

## Chemotherapy and Thyroid Cancer Risk: a Report from the Childhood Cancer Survivor Study

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### Abstract

**Background:** Although ionizing radiation is an established environmental risk factor for thyroid cancer, the effect of chemotherapy drugs on thyroid cancer risk remains unclear. We evaluated the chemotherapy-related risk of thyroid cancer in childhood cancer survivors and the possible joint effects of chemotherapy and radiotherapy.

**Methods:** The study included 12,547 five-year survivors of childhood cancer diagnosed during 1970 through 1986. Chemotherapy and radiotherapy information was obtained from medical records, and radiation dose was estimated to the thyroid gland. Cumulative incidence and relative risks were calculated with life-table methods and Poisson regression. Chemotherapy-related risks were evaluated separately by categories of radiation dose.

**Results:** Histologically confirmed thyroid cancer occurred in 119 patients. Thirty years after the first childhood cancer treatment, the cumulative incidence of thyroid cancer was 1.3% (95% CI, 1.0–1.6) for females and 0.6% (0.4–0.8) for males. Among patients with thyroid radiation doses of 20 Gy or less, treatment with alkylating agents was associated with a significant 2.4-fold increased risk of thyroid cancer (95% CI, 1.3–4.5;  $P = 0.002$ ). Chemotherapy risks decreased as radiation dose increased, with a significant decrease for patients treated with alkylating agents ( $P_{\text{trend}} = 0.03$ ). No chemotherapy-related risk was evident for thyroid radiation doses more than 20 Gy.

**Conclusions:** Treatments with alkylating agents increased thyroid cancer risk, but only in the radiation dose range less than 20 Gy, in which cell sparing likely predominates over cell killing.

**Impact:** Our study adds to the evidence for chemotherapy agent-specific increased risks of thyroid cancer, which to date, were mainly thought to be related to prior radiotherapy. *Cancer Epidemiol Biomarkers Prev*; 21(1); 92–101. ©2011 AACR.

### Introduction

Childhood cancer survivors treated with radiation for their first tumor are at elevated risk for thyroid cancer because the thyroid gland is one of the most radiosensitive human organs (1–3). Many of these children are treated

with chemotherapy drugs, either alone or in conjunction with radiation therapy. Although several childhood cancer studies have addressed the role of radiotherapy and chemotherapy in the development of second primary thyroid cancer (4–7), none have shown either a statistically significant association between chemotherapy and

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thyroid cancer or evidence of an interaction between radiotherapy and chemotherapeutic agents (4, 6, 8).

The Childhood Cancer Survivor Study (CCSS) is the largest cohort study to date with detailed treatment-related information. Our previous CCSS studies have shown that thyroid cancer risk increases linearly with radiation dose at low to moderate doses, with a downturn in risk at doses more than 20 Gy (6, 9–10). In our most recent cohort study analysis (9), a relatively weak association of thyroid cancer risk with chemotherapy was observed, after adjustment for radiation. Although chemotherapy has not been found to be a statistically significant confounder of the association between radiation and thyroid cancer risk, the relative risk (RR) associated with radiation dose was 5 times higher among patients who did not have chemotherapy than patients who received chemotherapy (9). This finding suggested a possible joint effect of chemotherapy and radiotherapy that needed further detailed evaluation.

Due to the strong radiation-related effect on thyroid cancer risk, we hypothesized that if chemotherapy drugs increased thyroid cancer risk, the relationship might be better observed in the lower radiation dose range than in the high-dose range in which the radiation effect would be expected to dominate.

Although radiation exposure was the main focus of our previous cohort study analysis (9), the aim of this work was to conduct additional analyses to evaluate the effect of chemotherapy drugs on thyroid cancer risk and their potential interaction with radiation in inducing thyroid cancer in the Childhood Cancer Survivor Study.

## Methods

### Study population

Detailed descriptions of the design and methods of the CCSS cohort have been published elsewhere (9, 11, 12). Briefly, the study consists of a retrospective longitudinal cohort of 14,363 childhood cancer survivors treated between 1970 and 1986 in 26 centers in the United States and Canada. Eligible were those diagnosed before age 21 years with leukemia, central nervous system (CNS) cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), Wilms tumor, neuroblastoma, soft-tissue sarcoma, or bone cancer and who had survived at least 5 years since diagnosis. The CCSS research protocol was approved by the human subjects committees at each participating institution, and informed consent was obtained from each participant or a proxy.

Of the 14,363 CCSS participants, we included in this cohort study only those who signed a medical release record (12,756 patients; 89%). From this, we excluded participants with missing information on follow-up ( $n = 3$ ), radiation treatment ( $n = 33$ ), or chemotherapy ( $n = 171$ ) and 2 patients who developed thyroid cancer within 5 years of their first cancer treatment. The remaining cohort of 12,547 childhood cancer survivors were followed from 5 years after the first cancer diagnosis until the earliest date

of thyroid cancer diagnosis, death, or last follow-up questionnaire, providing 202,523 person-years for analyses.

### Data collection and case ascertainment

Treatment information was abstracted from medical records with a standardized protocol. Data collected included all chemotherapy, radiotherapy, and surgical procedures, as well as dates of initiation and cessation of each course of chemotherapy and radiotherapy.

Thyroid cancers were initially ascertained through reports from participating centers, self-report from questionnaires, and validated by a study pathologist (SH) who reviewed all pathology reports. Between 1975 and 2005, 119 incident thyroid cancer cases were identified among the 12,547 eligible study participants. The most frequent histology was papillary and mixed papillary thyroid cancer ( $n = 96$ ) followed by follicular ( $n = 14$ ), others ( $n = 3$ ) and 6 cases with unknown histology. One hundred and eleven cases had thyroid cancer as their second malignancy and 8 cases as their third malignancy. The intervening cancers for those patients were NHL ( $n = 2$ ), osteosarcoma ( $n = 2$ ), soft tissue sarcoma, breast cancer, lung cancer, and cutaneous melanoma.

### Radiation dosimetry

Detailed radiation dosimetry for this cohort, described elsewhere (9), is summarized briefly here. Radiation therapy records were reviewed at the CCSS Radiation Physics Center at the University of Texas MD Anderson Cancer Center for thyroid dosimetry assessment. For each patient, doses from all radiation treatments given within 10 years after the first cancer were included. Among the 8 patients who had their thyroid cancer as their third malignancy, 5 received radiotherapy later than 10 years after the first cancer to treat a second cancer; thus, radiation dose from the second cancer treatment was not included in the dosimetry model for these patients. Only one of these 5 cases developed more than 5 years after the second cancer treatment.

Individual dose to each lobe of the thyroid gland was estimated for each person using a mathematical phantom and adjusting for the ages of patients at the time of first cancer treatment (9). Dose estimations accounted for typical beam shielding or blocking. The dose to each lobe was averaged to provide a single dose to the thyroid gland for analysis.

### Quantification of chemotherapy

Ninety three percent of the cohort (11,624 patients) received chemotherapy. Qualitative information was abstracted for 42 specific chemotherapy agents. Detailed information on cumulative dose, routes of administration, and dates of initiation and cessation of treatment were abstracted for a subset of 22 of the 42 chemotherapy agents used. Chemotherapy drugs were grouped into 5 major classes: alkylating agents, anthracyclines, epipodophyllotoxins, platinum-based compounds, and bleomycin (see Table 1 for details; refs. 13, 14). Each subject was

**Table 1.** Descriptive and treatment characteristics of patients

	Entire cohort	≤20 Gy	>20 Gy	Not treated with radiation
Number of patients (% of total) <sup>a</sup>	12,547 (100.0)	9,982 (82.5)	2,116 (17.5)	4,009 (31.9)
Mean thyroid gland dose, Gy <sup>b</sup>	11.0	1.6	35.5	0
Number of thyroid cancers	119	61	54	12
Mean age at first cancer (range in years)	8 (0–21)	7 (0–21)	13 (0–21)	8 (0–21)
Mean follow-up in years (range)	16 (0–29)	16 (0–29)	16 (0–29)	16 (0–29)
Mean number of years since first cancer (range)	14.3 (5–34)	14.1 (5–34)	14.9 (5–34)	13.8 (5–33)
Mean age at thyroid cancer diagnosis (range)	28 (12–47)	27 (13–47)	29 (12–42)	30 (17–37)
Number of females (%)	5,926 (47.2)	4,759 (47.7)	976 (46.1)	1,978 (49.3)
Calendar years of treatment	1970–1986	1970–1986	1970–1986	1970–1986
Number who had chemotherapy, (%)	10,111 (80.6)	8,324 (83.4)	1,431 (67.6)	3,086 (76.9)
Type of first cancer (%) <sup>c</sup>				
Leukemia	4,261 (33.9)	4,013 (40.2)	96 (4.5)	1,304 (33)
Bone cancer	1,041 (8.3)	996 (9.9)	21 (0.9)	655 (16.3)
CNS cancer	1,651 (13.2)	1,192 (11.9)	370 (17.5)	464 (11.6)
HL	1,669 (13.3)	250 (2.5)	1,350 (63.8)	98 (2.4)
Wilms tumor	1,083 (8.6)	1,045 (10.5)	6 (0.3)	382 (9.5)
Neuroblastoma	832 (6.6)	782 (7.8)	34 (1.6)	421 (10.5)
NHL	921 (7.3)	736 (7)	157 (7.4)	287 (7.2)
Soft tissue sarcoma	1,091 (8.7)	968 (9.7)	82 (3.9)	398 (9.9)
Treatment for first cancer (%) <sup>d</sup>				
No radiotherapy, no chemotherapy	923 (7.4)	923 (9.3)	0	923 (23.0)
Radiotherapy, no chemotherapy	1,512 (12.1)	735 (7.4)	685 (32.4)	—
Chemotherapy, no radiotherapy	3,086 (24.6)	3,086 (30.9)	0	3,086 (76.9)
Radiotherapy and chemotherapy	7,025 (55.9)	5,237 (52.5)	1,431 (67.6)	—
Chemotherapy drugs (%)				
Any alkylating agents <sup>e</sup>	6,733 (53.7)	5,191 (52.1)	1,286 (60.9)	1,860 (46.3)
Any anthracyclines <sup>f</sup>	5,179 (41.3)	4,493 (45.1)	477 (20.6)	1,572 (39.3)
Any bleomycin	755 (6.0)	448 (4.5)	281 (13.3)	301 (7.5)
Any platinum compounds <sup>g</sup>	772 (6.2)	608 (6.1)	131 (6.2)	304 (7.6)
Any epipodophyllotoxins <sup>h</sup>	1,196 (9.5)	1,035 (10.4)	113 (5.3)	296 (7.4)

<sup>a</sup>Entire cohort includes 449 patients with unknown radiation dose (4 cases). Total number of patients with thyroid dose estimation is 12,098.

<sup>b</sup>For the whole cohort, mean dose is among exposed patients.

<sup>c</sup>Percentages may not sum to 100% due to rounding.

<sup>d</sup>Treatment may also include surgery.

<sup>e</sup>Alkylating agents include diaziquone, carmustine, lomustine, chlorambucil, procarbazine, cyclophosphamide, dacarbazine, ifosfamide, melphalan, nitrogen mustard, and busulfan.

<sup>f</sup>Anthracyclines include daunorubicin, doxorubicin, and idarubicin.

<sup>g</sup>Platinum-based compounds include carboplatin and cis-platinum.

<sup>h</sup>Epipodophyllotoxins include teniposide and etoposide.

assigned an alkylating agent score of 0, 1, 2, or 3, depending on whether the subject was not treated (0) or fell into the lower, middle, or upper tertiles of the cumulative dose distribution (14, 15). Cumulative dose for anthracyclines was the sum of the doxorubicin and daunorubicin doses and idarubicin (multiplied by 3 to approximate doxorubicin equivalence; refs. 14, 15) and grouped as follows: not exposed, less than 340 mg/m<sup>2</sup>, and 340 mg/m<sup>2</sup> or more. Bleomycin dose was grouped into 3 categories: not exposed, less than 100 mg/m<sup>2</sup>, and 100 mg/m<sup>2</sup> or more.

Cumulative dose could not be abstracted for some patients and they were excluded from the analysis of thyroid cancer risk by cumulative dose (see Table 4 for details). We also categorized all yes/no permutations of the combinations of alkylating agents, anthracyclines, and bleomycin.

### Statistical analysis

We calculated the cumulative incidence of thyroid cancer during the follow-up period accounting for death

from any cause as a competing risk event (16). Calculations were done using Stata software (Stata, release 10.1).

The risk of developing thyroid cancer was determined according to type of treatment, chemotherapy classes, and cumulative doses of chemotherapy drugs. We included drug classes if more than 5 thyroid cancer cases were in the exposed group. We fit standard multivariate Poisson regression models with multiplicative effects of categorized radiation dose, chemotherapy, and potential confounders such as gender, attained age, year, and type of first cancer (HL, leukemia and all other cancers combined).

We assessed chemotherapy-related risk separately in the overall cohort and also in 3 subgroups defined as follows: no-radiation to the thyroid gland, 0 Gy ( $n = 4,009$ ), 20 Gy or less ( $n = 9,982$  and includes the 4,009 with 0 Gy), and more than 20 Gy ( $n = 2,116$ ). The RR of developing thyroid cancer was determined with appropriate adjustment for background risk and by adjusting for thyroid radiation dose as a continuous variable (for the  $\leq 20$  Gy and  $>20$  Gy subgroups). Patients with unknown radiation dose ( $n = 449$ ) were excluded from the assessment of chemotherapy-related cancer risk.

Effect modification of radiation and chemotherapy was assessed among patients who received any chemotherapy (yes/no) and any classes of chemotherapy drugs (yes/no) within radiation dose categories. Linear trend of the effect modification of radiation dose and chemotherapy was tested by comparing the model with an interaction term, dose (as continuous variable)  $\times$  chemotherapy (yes/no), to the model without the interaction term. Nested models were compared using likelihood-ratio tests (LRT). Two-sided  $P$  values were used throughout. All parameter estimates, LRT, and likelihood-based 95% CIs were computed using the AMFIT module of the EPICURE statistical program (17).

## Results

### Cohort and subgroup characteristics

Descriptive characteristics of the overall CCSS cohort and the subgroups are summarized in Table 1. Except for type of first cancer and age at first cancer, differences in descriptive characteristics for the overall cohort and the subgroups were not of clinical importance. The patients who received radiation dose more than 20 Gy were most likely treated for HL (64%) and had the highest mean age at first cancer (13 years old) as compared with the cohort overall and the other 2 subgroups (7-8 years).

The proportion of patients treated with chemotherapy was lower in the more than 20 Gy subgroup (67%) than the 20 Gy or less (83%) subgroup or among patients not treated with radiation (77%). In the overall cohort, 81% were treated with chemotherapy. Among those receiving chemotherapy, alkylating agents and anthracyclines were the most commonly used classes of drugs.

The mean size of the thyroid tumors at the time of diagnosis was 1.7 cm (range: 0.1–8.5 cm). No statistically significant difference in tumor size was observed between survivors of HL as compared with other types of first cancer ( $t$  test,  $P = 0.53$ ; Table 2). Among the patients who developed thyroid cancer, neuroblastoma survivors were youngest at first cancer treatment (mean, 1.5 years), whereas survivors of bone cancer, HL, and NHL were oldest (approximately 13 years) at time of treatment.

### Cumulative incidence

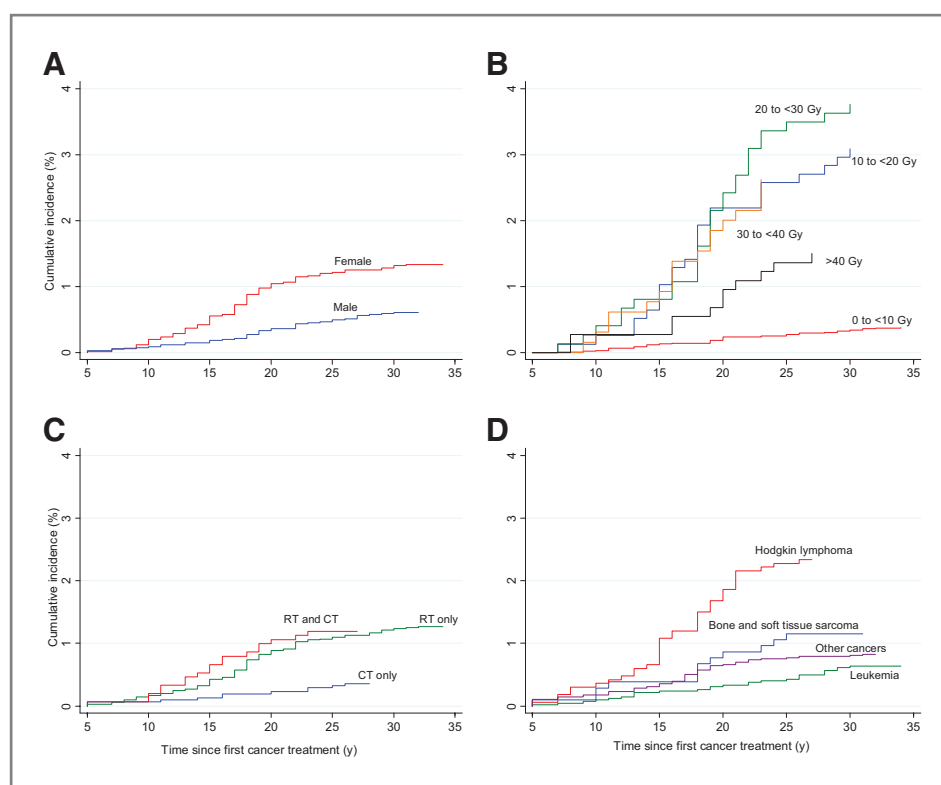
Cumulative incidences of thyroid cancer by gender, first cancer, type of treatment, and thyroid radiation dose categories are presented in Fig. 1. The cumulative incidence 30 years after first treatment was 1.3% (95% CI, 1.0–1.6) for females and 0.6% (0.4–0.8) for males. By type of first cancer, survivors of HL had the

**Table 2.** Characteristics of the 119 patients who developed thyroid cancers among the 12,547 five-year childhood cancer survivors, Childhood Cancer Survivor Study

Primary cancer	Number of thyroid cancers	Mean tumor size [cm, (SD)]	Mean age at first cancer [y, (SD)]	Mean thyroid radiation dose Gy <sup>a</sup> , (SD)	Mean time since first cancer [y, (SD)]
Bone cancer	12	2.7 (2.6)	13.4 (4.2)	5.0 (7.1)	19.2 (6.3)
CNS cancer	14	2.0 (2.1)	8.0 (3.5)	20.7 (12.0)	17.1 (3.0)
HL	39	1.6 (1.7)	13.2 (2.9)	31.0 (13.3)	17.4 (5.0)
Wilms tumor	3	2.2 <sup>b</sup>	2.8 (2.4)	2.5 (4.2)	16.0 (3.0)
Leukemia	27	1.9 (2.1)	5.7 (4.0)	12.5 (7.6)	21.0 (7.7)
NHL	7	1.3 (0.4)	13.1 (3.3)	17.3 (8.7)	19.6 (7.0)
Neuroblastoma	9	1.5 (0.4)	1.5 (1.4)	11.4 (10.9)	18.3 (5.0)
Soft tissue sarcoma	8	1.2 (1.1)	9.4 (4.5)	10.9 (14.7)	19.2 (9.0)
All	119	1.7 (1.8)	9.5 (5.3)	18.8 (14.5)	18.7 (6.1)

<sup>a</sup>Weighted by person-years among those who received radiation.

<sup>b</sup>Tumor size was available for only 1 case.



**Figure 1.** Cumulative incidence of thyroid cancer in the CCSS cohort according to time since first cancer treatment. CI by gender (A), CI by thyroid radiation dose categories (B), CI by type of treatment (C), CI by type of first cancer (other cancers include neuroblastoma, Wilms tumor, CNS cancer, and NHL; D). RT, radiation treatment; CT, chemotherapy; RT&CT, radiation and chemotherapy, CI, cumulative incidence.

highest cumulative incidence, reaching 2.3% (95% CI, 1.7–3.1) 27 years after their first cancer treatment. Twenty years after first cancer treatment, the highest cumulative incidence of developing thyroid cancer was observed for patients treated with both chemotherapy and radiotherapy (0.8%, 95% CI, 0.6–1.1). By thyroid radiation dose, the cumulative incidence after 20 years of first cancer treatment was highest among those receiving between 10 and 40 Gy with cumulative thyroid cancer incidence of 2.2% (95% CI, 1.3–3.4) for 10 to less than 20 Gy category, 2.4% (1.5–3.7) for 20 to less than 30 Gy category, and 2.1% (1.2–3.5) for 30 to less than 40 Gy category, compared with 1.0% (0.4–1.8) for patients receiving thyroid radiation doses more than 40 Gy or 0.2% (95% CI, 0.1–0.4) for patients receiving between 0 and less than 10 Gy.

### Effects of chemotherapy

Risk of thyroid cancer by type of treatment is summarized in Table 3. The adjusted risk of thyroid cancer differed significantly by type of treatment, with a higher risk for patients receiving any radiation treatment (radiotherapy alone or combined radiotherapy and chemotherapy) compared with patients not treated with radiation ( $P = 0.04$ ). No significantly increased risks of thyroid cancer for patients receiving chemotherapy and radiotherapy (concomitant or sequential) versus patients receiving radiotherapy alone were observed ( $P = 0.13$ ). For combined modality treatment, there also was no

statistically significant difference in thyroid cancer risk if chemotherapy occurred before or after radiation therapy ( $P = 0.30$ ).

Table 4 summarizes the RRs according to chemotherapy for the entire cohort and the subgroups. For the whole cohort, no statistically significant excess risk was observed for chemotherapy overall nor for different classes of drugs. When combinations of alkylating agents, anthracyclines, and bleomycin were taken into account, a borderline significant excess risk was observed for patients who received both alkylating agents and anthracyclines (RR = 1.9, 95% CI, 1.1–3.1). For the subgroups, neither chemotherapy nor any specific drug was associated with significant excess risk among patients exposed to radiation dose to the thyroid gland more than 20 Gy. Chemotherapy was associated with a 4-fold statistically significant excess risk among patients who received 20 Gy or less to the thyroid gland ( $P = 0.006$ ). Anthracyclines and alkylating agents seemed to increase thyroid cancer risk among these patients. The no-radiation subgroup also had a higher chemotherapy-related thyroid cancer risk, but the association was not statistically significant. Despite the wide confidence interval, this no-radiation subgroup had a statistically significant increased risk associated with use of anthracyclines (RR = 4.0, 95% CI, 1.2–18.0) and bleomycin (RR = 4.6, 95% CI, 1.3–15.8).

Compared with those not treated with alkylating agents, risk seemed to increase with alkylating score for the 20 Gy or less [low/medium exposed, RR = 2.3



**Table 3.** Risk of thyroid cancer according to type of treatment

Characteristics	Categories	PYR	Mean thyroid radiation dose (Gy)	Cases	RR <sup>a</sup> (95% CI)	P
Type of treatment <sup>b</sup>	No RT, had CT <sup>c</sup>	63,189	0	12	1.0 (ref)	0.04 <sup>d</sup>
	RT alone	26,817	19.7	18	3.0 (0.9–9.7)	
	Concomitant CT and RT	90,458	7.2	69	<b>4.7 (1.5–15.0)</b>	
	Sequential CT and RT	16,092	18.3	20	<b>5.4 (1.6–18.4)</b>	
	RT, then CT	12,417	18.3	15	<b>8.0 (2.2–28.5)</b>	
	CT, then RT	3,677	18.2	5	<b>5.2 (1.3–21.3)</b>	

NOTE: Numbers in bold indicate statistical significance at  $P < 0.05$ .

Abbreviations: RT, radiation treatment; CT, chemotherapy.

<sup>a</sup>Background model includes sex, natural logarithm of attained age, first cancer (HL, leukemia, and others), radiation dose categories, and chemotherapy (yes/no).

<sup>b</sup>Treatment may also include surgery. On the basis of dates of initiation and cessation of RT and CT, 2 sequences of treatments were defined: (i) concomitant chemoradiotherapy, defined as RT and CT administered in overlapping time periods; (ii) sequential chemoradiotherapy, defined as RT and CT administered in separate time periods. Patients who had no information on dates of chemotherapy and radiotherapy ( $n = 407$ ) were excluded from this analysis.

<sup>c</sup>As only 1 thyroid cancer occurred among patients who did not receive RT or CT, we considered patients who did not receive any radiation treatment as the reference group. When considering patients who received only radiation as the reference group (RT alone), RR for concomitant CT and RT was 0.9 (0.3–3.0) and sequential CT and RT was 1.9 (95% CI: 0.9–3.6),  $P_{\text{heterogeneity}} = 0.13$ .

<sup>d</sup> $P$  value tests the heterogeneity of the first 4 categories (No RT, had CT, RT alone, concomitant CT and RT and sequential CT and RT). When considering patients that received sequential CT and RT, there was no difference in risk if chemotherapy was administered before or after radiation therapy (test for heterogeneity,  $P = 0.30$ ).

(95% CI, 1.3–4.5) and highly exposed, RR = 2.8 (1.1–6.7).  $P_{\text{heterogeneity}} = 0.009$ ] and also for the no-radiation subgroups [low/medium exposed, RR = 1.8 (95% CI, 0.3–10.0) and highly exposed, RR = 9.4 (1.4–56.8).

$P_{\text{heterogeneity}} = 0.008$ ; Table 4]. We also evaluated whether there was an increased risk by alkylating dose score among patients who received thyroid radiation dose less than 10 Gy. We found a significant increase in risk

**Table 4.** Risk of thyroid cancer with respect to chemotherapy by thyroid radiation dose

Treatment	No-radiation (thyroid dose = 0 Gy) 12 cases		Radiation (thyroid dose ≤20 Gy) 61 cases		Radiation (thyroid dose >20 Gy) 54 cases		Overall <sup>a</sup> 115 cases	
	PYR	RR <sup>b</sup> (95% CI)	PYR	RR <sup>c</sup> (95% CI)	PYR	RR <sup>c</sup> (95% CI)	PYR	RR <sup>d</sup> (95% CI)
Chemotherapy								
No	15,795	1.0 (ref.)	28,477	1.0 (ref.)	12,374	1.0 (ref.)	40,851	1.0 (ref.)
Yes	49,599	4.6 (0.8–86.3)	133,457	<b>4.0 (1.4–16.5)</b>	21,543	1.1 (0.6–2.1)	155,026	1.6 (1.0–2.7)
<i>P</i>		0.08		0.006		0.72		0.06
Alkylating agents								
No	35,235	1.0 (ref.)	82,004	1.0 (ref.)	14,715	1.0 (ref.)	96,744	1.0 (ref.)
Yes	30,061	2.8 (0.7–13.2)	79,770	<b>2.4 (1.3–4.5)</b>	19,156	0.9 (0.5–1.6)	98,926	1.4 (1.0–2.1)
<i>P</i>		0.13		0.002		0.76		0.07
Anthracyclines								
No	40,112	1.0 (ref.)	95,251	1.0 (ref.)	28,368	1.0 (ref.)	123,645	1.0 (ref.)
Yes	25,185	<b>4.0 (1.2–18.0)</b>	66,523	<b>1.8 (1.1–3.1)</b>	5,502	0.9 (0.5–1.9)	72,026	1.4 (0.9–2.1)
<i>P</i>		0.02		0.02		0.89		0.10
Bleomycin								
No	60,885	1.0 (ref.)	155,350	1.0 (ref.)	30,630	1.0 (ref.)	186,005	1.0 (ref.)
Yes	4,411	4.6 (1.3–15.8)	6,425	1.9 (0.7–4.4)	3,240	0.7 (0.2–1.9)	9,665	1.1 (0.6–2.0)
<i>P</i>		0.02		0.21		0.45		0.98

(Continued on the following page)

**Table 4.** Risk of thyroid cancer with respect to chemotherapy by thyroid radiation dose (Cont'd)

Treatment	No-radiation (thyroid dose = 0 Gy) 12 cases		Radiation (thyroid dose ≤20 Gy) 61 cases		Radiation (thyroid dose >20 Gy) 54 cases		Overall <sup>a</sup> 115 cases	
	PYR	RR <sup>b</sup> TC (95% CI)	PYR	RR <sup>c</sup> TC (95% CI)	PYR	RR <sup>c</sup> TC (95% CI)	PYR	RR <sup>d</sup> TC (95% CI)
Alkylating agent score <sup>e</sup>								
Not exposed	35,235	3 1.0 (ref.)	82,004	15 1.0 (ref.)	14,714	24 1.0 (ref.)	96,744	39 1.0 (ref.)
Low/medium exposed	21,999	3 1.8 (0.3–10.0)	58,974	31 <b>2.3 (1.3–4.5)</b>	7,300	13 1.0 (0.5–2.1)	66,275	44 <b>1.5 (1.0–2.3)</b>
Highly exposed	4,432	4 <b>9.4 (1.4–56.8)</b>	11,227	10 <b>2.8 (1.1–6.7)</b>	7,894	13 1.0 (0.5–2.1)	19,121	23 1.5 (0.8–2.6)
<i>P</i>		0.08		0.009		0.99		0.14
Bleomycin dose (mg/m <sup>2</sup> ) <sup>f</sup>								
Not exposed	60,886	7 1.0 (ref.)	155,350	55 1.0 (ref.)	30,630	50 1.0 (ref.)	186,005	105 1.0 (ref.)
>0 to <100	1,638	2 4.5 (0.6–20.7)	2,751	3 1.5 (0.4–5.3)	2,117	1 0.2 (0.03–1.9)	4,869	4 0.7 (0.2–1.9)
≥100	2,385	2 3.3 (0.5–15.2)	2,990	2 2.2 (0.5–9.3)	620	0 —	3,610	2 1.0 (0.2–4.2)
<i>P</i>		0.17		0.69		0.09		0.56
Anthracycline dose (mg/m <sup>2</sup> ) <sup>g</sup>								
Not exposed	40,112	3 1.0 (ref.)	95,251	27 1.0 (ref.)	28,368	44 1.0 (ref.)	123,645	71 1.0 (ref.)
>0 to <340	11,342	4 4.5 (0.9–22.9)	36,470	19 <b>1.9 (1.0–3.4)</b>	3,872	7 0.9 (0.4–2.1)	40,343	26 1.3 (0.8–2.1)
≥340	11,688	5 4.3 (1.0–21.4)	25,084	12 1.7 (0.8–3.3)	1,240	2 0.8 (0.2–3.4)	26,324	14 1.4 (0.7–2.5)
<i>P</i>		0.05		0.07		0.97		0.36
Treatment	No-radiation (thyroid dose = 0 Gy) 12 cases		Radiation (thyroid dose ≤20 Gy) 61 cases		Radiation (thyroid dose >20 Gy) 37 cases		Overall <sup>a</sup> 115 cases	
	PYR	RR <sup>b</sup> TC (95% CI)	PYR	RR <sup>c</sup> TC (95% CI)	PYR	RR <sup>c</sup> TC (95% CI)	PYR	RR <sup>d</sup> TC (95% CI)
Drug combinations								
Not exposed <sup>h</sup>	29,700	2 1.0 (ref.)	65,655	10 1.0 (ref.)	14,145	22 1.0 (ref.)	79,825	32 1.0 (ref.)
ANTH alone	5,415	1 3.1 (0.1–26.9)	16,094	5 2.4 (0.7–6.7)	125	0 —	16,219	5 1.2 (0.4–2.8)
BLEO alone	13	0 —	44	0 —	96	1 <b>9.8 (1.3–74.1)</b>	42,869	1 11.7 (0.6–57.6)
ALKY alone	10,202	0 —	29,329	16 <b>2.5 (1.1–5.8)</b>	13,540	20 0.9 (0.5–1.8)	140	36 1.3 (0.8–2.1)
ALKY + BLEO	196	1 <b>35.9 (1.6–408)</b>	223	1 <b>19.1 (2.2–162)</b>	586	1 1.4 (0.2–10.4)	809	2 2.8 (0.5–10.5)
ANTH + BLEO	106	0 —	211	0 —	348	1 1.2 (0.1–9.9)	559	1 1.4 (0.1–8.4)
ANTH + ALKY	15,567	4 <b>5.5 (1.1–40.3)</b>	44,272	24 <b>3.1 (1.5–6.8)</b>	2,819	8 1.4 (0.6–3.3)	<b>47,091</b>	<b>32 1.9 (1.1–3.1)</b>
ANTH + ALKY + BLEO	4,095	4 <b>9.0 (1.7–66.8)</b>	5,947	5 <b>3.7 (1.1–11.2)</b>	2,210	1 0.2 (0.03–1.8)	8,156	6 1.1 (0.4–2.2)
<i>P</i>		0.03		0.01		0.37		0.36

NOTE: Four patients with missing thyroid radiation dose were excluded in this analysis. Significant associations are shown in bold print. Abbreviations: PYR, person-year; TC, thyroid cancer cases; BLEO, bleomycin; ALKY, alkylating agents; ANTH, anthracyclines.

<sup>a</sup>A nonsignificant risk of epipodophyllotoxins [RR = 1.1 (95% CI, 0.5–2.4)] and platinum compounds [RR = 0.9 (95% CI, 0.3–2.6)] was estimated for the overall cohort but not for the subgroups due to the small number of cases.

<sup>b</sup>RR adjusted for sex, natural logarithm of attained age, type of first cancer (HL, leukemia, and others).

<sup>c</sup>RR adjusted for sex, natural logarithm of attained age, type of first cancer (HL, leukemia, and others) and radiation dose as continuous variables.

<sup>d</sup>RR adjusted for sex, natural logarithm of attained age, type of first cancer (HL, leukemia, and others) and radiation dose categories.

<sup>e</sup>Cumulative dose of alkylating agents could not be estimated among 891 patients (9 cases). Not exposed—alkylating agents score of 0; low/medium exposed—alkylating agents score of 1 and 2; highly exposed—alkylating agents score of 3.

<sup>f</sup>Cumulative dose of bleomycin could not be estimated among 94 patients (4 cases).

<sup>g</sup>Cumulative dose of anthracycline could not be estimated among 380 patients (4 cases).

<sup>h</sup>Not exposed category means not exposed to alkylating agents or anthracyclines or bleomycin, but could have been treated with other types of drugs.

by alkylating agent score in comparison with patients not exposed to alkylating agents [low/medium exposed, RR = 2.5 (95% CI, 1.1–6.1) and highly exposed, RR = 4.6 (1.5–13.6).  $P_{\text{heterogeneity}} = 0.02$ ]. The increased risk for alkylating agents remained after adjustment for other drug classes. Thyroid cancer risk was not associated with cumulative dose of anthracyclines or bleomycin in any of the radiation subgroups. When all drug class combinations were taken into account in one multivariable statistical model, the risk of thyroid cancer in patients receiving alkylating agents alone remained significant in the 20 Gy or less subgroup [RR = 2.5 (95% CI, 1.1–5.8)]. Risk for patients treated with any drug combination that included alkylating agents relative to patients receiving neither drug was significantly increased in the 20 Gy or less group [any combination of alkylating agents and bleomycin, RR = 19.1 (95% CI, 2.2–162); any combination of alkylating agents and anthracyclines, RR = 3.1 (1.5–6.8); any combination of alkylating agents, anthracyclines, and bleomycin, RR = 3.7 (1.1–11.2)] and also among the no-radiation subgroup [any combination of alkylating agents and bleomycin, RR = 35.9 (1.6–408); any combination of alkylating agents and anthracyclines, RR = 5.5 (1.1–40.3); any combination of alkylating agents, anthracyclines, and bleomycin, 9.0 (1.7–66.8)].

Excess thyroid cancer risks for any of the specific alkylating agents or anthracycline drugs were evaluated in the 20 Gy or less subgroup (Supplementary Table S1). The reference group was either patients who were not

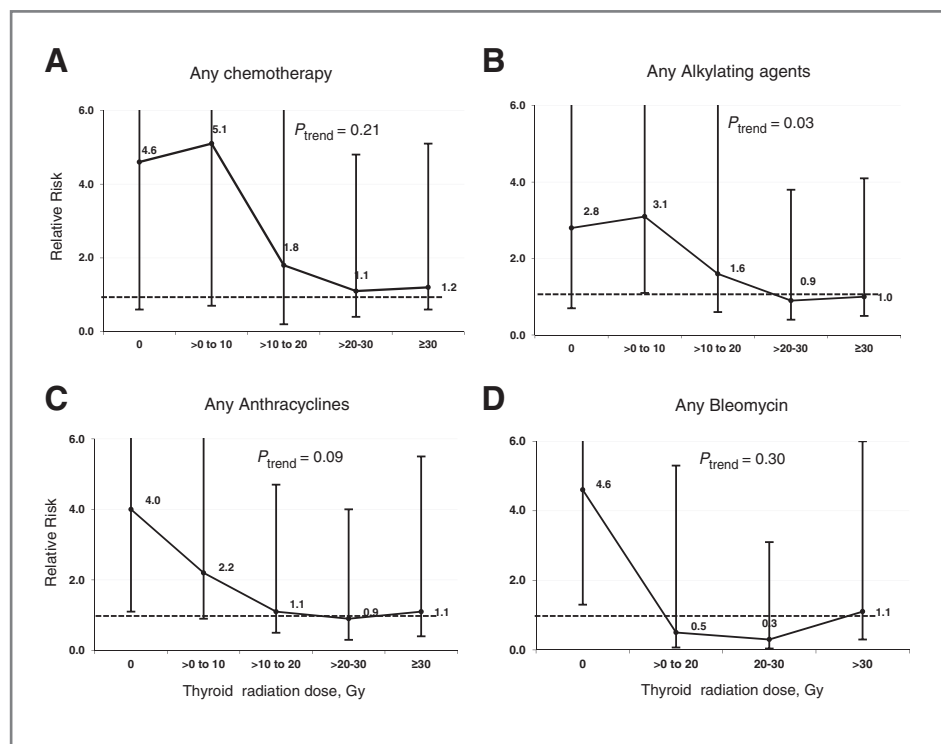
treated with chemotherapy or who were not treated with the respective drugs. No specific drugs were associated with significantly increased risks of thyroid cancer, but the RR for procarbazine (an alkylating agent) was nearly significant (RR = 3.5, 95% CI, 0.9–11.3) and remained elevated after adjustment for other alkylating agents (RR = 3.5 (0.8–15.4). Compared with patients not treated with procarbazine, medium (>0 to <5,000 mg/m<sup>2</sup>) and high (>5,000 mg/m<sup>2</sup>) cumulative doses of procarbazine were associated with similarly elevated risks ( $P_{\text{heterogeneity}}$  across categories = 0.09; results not shown). The distribution of different classes of drugs by type of first cancer in the irradiated and nonirradiated groups in the CCSS cohort is described in Supplementary Table S2.

Joint effects of radiation with chemotherapy and classes of drugs are presented in Fig. 2. We found that, in general, risk for thyroid cancer decreased with increasing radiation dose category for any chemotherapy ( $P = 0.21$ ), alkylating agents ( $P = 0.03$ ), anthracyclines ( $P = 0.09$ ), and bleomycin ( $P = 0.30$ ), suggesting that the cell-killing effect observed for high radiation doses decreased the chemotherapy effect. However, a statistically significant decrease in risk was observed only among patients treated with alkylating agents.

## Discussion

This study is unique because the large sample size allowed the first detailed evaluation of the effect of chemotherapy classes of drugs on thyroid cancer risk

**Figure 2.** RR of thyroid cancer by chemotherapy and classes of drugs within radiation dose categories. A, any chemotherapy (yes/no); B, any alkylating agents (yes/no); C, any anthracyclines (yes/no); D, any bleomycin (yes/no). For bleomycin, radiation dose categories (>0 to 10 and >10 to 20 Gy) were collapsed because of the small number of cases. Dotted line indicates RR = 1.0.  $P_{\text{trend}}$  in RRs for treatment across dose categories.





among childhood cancer survivors. In contrast to previous childhood cancer survivor studies, we assessed the chemotherapy risks in subgroups defined by thyroid radiation dose. Our results support the hypothesis that chemotherapy risks decreased as radiation dose increased, suggesting that the cell-killing effect of high radiation doses may indeed obscure the effects of chemotherapy.

New findings include evidence of an increased risk of thyroid cancer associated with alkylating agents among patients receiving radiation doses up to 20 Gy. Risk seemed to increase with alkylator score, with a highly significant risk in patients exposed in the highest category. Risk associated with alkylating agents decreased significantly with increasing thyroid radiation dose ( $P_{\text{trend}} = 0.03$ ). Drug combinations (alkylating agents, anthracyclines, and/or bleomycin) did not increase risk beyond that associated with alkylating agents alone. Some evidence of an increased risk related to treatment with anthracyclines was also observed among patients receiving radiation doses up to 20 Gy and also among patients not treated with radiation. Nevertheless, risk did not seem to increase with cumulative dose of anthracyclines.

Previous studies of childhood cancer survivors were unable to identify a statistically significant association of thyroid cancer risk and exposure to chemotherapy agents (4–7), possibly due to low statistical power to detect risks or the analytic strategies employed. A borderline increased risk for anthracyclines was suggested in the previous nested case-control study conducted within the CCSS (6). D'Angio and colleagues (8) suggested that dactinomycin (an alkylating agent) might decrease thyroid cancer risk but Tucker and colleagues (4) reported that dactinomycin may increase thyroid cancer risk at doses more than 10 Gy. These analyses were conducted using the full radiation dose range, and thus an independent chemotherapy effect evident only in the lower thyroid radiation dose range (<20 Gy) would not have been detected. Less than 20 Gy is a dose range in which cell sparing in the thyroid gland would be expected to predominate over cell killing or blocked cellular replication.

Alkylating agent chemotherapy has been reported to increase overall risk of second malignant neoplasms (14) and also of specific radiation-related cancers including leukemia (18, 19), bone sarcomas (20–23), lung cancer (24), bladder cancer (25), and stomach cancer (26). A reduced risk for radiation-related breast cancer was observed, likely due to suppression of ovarian hormone production by alkylating agents (27). Our study provides new evidence that, at lower radiation doses, there is an association between exposure to alkylating agents and subsequent thyroid cancer risk, plus an indication of increasing risk with higher doses of alkylating agents.

Strengths of this study include the large cohort size and long-term follow-up, substantial numbers of thyroid cancer cases, pathologic confirmation of reported

cancers, chemotherapy, and radiotherapy information on all members of the cohort, and individual radiation dosimetry. However, when interpreting the results of this study, especially for chemotherapy risk, certain limitations should be considered. Due to the strong correlation between type of treatment and type of first cancer, it can be difficult to distinguish an effect of a particular aspect of treatment from an effect of the first cancer. The inclusion of an adjustment variable does not always mitigate this effect. This is perhaps most relevant for procarbazine, an agent predominantly used to treat HL and CNS cancers in children (see Supplementary Table S1). When HL patients were removed from the analysis, the procarbazine effect remained of borderline significance, but the effect was not apparent when the CNS cancer patients were excluded. The small number of cases requires cautious interpretation, but it seemed that the procarbazine association was most influenced by patients treated for CNS cancers. Interestingly, procarbazine has recently been implicated in the etiology of second primary cancers of the lung (24) and stomach (26). As described in our previous report (9), other limitations are: (i) the reliance on self-reported occurrence of subsequent neoplasm; (ii) some uncertainty in radiation doses to the thyroid gland because only typical blocking procedures of the gland were incorporated in the dosimetry and, (iii) the possibility of targeted clinical surveillance for HL patients due to the high radiation dose these patients usually received. However, we did not observe a significant difference in tumor size between HL patients and others type of first cancer. This suggests that if these patients were under a greater clinical surveillance it was uniform across type of first cancer. The possibility of different levels of surveillance among the participating institutions was not evaluated.

In summary, results from this large cohort study suggest that alkylating agents play a role in the overall risk of secondary thyroid cancer after treatment for childhood cancer, although the effect is small relative to that associated with radiation. The effect of chemotherapy was observed exclusively among those exposed to less than 20 Gy of thyroid radiation, likely due to cell killing at higher radiation doses. Our study adds to a small but growing evidence base for chemotherapy agent-specific increased risks of thyroid cancer, which to date, were mainly thought to be related to prior radiotherapy.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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