remained elevated more than 25 years after exposure.
3. Radiation-related risk was not significantly associated with type of cancer or chemotherapy overall; however, it was significantly greater among persons treated with bleomycin.
4. The linear component of the radiation dose-response relationship for the pituitary, but not the thyroid, was significantly increased among persons treated with CCNU. We note, however, that relatively few survivors had been treated with CCNU, and this result is based on 55 exposed hypothyroidism cases.

Although homogeneity of effects for thyroid dose and pituitary dose with respect to time since exposure as an effect modifier was not rejected ($P = 0.41$), we further explored possible differences in latency for presumptive primary versus central hypothyroidism by assuming that most radiation-related cases among survivors with pituitary doses <1 Gy (mean, 0.2 Gy) were primary hypothyroidism and most radiation-related cases among survivors with thyroid doses <2 Gy (mean, 0.6 Gy) were central hypothyroidism and then evaluating temporal trends separately for the two groups (Supplementary Table S5; http://dx.doi.org/10.1667/RR14888.1.S1). We stress that this distinction between radiation-related primary and central hypothyroidism is inferential and not based on hormone measurements and that both groups also include cases due to chemotherapy and background causes. Differences are not striking, though in the direction of (presumptive) radiation-related primary hypothyroidism tending to occur relatively more often within the first 15 years after exposure.

Sensitivity Analysis

Because the diagnosis of hypothyroidism was self-reported, we reanalyzed data under a more stringent definition of outcome, requiring both self-reported hypothyroidism and use of medications specific for hypothyroidism (Supplementary Tables S6 and S7; http://dx.doi.org/10.1667/RR14888.1.S1). When compared with Table 5, the joint thyroid and pituitary radiation dose-response pattern is the same, though with somewhat higher incidence

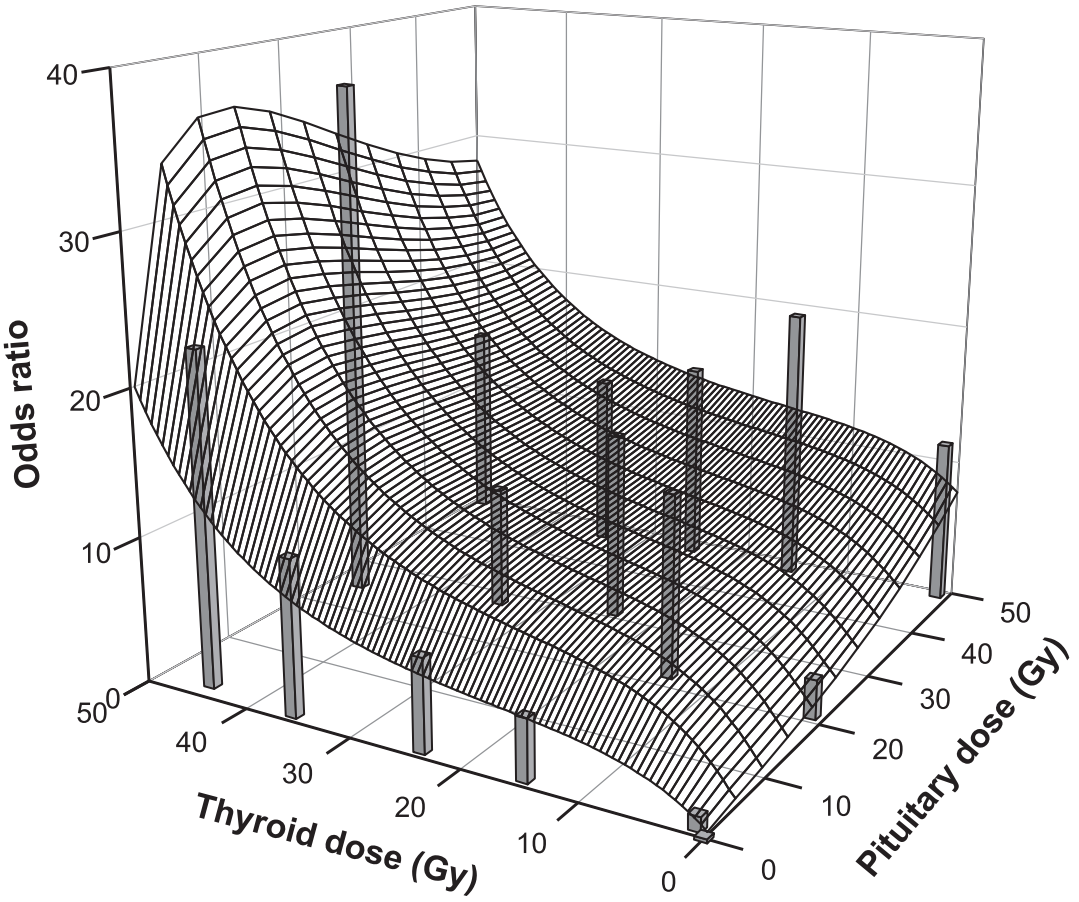

FIG. 3. Fitted joint thyroid and pituitary dose response for prevalence of hypothyroidism five years after cancer diagnosis among five-year survivors of childhood cancer [odds ratio specified with Eq. (1)]: Childhood Cancer Survivor Study. Vertical bars represent observed prevalence odds ratios by categories of radiation dose to the thyroid gland and pituitary gland from Supplementary Table S2 (http://dx.doi.org/10.1667/RR14888.1.S1) and are centered at the category-specific, mean thyroid and pituitary doses. Width of bars is arbitrary.

TABLE 6
Observed and Fitted Numbers of Hypothyroidism Cases among Five-Year Survivors of Childhood Cancer, and Estimated Numbers of Cases due to Background, Radiation Treatment and Chemotherapy, Separately by Type of Cancer Treatment: Childhood Cancer Survivor Study

Treatment		Number of cases		Estimated number of cases[a] due to:			
Chemotherapy	Radiotherapy	Observed	Fitted	Background	Radiotherapy	Chemotherapy	Percentage[b]
No	No	25	24.6	24.6			-
No	Yes	165	165.7	28.6	137.1		82.7%
Yes	No	92	90.9	68.6		22.3	24.5%
Yes	Yes	478	478.8	130.0	299.7	49.1	72.8%
	Total	760	760.0	251.7	436.8	71.4	

[a] Based on fitted joint thyroid and pituitary dose-response model. Fitted model also includes an additive adjustment for an interaction term of chemotherapy and type of cancer (leukemia, central nervous system cancer, Hodgkin lymphoma and other cancers). Type of first cancer included to account for possible differential surveillance and shared predisposition. Baseline was adjusted for sex, attained age, type of cancer and attained calendar year.

[b] Percentage of estimated number of cases divided by total number of fitted cases in given treatment sub-group, including background cases. For example, the estimated percentage of cases attributable to radiation among those treated by radiation only is: $137.1 \div 165.7 = 82.7\%$. The estimated percentage of cases due to radiation and chemotherapy among those treated by both modalities is: $(299.7 + 49.1) \div 478.8 = 72.8\%$.

TABLE 7
Analysis of Effect Modification for the Effects of Thyroid and Pituitary Radiation Doses on the Incidence of Hypothyroidism:[a] Childhood Cancer Survivor Study

Modifier	Cases	PYR/10,000	$\exp(\delta_j)$	P^b	P^c
Time since exposure, years					
<10	228	5.4	1.00[d]	<0.01	0.41
10-14	202	4.5	0.90		
15-19	139	3.7	0.63		
20-24	106	2.8	0.33		
≥25	85	2.1	0.21		
Age at exposure, years					
<5	238	7.1	1.00[d]	0.01	0.16
5-9	154	4.5	0.60		
≥10	368	6.9	0.56		
Attained age, years					
<25	383	11.0	1.00[d]	0.01	0.55
25-29	133	3.2	0.54		
30-39	184	3.4	0.33		
≥40	60	0.8	0.30		
Sex					
Male	308	9.7	1.00[d]	<0.01	0.45
Female	452	8.7	0.41		
Type of cancer [e]					
Other cancers	193	8.1	1.00[d]	0.08	0.53
Leukemia	194	6.5	0.07		
CNS cancer	127	2.0	0.46		
HL	246	1.8	0.33		
Chemotherapy[f]					
No	190	3.5	1.00[d]	0.96	0.18
Yes	570	14.9	0.98		
CCNU					
No	704	18.0	1.00[d]	0.33	<0.01[g]
Yes	55	0.4	1.39[g]		
Cyclophosphamide					
No	450	10.3	1.00[d]	0.88	0.63
Yes	309	8.1	1.01		
Bleomycin					
No	690	17.6	1.00[d]	<0.01	0.12
Yes	69	0.8	1.77		

Notes. CCNU = cyclohexyl-chloroethyl-nitrosourea; CNS = central nervous system; HL = Hodgkin lymphoma; PYR = person-years.

[a] Fitted model takes the form: $RR(d_t,d_p,c) = 1 + G_t(d_t) \times H(d_p) + G_p(d_p) + \theta c$, where $G_t(d_t) = \beta_t d_t e^{\gamma_1 d_t + \gamma_2 d_t^2}$, $G_p(d_p) = \beta_p d_p e^{\varphi d_p}$ and $H(d_p) = e^{\gamma_3 d_p + \gamma_4 \ln(d_p)}$ and where d_t and d_p are radiation dose to thyroid and pituitary, respectively, and c is chemotherapy (yes = 1/no = 0). See Eq. (1) for additional specifications. For effect modification of variable z with J levels, $\beta_t \exp\{\Sigma_j \delta_{t,j} z_j\}$ replaces β_t and $\beta_p \exp\{\Sigma_j \delta_{p,j} z_j\}$ replaces β_p, where z_j, $j = 1, \ldots$, J is an indicator variable and $\exp(\delta_{t,j})$ and $\exp(\delta_{p,j})$ represent the relative changes in the linear slope parameters for the jth category in relationship to level 1, where $\exp\delta_{t,1} = 0$ and $\delta_{p,1} = 0$ for identifiability. Model includes 2×(J-1) distinct $\delta_{t,j}$ and $\delta_{p,j}$ parameters; however, the relative changes across levels of a modifier are statistically homogeneous for thyroid dose and for pituitary dose, i.e., $\delta_{t,j}$ and $\delta_{p,j}$ for all j. Entries are homogeneous relative effect estimates.

[b] P value for test of homogeneity across levels of modifier; $\delta_2 = \cdots = \delta_J = 0$.

[c] P value for test of homogeneity of modifying effects for thyroid radiation dose and pituitary radiation dose, i.e., $\delta_{t,j}, = \delta_{p,j}$ for all j.

[d] Referent category.

[e] Model includes additional terms for the interaction of type of cancer and chemotherapy, θ_k, $k = 1, \ldots, 4$.

[f] Model includes additional terms for the interaction of CNS cancer and chemotherapy, θ_k, $k = 1, 2$.

[g] The relative effects for thyroid dose and pituitary dose differed significantly. Among persons treated with CCNU, $\exp(\delta_j)$ was 4.5 (95% CI: 2.4–8.6) for pituitary dose and 0.82 (95% CI: 0.36–1.9) for thyroid dose relative to those not treated with CCNU. The value of 1.39 is based on a model in which relative effects for thyroid dose and pituitary dose were constrained to be the same.

rate ratios in the higher thyroid dose categories. Most (79%) of the 777 self-reported cases of incident hypothyroidism also reported use of a hypothyroidism medication.

DISCUSSION

In this large cohort of five-year survivors of childhood cancer followed to an average of 21 years after their cancer diagnosis, radiation dose to both the thyroid gland and hypothalamic-pituitary axis emerged as important predictors of the risk of hypothyroidism, reflecting the multilevel regulation of production of thyroid hormones. The thyroid dose-response relationship was contingent on dose to the pituitary and vice-versa,[3] with the thyroid showing greater radiation sensitivity. This complex joint dose-response pattern reflects a combination of primary and central hypothyroidism, with the latter becoming quantitatively important only at very high doses to the pituitary and/or hypothalamus, which occurred most commonly after irradiation for cancer of the CNS (median dose, 41.3 Gy). We estimate that a transition to sub-additivity of effects occurs at a hypothalamic-pituitary dose of approximately 16 Gy, though this value was estimated with substantial uncertainty and partially the consequence of the form of the interaction model. Flattening of the thyroid dose response only becomes readily apparent at hypothalamic-pituitary doses substantially higher than 16 Gy. Very high doses to the hypothalamic-pituitary region likely result in reduced secretion of TSH by the anterior pituitary, whether the most relevant target cells for radiation are in the pituitary or hypothalamus (*21–23*). Due to this radiation-induced damage to the hypothalamic-pituitary axis, the positive feedback of low levels of thyroid hormones on the pituitary is compromised. The THS deficit presumably becomes more severe with increasing hypothalamic/pituitary dose such that above some dose, perhaps 45–50 Gy, little TSH is secreted. At this point, differences in thyroid dose would be of little consequence. The reverse also holds. At very high thyroid doses, secretion of T3 and T4 by the thyroid gland is minimal, regardless of level of stimulation by TSH, and differences in dose to the hypothalamic-pituitary region become less important. The current analysis provides quantitative information about the joint thyroid and pituitary/hypothalamus radiation dose dependence of these relationships. The estimated crossover dose for sub-additivity of effects is similar to the recommended dose limit for the hypothalamus (16.1 Gy) for purposes of radiation treatment planning noted by Sklar and Wolden (*24*). As these authors also noted, we caution against interpreting this value as a threshold dose.

[3] ''Thyroid dose response'' here refers to dose response for hypothyroidism rather than dose response for thyroid damage. We do not suggest that the dose response for thyroid damage depends on dose to the pituitary.

The available literature concerning effects of hypothalamic-pituitary irradiation on the occurrence of central hypothyroidism, TSH deficiency and, more generally, hypopituitarism, is broadly consistent with our findings. Radiation doses >20 Gy to the hypothalamic-pituitary region have been reported to increase the risk of central hypothyroidism (*11, 23, 25*), and the cumulative incidence of hypopituitarism increased with dose to the pituitary of 20–>50 Gy (*23, 25–28*). Radiation-related damage to the hypothalamic-pituitary axis can result in deficiencies of other hormones that are normally produced by the anterior pituitary, in addition to TSH. This includes growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and adrenocorticotropic hormone (ACTH) (*14, 15, 22, 23*). In their published study of 748 adult survivors of childhood cancer who were treated with cranial radiotherapy, Chemaitilly *et al.* (*14*) evaluated risk of hormonal deficiencies in relationship to radiation dose (referent: ≤22 Gy). Doses ≥30 Gy were associated with deficiencies of TSH and ACTH; doses of 22–<30 Gy were associated with a deficiency of GH; and doses >22 Gy were associated with deficiencies of LH and FSH. Darzy and Shalet (*27, 28*) note that both incidence and severity of radiation-related damage to the hypothalamic-pituitary axis increase with time since exposure as well as radiation dose.

In the current study, we observed an increased occurrence (cumulative proportion affected) of hypothyroidism among survivors of HL as well as CNS cancer. Among HL survivors, the occurrence of hypothyroidism was extraordinarily high: 32% of five-year survivors who participated in the study developed hypothyroidism by 30 years after cancer diagnosis. Among HL survivors who received radiation, thyroid doses typically were very high (median, 35 Gy), whereas pituitary doses were low (median, 1.3 Gy). It is likely that a large majority of the cases of hypothyroidism among HL survivors were primary hypothyroidism (*5*).

Like CNS cancer patients, acute lymphoblastic leukemia (ALL) patients in the CCSS also were treated with cranial or craniospinal radiotherapy but with lower radiation doses. Median doses to the pituitary and thyroid glands for the leukemia survivors who received radiation in the current study were 21 Gy and 0.8 Gy, respectively, versus 41 Gy and 1.7 Gy for CNS cancer survivors. We did not observe a significantly increased incidence rate of hypothyroidism among leukemia survivors, relative to survivors of cancers other than CNS cancer or HL. We suggest that cranial or craniospinal radiotherapy for leukemia survivors in the CCSS was insufficient to cause central hypothyroidism to a marked degree. However, if, in irradiated leukemia survivors, the hypothalamus was still producing TRH and the pituitary was still producing TSH, even if at diminished levels, radiation effects on the thyroid could still be determinative of the occurrence of hypothyroidism, most of which would be expected to be primary hypothyroidism. One would expect a thyroid dose response. We note that,

unlike the earlier CCSS study by Chow *et al*. (*6*), the current study also included survivors of types of leukemia other than ALL (mostly acute myelogenous leukemia) and that 83% of leukemia survivors received thyroid doses between 0 and 1.5 Gy. Our results suggest that the risk of hypothyroidism associated with thyroid doses of this magnitude is small.

The most relevant basis for comparison with our overall results comes from the British Childhood Cancer Survivor Study (BCCSS), a large cohort (n = 17,981) of five-year childhood cancer survivors in the UK, 71% of whom were followed for ≥16 years (*13*). The overall prevalence of hypothyroidism at the end of follow-up was 7%. The highest prevalence (cumulative proportions) was among survivors of HL (19.9%), CNS cancer (15.3%), NHL (6.2%) and leukemia (5.2%), an ordering similar to that in the current study. The BCCSS study of hypothyroidism did not include radiation dosimetry.

Among survivors of CNS cancer and HL in the current study, hypothyroidism tended to be diagnosed relatively soon after the childhood cancer, with a median interval of 5–6 years (including prevalent and incident cases). This is not simply a matter of poor survival among patients with these cancers, insofar as appreciable numbers of persons remained under observation for more than 20 years. If radiation-related hypothyroidism tends to begin to occur very soon after radiation exposure, and the largest proportions of hypothyroidism cases due to radiation occurred among survivors of HL (mostly primary hypothyroidism) and CNS cancer (central and primary hypothyroidism), then one would expect shorter average latency intervals among survivors of these cancers. Part of the explanation also could be differential surveillance related to type of cancer and type of hypothyroidism. Close surveillance of HL survivors for thyroid abnormalities has been part of standard follow-up care for many years (*3*). The situation with CNS cancer survivors is less clear, as is the impact of surveillance as it relates to primary versus central hypothyroidism. Screening for thyroid disease typically has relied almost exclusively on TSH concentrations, which would detect primary hypothyroidism but not central hypothyroidism (*26*). For detection of the latter, serum levels of free T4 must also be addressed,[4] although historically, this was not done routinely, at least in the UK (*13*).

Among survivors of CNS cancer in the BCCSS who received radiation treatment, the prevalence of self-reported hypothyroidism decreased with follow-up time, and the prevalence was lower among patients discharged for follow-up care to primary care physicians than among those who continued to be followed in the hospital, where more specialized care, including that by endocrinologists, would be available (*13*). This difference increased with follow-up time. The authors hypothesized that the difference was due to under-diagnosis of central hypothyroidism among survivors of CNS cancer and that the reason for the difference between primary care and specialized care settings could be the nature of the monitoring for thyroid disease. Insofar as radiation-induced hypopituitarism may take many years to develop or become symptomatic (*27, 28*), under-diagnosis of central hypothyroidism might increase with time.

The incidence rate of hypothyroidism among childhood cancer survivors in the CCSS was higher for calendar years of follow-up after 1990 than in earlier years. Part of this may be due to increased awareness of the risk of treatment-related thyroid dysfunction, more frequent thyroid function testing, and/or improvements in the accuracy and sensitivity of laboratory tests. These factors could be particularly important in the context of central hypothyroidism and subclinical hypothyroidism of both types; however, the shorter average follow-up intervals for more recent calendar years may also be a factor, insofar as the age-adjusted RR for hypothyroidism decreased with time since diagnosis of childhood cancer.

While the estimated attributable risk of hypothyroidism due to chemotherapy was much lower than that for radiotherapy, we observed positive associations between risk of hypothyroidism and treatment with CCNU, bleomycin and cyclophosphamide, with the strongest chemotherapy-associated risk occurring among survivors of CNS cancer. CCNU was used most commonly to treat CNS cancer. An earlier published study using rats indicated that exposure to CCNU altered neurosecretory function in the hypothalamic-pituitary axis (*29*). In a published study of fertility in the CCSS cohort, CCNU treatment or radiation treatment at a dose >30 Gy to the hypothalamus/pituitary (relative to ≤10 Gy) was associated with a reduced likelihood of becoming pregnant (*30*). Chemaitilly *et al*. (*14*) reported that cranial radiation doses >22 Gy were associated with deficiencies of LH and FSH. This raises the possibility that toxicity to the hypothalamus and/or anterior pituitary, whether caused by radiation or CCNU, may influence levels of LH and/or FSH as well as TSH, affecting both fertility and susceptibility to central hypothyroidism. However, few human studies have directly implicated chemotherapy in the pathogenesis of central hypothyroidism, hypopituitarism or LH/FSH deficits (*31*), and effects of CCNU on the likelihood of becoming pregnant may relate to gonadal rather than pituitary dysfunction. Rose *et al*. (*32*) reported evidence of hypothalamic dysfunction among childhood cancer survivors who received chemotherapy but not radiotherapy, but most previously published studies have not indicated a strong effect of chemotherapy on the risk of either primary or central hypothyroidism (*31*). Part of the increased risk of hypothyroidism among brain cancer

[4] The diagnosis of primary hypothyroidism is based on an elevated serum TSH level accompanied by low serum free T4 (fT4) in clinical hypothyroidism and low to low-normal fT4 in subclinical hypothyroidism (*11, 13*). In central hypothyroidism, serum TSH levels typically are low or within the normal range, with low fT4 levels in clinical disease and low-normal fT4 in subclinical disease (*11, 13*).

survivors may relate to effects of the disease on the hypothalamic-pituitary axis other than those due to radiation or chemotherapy; these might include mechanical effects associated with the tumor (e.g., increased intracranial pressure) or tumor surgery (*31*). Nonetheless, we note that, in the current study, increased risk associated with CCNU was seen among survivors of other types of cancer as well as CNS cancer and among those with pituitary doses <1 Gy, minimizing the possibility of confounding by radiation. Furthermore, treatment with CCNU appeared to modify the effect of radiation dose to the pituitary but not the thyroid. In contrast, bleomycin appeared to modify effects of radiation dose to the thyroid and pituitary nondifferentially. Caution in interpretation of the association of risk with bleomycin is indicated by the fact that it was attenuated among persons who received low radiation doses to the pituitary. The association with cyclophosphamide, though modest and of borderline significance, is noteworthy in light of the frequent use of this drug. Our results concerning chemotherapy and hypothyroidism, while provocative, require confirmation.

Age at exposure, time since exposure (or attained age) and sex also appeared to modify the effect of radiation. As is the case with thyroid cancer, radiation-related risk was inversely associated with age at exposure, possibly due to greater sensitivity of the thyroid at young ages. In the current study, this modifying effect of age at exposure was equally apparent for dose to the thyroid and hypothalamic-pituitary axis. The decrease in the ERR/Gy with increasing time since exposure (or attained age), which also was seen for both thyroid dose and pituitary dose, may reflect diminution of radiation effects with time, reduced surveillance of irradiated survivors over time or increasing relative importance of non-radiation causes of hypothyroidism. Nonetheless, a positive association with radiation persisted more than 25 years after exposure. Although the radiation-related ERR of hypothyroidism was greater in males than females, the cumulative proportion affected was greater in females, due to the higher background incidence rate.

Based on Table 6, we estimate that 57.5% of hypothyroidism cases were attributable to radiotherapy, 9.4% to chemotherapy and 33.1% to background. This suggests that two-thirds of cases were due to cancer treatment and one-third were unrelated to treatment, assuming that the only relevant treatment factors were radiation and chemotherapy. Multiplying one-third (0.33) by the overall prevalence of hypothyroidism in our study, combining prevalent and incident cases through 30 years after the cancer diagnosis ($=$ 11.2%), yields an estimated prevalence of 3.7% in the absence of radiation or chemotherapy. This value is somewhat higher than the value of 2.4% for persons ages 12–49 years in the U.S. general population for 1999–2002 based on data from the National Health and Nutrition Examination Survey (NHANES) for 1999–2002 (*33*). The difference could be due, in part, to cancer survivors being under closer surveillance for thyroid disorders than the general population (particularly during early years after cancer treatment), differences in underlying susceptibility to hypothyroidism, differences in how hypothyroidism was defined or measured or effects of cancer or its treatment other than radiation and chemotherapy.

Strengths of this study include its large size, long follow-up, longitudinal ascertainment of hypothyroidism at two widely separated time points after treatment for childhood cancer, systematic and detailed ascertainment of treatments for the childhood cancer and estimation of radiation doses to the thyroid gland and pituitary gland for individual childhood cancer survivors based on radiotherapy records.

The most important limitation is reliance on self-reported outcome information from cancer survivors in the absence of serological measurements that would allow for: 1. confirmation of the presence of reported hypothyroidism; 2. direct assessment of primary versus central hypothyroidism; and 3. detection of unreported hypothyroidism, including subclinical disease. When we used a more stringent definition of hypothyroidism that required both self-reported diagnosis of hypothyroidism by a physician and the use of prescription medications for hypothyroidism, the joint thyroid and pituitary radiation dose-response pattern was little changed. This suggests that under-reporting or under-diagnosis of hypothyroidism may be a more important source of outcome misclassification than over-reporting of hypothyroidism. Our overall estimates of absolute risks of hypothyroidism also could be biased downward because we excluded persons with missing age at diagnosis of the thyroid disorder.

Because the CCSS was limited to five-year cancer survivors, we could not address latency for hypothyroidism occurring within the first five years. Radiation-related risk is high during this early time window, as reflected in the generally higher dose-specific prevalence odds ratios (Supplementary Table S2; http://dx.doi.org/10.1667/RR14888.1.S1) than incidence rate ratios (Table 5). Furthermore, reliance on self-reported date (age) of diagnosis of hypothyroidism means that we might have erroneously placed the date as being inside or outside of the five-year window after the date of cancer diagnosis.

We cannot distinguish between radiation-induced damage to the hypothalamus (and attendant reduction in TRH secretion) from damage to the pituitary gland; either can ultimately result in reduced serum levels of TSH (*21–23*). It has been suggested that the hypothalamus is somewhat more radiosensitive than the pituitary (*22*) and that effects on the hypothalamus appear earlier (*23*). In the context of partial brain irradiation, doses to the pituitary and hypothalamus may differ. We estimated only the former and assumed it to be applicable to both sites.

Misclassification of treatment, including radiation dose, also is possible. Radiotherapy and chemotherapy given at another institution or facility for a recurrence of the cancer may have been under-ascertained. While persons with hyperthyroidism may go on to develop hypothyroidism,

sometimes as a result of radiation treatment for hyperthyroidism, this should not be an important issue here, because we censored persons from follow-up at the time of diagnosis of the first functional thyroid disorder. A further limitation is our inability to evaluate aspects of radiation treatment apart from organ dose. Nearly all irradiated patients in the current study were treated with high-energy photons, and fractionation schedules were highly standardized. With respect to chemotherapy, we evaluated specific chemotherapeutic agents rather than chemotherapy regimens.

Two-thirds of persons eligible for membership in the cohort were located and agreed to participate. Their experience with respect to the occurrence of hypothyroidism might not be representative of the experience of all eligible persons (*34, 35*).

In summary, the current study provides new information concerning the radiation dose dependence for hypothyroidism, in particular, concerning the joint thyroid and pituitary dose response and factors that modify the dose response. The combined effects of thyroid and hypothalamic-pituitary doses appear to be less than additive when pituitary or thyroid doses are very high. Although we could not address primary versus central hypothyroidism explicitly, it is very likely that radiation-related cases of hypothyroidism occurring among survivors of CNS cancer were a mixture of central and primary hypothyroidism (primarily the former), and that a large majority of radiation-related cases among survivors of all other types of childhood cancer were primary hypothyroidism. For low pituitary doses (e.g., <10 Gy), the thyroid dose response may approximate the dose response for primary hypothyroidism among childhood cancer survivors, whereas the pituitary dose response for hypothyroidism at very low thyroid doses (<1 Gy) may approximate the radiation dose dependence for central hypothyroidism. Radiation-related risk remained elevated more than 25 years after exposure, highlighting the importance of long-term surveillance for both types of hypothyroidism. Results of this study illustrate how irradiation of one anatomic site may influence the risk of adverse outcomes typically associated with radiation-induced dysfunction in a distant organ. Although the risk of hypothyroidism due to radiotherapy predominates over that due to chemotherapy among childhood cancer survivors, our results also suggest that certain types of chemotherapy may increase the risk.

SUPPLEMENTARY INFORMATION

Table S1. Relative risk (incidence rate ratio) for hypothyroidism according to type of treatment with chemotherapy agents in the Childhood Cancer Survivor Study cohort. Analysis was restricted to patients who received pituitary doses <1 Gy.

Table S2. Estimated prevalence odds ratio for hypothyroidism (95% CI) by radiation dose to the thyroid gland and pituitary gland at five years after childhood cancer diagnosis: Childhood Cancer Survivor Study.

Table S3. Parameter estimates for fitted joint thyroid and pituitary dose-response models for incident and prevalent hypothyroidism among five-year survivors of childhood cancer: Childhood Cancer Survivor Study.

Table S4. Observed and fitted numbers of hypothyroidism cases among irradiated childhood cancer survivors, and the estimated proportions of the fitted cases due to thyroid and pituitary irradiation, separately by radiation dose to the thyroid and pituitary: Childhood Cancer Survivor Study.

Table S5. Analysis of effect modification by time since exposure for the effect of thyroid radiation dose on the incidence of presumptive radiation-related primary hypothyroidism (analysis restricted to pituitary doses <1 Gy) and pituitary radiation dose on the incidence of presumptive radiation-related central hypothyroidism (analysis restricted to thyroid doses <2 Gy).

Table S6. Sensitivity analysis for estimated incidence rate ratio for hypothyroidism (95% CI) by radiation dose to the thyroid gland and pituitary gland, using a definition of outcome requiring both self-reported hypothyroidism and use of hypothyroidism-related medication: Childhood Cancer Survivor Study.

Table S7. Sensitivity analysis for parameter estimates of joint thyroid and pituitary dose-response models for incidence of hypothyroidism among five-year survivors of childhood cancer: Childhood Cancer Survivor Study.

ACKNOWLEDGMENTS

This study was supported by the Intramural Research Program of the U.S. National Institutes of Health (NIH), National Cancer Institute Division of Cancer Epidemiology and Genetics. The Childhood Cancer Survivor Study is supported by the National Cancer Institute (grant no. CA55727; principal investigator, GTA) and the Lance Armstrong Foundation (grant no. 147149). Support to St. Jude Children's Research Hospital is also provided by a Cancer Center Support (CORE) grant (no. CA21765; principal investigator, C. Roberts) and by the American Lebanese-Syrian Associated Charities (ALSAC).

Received: July 19, 2017; accepted: April 10, 2018; published online: May 15, 2018

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