Chemotherapy and thyroid cancer risk: A report from the Childhood Cancer Survivor Study

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Abstract

Background—While 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 using 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 ≤ 20 Gy, 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-trend = 0.03).
No chemotherapy-related risk was evident for thyroid radiation doses >20 Gy.

**Conclusions**—Treatments with alkylating agents increased thyroid cancer risk, but only in the radiation dose range under 20 Gy, where 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.

**Keywords**
Thyroid cancer; second cancer; chemotherapy; radiation risk; cohort study

**Introduction**

Childhood cancer survivors treated with radiation for their first tumor are at elevated risk for thyroid cancer since 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 demonstrated either a statistically significant association between chemotherapy and 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 demonstrated that thyroid cancer risk increases linearly with radiation dose at low to moderate doses, with a downturn in risk at doses > 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 five times higher among patients who did not have chemotherapy compared to 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 where the radiation effect would be expected to dominate.

While radiation exposure was the main focus of our previous cohort study analysis (9), the aim of the present 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 USA 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 two patients who developed thyroid cancer within five years of their first cancer treatment. The remaining cohort of 12,547 childhood cancer survivors were followed from five 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 using 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 M. D. 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, five 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 five cases developed more than five 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 five major classes: alkylating agents, anthracyclines, epipodophyllotoxins, platinum-based compounds and bleomycin (See Table 1 for details)
(13–14). Each subject was 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 three to approximate doxorubicin equivalence) (14–15) and grouped as follows: not exposed, <340 mg/m² and ≥ 340 mg/m². Bleomycin dose was grouped into three categories: not exposed, <100 mg/m² and ≥100 mg/m². 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, College Station, TX).

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 five 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 three subgroups defined as follows: no radiation to the thyroid gland, 0 Gy (n=4,009), ≤20 Gy (n = 9,982 and includes the 4,009 with 0 Gy), and >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 ≤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)*chemotherapy (y/n), 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% confidence intervals 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 greater than 20 Gy were most likely treated for HL (64%) and had the highest mean age at first cancer (13 years old) as compared to the cohort overall and the other two subgroups (7–8 years).

The proportion of patients treated with chemotherapy was lower in the >20 Gy subgroup (67%) than the ≤20 Gy (83%) subgroup or among patients not treated with radiation (77%).

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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 to 8.5 cm). No statistically significant difference in tumor size was observed between survivors of HL as compared to 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 Figure 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 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–<20 Gy category, 2.4% (1.5–3.7) for 20–<30 Gy category and 2.1% (1.2–3.5) for 30–<40 Gy category, compared to 1.0% (0.4–1.8) for patients receiving thyroid radiation doses over 40 Gy or 0.2% (CI, 0.1–0.4) for patients receiving between 0–<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 to patients not treated with radiation (P= 0.04). No significantly increased risks of thyroid cancer for patients receiving chemotherapy and radiotherapy (concomitant or sequential) vs. 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 relative risks 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 greater than 20 Gy. Chemotherapy was associated with a four-fold statistically significant excess risk among patients who received ≤20 Gy to the thyroid gland (p=0.006). Anthracyclines and alkylating agents appeared 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 to those not treated with alkylating agents, risk appeared to increase with alkylating score for the ≤ 20 Gy [low/medium exposed, RR=2.3 (95% CI, 1.3–4.5) and highly exposed, RR=2.8 (1.1–6.7). P-value for 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-value for heterogeneity=0.008] (Table 4). We also evaluated if 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 by alkylating agent score in comparison to 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-value for 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 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 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 subgroup (supplementary Table 1). 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 relative risk 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 to patients not treated with procarbazine, medium (>0 to <5000 mg/m$^2$) and high (>5000 mg/m$^2$) cumulative doses of procarbazine were associated with similarly elevated risks (P-value for heterogeneity across categories=0.09) (results not shown). The distribution of different classes of drugs by type of first cancer in the irradiated and non-irradiated groups in the CCSS cohort is described in supplementary Table 2.

Joint effects of radiation with chemotherapy and classes of drugs are presented in Figure 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 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.

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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 appeared 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-value for 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 appear 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 over 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. Under 20 Gy is a dose range where 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 1). 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 appeared 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: a) the reliance on self-reported occurrence of subsequent neoplasm; b) some uncertainty in radiation doses to the thyroid gland because only typical blocking procedures of the gland were incorporated in the dosimetry and, c) the possibility of targeted clinical surveillance for Hodgkin lymphoma patients due to the high radiation dose these patients usually received. However, we did not observe a significant difference in tumor size
between Hodgkin lymphoma 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.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


Figure 1. Cumulative incidence of thyroid cancer in the CCSS cohort according to time since first cancer treatment
Abbreviation: RT, radiation treatment; CT, chemotherapy; RT&CT, radiation and chemotherapy, CI, cumulative incidence.
(A) CI by gender; (B) CI by thyroid radiation dose categories; (C) CI by type of treatment; (D) CI by type of first cancer (Other cancers include neuroblastoma, Wilms tumor, central nervous system cancer and non-Hodgkin lymphoma).
Figure 2. Relative risk 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 due to the small number of cases. Dotted line indicates RR=1.0. P-value for trend in RRs for treatment across dose categories.
### Table 1

Descriptive and treatment characteristics of patients

<table>
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<th>Entire Cohort</th>
<th>≤ 20 Gy</th>
<th>&gt;20 Gy</th>
<th>Not treated with radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (% of total)</td>
<td>12,547(100.0)</td>
<td>9,982 (82.5)</td>
<td>2,116(17.5)</td>
<td>4,009 (31.9)</td>
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<tr>
<td>Mean thyroid gland dose, Gy b</td>
<td>11.0</td>
<td>1.6</td>
<td>35.5</td>
<td>0</td>
</tr>
<tr>
<td>Number of thyroid cancers</td>
<td>119</td>
<td>61</td>
<td>54</td>
<td>12</td>
</tr>
<tr>
<td>Mean age at first cancer (range in years)</td>
<td>8 (0–21)</td>
<td>7 (0–21)</td>
<td>13 (0–21)</td>
<td>8 (0–21)</td>
</tr>
<tr>
<td>Mean follow-up in years (range)</td>
<td>16 (0–29)</td>
<td>16 (0–29)</td>
<td>16 (0–29)</td>
<td>16 (0–29)</td>
</tr>
<tr>
<td>Mean number of years since first cancer (range)</td>
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<td>14.1 (5–34)</td>
<td>14.9 (5–34)</td>
<td>13.8 (5–33)</td>
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<tr>
<td>Mean age at thyroid cancer diagnosis (range)</td>
<td>28 (12–47)</td>
<td>27 (13–47)</td>
<td>29 (12–42)</td>
<td>30 (17–37)</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>5,926 (47.2)</td>
<td>4,759 (47.7)</td>
<td>976 (46.1)</td>
<td>1,978 (49.3)</td>
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<tr>
<td>Number who had chemotherapy, (%)</td>
<td>10,111 (80.6)</td>
<td>8,324 (83.4)</td>
<td>1,431 (67.6)</td>
<td>3,086 (76.9)</td>
</tr>
</tbody>
</table>

#### Type of first cancer (%)

- **Leukemia**
  - Entire Cohort: 4,261 (33.9)
  - ≤ 20 Gy: 4,013 (40.2)
  - >20 Gy: 96 (4.5)
  - Not treated with radiation: 1,304 (33)
- **Bone cancer**
  - Entire Cohort: 1,041 (8.3)
  - ≤ 20 Gy: 996 (9.9)
  - >20 Gy: 21 (0.9)
  - Not treated with radiation: 655 (16.3)
- **Central nervous system cancer**
  - Entire Cohort: 1,651 (13.2)
  - ≤ 20 Gy: 1,192 (11.9)
  - >20 Gy: 370 (17.5)
  - Not treated with radiation: 464 (11.6)
- **Hodgkin lymphoma**
  - Entire Cohort: 1,669 (13.3)
  - ≤ 20 Gy: 250 (2.5)
  - >20 Gy: 1,350 (63.8)
  - Not treated with radiation: 98 (2.4)
- **Wilms tumor**
  - Entire Cohort: 1,083 (8.6)
  - ≤ 20 Gy: 1,045 (10.5)
  - >20 Gy: 6 (0.3)
  - Not treated with radiation: 382 (9.5)
- **Neuroblastoma**
  - Entire Cohort: 832 (6.6)
  - ≤ 20 Gy: 782 (7.8)
  - >20 Gy: 34 (1.6)
  - Not treated with radiation: 421 (10.5)
- **Non-Hodgkin lymphoma**
  - Entire Cohort: 921 (7.3)
  - ≤ 20 Gy: 736 (7)
  - >20 Gy: 157 (7.4)
  - Not treated with radiation: 287 (7.2)
- **Soft tissue sarcoma**
  - Entire Cohort: 1,091 (8.7)
  - ≤ 20 Gy: 968 (9.7)
  - >20 Gy: 82 (3.9)
  - Not treated with radiation: 398 (9.9)

#### Treatment for first cancer (%)

- **No radiotherapy, no chemotherapy**
  - Entire Cohort: 923 (7.4)
  - ≤ 20 Gy: 923 (9.3)
  - >20 Gy: 0
  - Not treated with radiation: 923 (23.0)
- **Radiotherapy, no chemotherapy**
  - Entire Cohort: 1,512 (12.1)
  - ≤ 20 Gy: 735 (7.4)
  - >20 Gy: 685 (32.4)
  - Not treated with radiation: -
- **Chemotherapy, no radiotherapy**
  - Entire Cohort: 3,086 (24.6)
  - ≤ 20 Gy: 3,086 (30.9)
  - >20 Gy: 0
  - Not treated with radiation: 3,086 (76.9)
- **Radiotherapy and chemotherapy**
  - Entire Cohort: 7,025 (55.9)
  - ≤ 20 Gy: 5,237 (52.5)
  - >20 Gy: 1,431 (67.6)
  - Not treated with radiation: -

#### Chemotherapy drugs (%)

- **Any alkylating agents**
  - Entire Cohort: 6,733 (53.7)
  - ≤ 20 Gy: 5,191 (52.1)
  - >20 Gy: 1,286 (60.9)
  - Not treated with radiation: 1,860 (46.3)
- **Any anthracylines**
  - Entire Cohort: 5,179 (41.3)
  - ≤ 20 Gy: 4,493 (45.1)
  - >20 Gy: 477 (20.6)
  - Not treated with radiation: 1,572 (39.3)
- **Any bleomycin**
  - Entire Cohort: 755 (6.0)
  - ≤ 20 Gy: 448 (4.5)
  - >20 Gy: 281 (13.3)
  - Not treated with radiation: 301 (7.5)
- **Any platinum compounds**
  - Entire Cohort: 772 (6.2)
  - ≤ 20 Gy: 608 (6.1)
  - >20 Gy: 131 (6.2)
  - Not treated with radiation: 304 (7.6)
- **Any epipodophyllotoxin**
  - Entire Cohort: 1,196 (9.5)
  - ≤ 20 Gy: 1,035 (10.4)
  - >20 Gy: 113 (5.3)
  - Not treated with radiation: 296 (7.4)

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aEntire cohort includes 449 patients with unknown radiation dose (4 cases). Total number of patients with thyroid dose estimation is 12,098.

bFor the whole cohort, mean dose is among exposed patients

cPercentages may not sum to 100% due to rounding

dTreatment may also include surgery

eAlkylating agents include: diaziquone, carmustine, lomustine, chlorambucil, procarbazine, cyclophosphamide, dacarbazine, ifosfamide, melphalan, nitrogen mustard and busulfan.
Anthracyclines include: daunorubicin, doxorubicin and idarubicin

Platinum-based compounds include carboplatin and cis-platinum

Epipodophyllotoxins include teniposide and etoposide
Table 2

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

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

$^a$Weighted by person-years among those who received radiation.

$^b$Tumor size was available for only one case

Note: SD, Standard Deviation
### Risk of thyroid cancer according to type of treatment

#### Table 3

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

\(^a\)Background model includes sex, natural logarithm of attained age, first cancer (Hodgkin lymphoma, leukemia and others), radiation dose categories and chemotherapy (yes/no).

\(^b\) Treatment may also include surgery. Based on dates of initiation and cessation of RT and CT, two sequences of treatments were defined: a) concomitant chemo-radiotherapy, defined as RT and CT administered in overlapping time periods; b) Sequential chemo-radiotherapy, 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.

\(^c\) As only one 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 (0.3–3.6) and sequential CT and RT was 1.9 (95% CI, 0.9–3.6), p-value for heterogeneity =0.13.

\(^d\) P-value tests the heterogeneity of the first four categories (No RT, had CT, RT alone, Concomitant CT&RT and Sequential CT&RT). When considering patients that received sequential CT&RT, there was no difference in risk if chemotherapy was administered before or after radiation therapy (Test for heterogeneity, p-value=0.30).

Note: RR, relative risk; RT, radiation treatment; CT, chemotherapy; Numbers in bold indicate statistical significance at p<0.05.
Table 4

Risk of thyroid cancer with respect to chemotherapy by thyroid radiation dose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No radiation (thyroid dose=0 Gy)</th>
<th>Radiation, thyroid dose ≤ 20 Gy</th>
<th>Radiation, thyroid dose &gt; 20 Gy</th>
<th>Overall^d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PYR</td>
<td>TC</td>
<td>RR (95% CI)</td>
<td>PYR</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15,795</td>
<td>1</td>
<td>1.0 (ref.)</td>
<td>28,477</td>
</tr>
<tr>
<td>Yes</td>
<td>49,599</td>
<td>11</td>
<td>4.6 (0.8–86.3)</td>
<td>133,457</td>
</tr>
<tr>
<td>P-value</td>
<td>0.08</td>
<td>0.06</td>
<td>0.72</td>
<td>0.06</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35,235</td>
<td>3</td>
<td>1.0 (ref.)</td>
<td>82,004</td>
</tr>
<tr>
<td>Yes</td>
<td>30,061</td>
<td>9</td>
<td>2.8 (0.7–13.2)</td>
<td>79,770</td>
</tr>
<tr>
<td>P-value</td>
<td>0.13</td>
<td>0.02</td>
<td>0.76</td>
<td>0.07</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40,112</td>
<td>3</td>
<td>1.0 (ref.)</td>
<td>95,251</td>
</tr>
<tr>
<td>Yes</td>
<td>25,185</td>
<td>9</td>
<td>4.0 (1.2–18.0)</td>
<td>66,523</td>
</tr>
<tr>
<td>P-value</td>
<td>0.02</td>
<td>0.02</td>
<td>0.89</td>
<td>0.10</td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>60,886</td>
<td>7</td>
<td>1.0 (ref.)</td>
<td>155,350</td>
</tr>
<tr>
<td>Yes</td>
<td>4,411</td>
<td>5</td>
<td>4.6 (1.3–15.8)</td>
<td>6,425</td>
</tr>
<tr>
<td>P-value</td>
<td>0.02</td>
<td>0.21</td>
<td>0.45</td>
<td>0.98</td>
</tr>
<tr>
<td>Alkylating agent score^e</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>35,235</td>
<td>3</td>
<td>1.0 (ref.)</td>
<td>82,004</td>
</tr>
<tr>
<td>Low/medium exposed</td>
<td>21,999</td>
<td>3</td>
<td>1.8 (0.3–10.0)</td>
<td>58,974</td>
</tr>
<tr>
<td>Highly exposed</td>
<td>4,432</td>
<td>4</td>
<td>9.4 (1.4–56.8)</td>
<td>11,227</td>
</tr>
<tr>
<td>P-value</td>
<td>0.08</td>
<td>0.009</td>
<td>0.99</td>
<td>0.14</td>
</tr>
<tr>
<td>Bleomycin dose (mg/m^2)^f</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>60,866</td>
<td>7</td>
<td>1.0 (ref.)</td>
<td>155,350</td>
</tr>
<tr>
<td>&gt;0 – &lt; 100</td>
<td>1,638</td>
<td>2</td>
<td>4.5 (0.6–20.7)</td>
<td>2,751</td>
</tr>
<tr>
<td>≥100</td>
<td>2,385</td>
<td>2</td>
<td>3.3 (0.5–15.2)</td>
<td>2,990</td>
</tr>
<tr>
<td>Treatment</td>
<td>No radiation (thyroid dose=0 Gy)</td>
<td>Radiation, thyroid dose ≤ 20 Gy</td>
<td>Radiation, thyroid dose &gt; 20 Gy</td>
<td>Overall&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>12 cases</td>
<td>61 Cases</td>
<td>54 cases</td>
<td>115 cases</td>
</tr>
<tr>
<td>P-value</td>
<td>0.17</td>
<td>0.69</td>
<td>0.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Anthracycline dose (mg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>40,112</td>
<td>95,251</td>
<td>123,645</td>
<td>71</td>
</tr>
<tr>
<td>&gt;0 – &lt;340</td>
<td>11,342</td>
<td>36,470</td>
<td>40,343</td>
<td>26</td>
</tr>
<tr>
<td>≥340</td>
<td>11,688</td>
<td>25,084</td>
<td>26,324</td>
<td>14</td>
</tr>
<tr>
<td>P-value</td>
<td>0.17</td>
<td>0.69</td>
<td>0.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Drug combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>29,700</td>
<td>65,655</td>
<td>79,825</td>
<td>32</td>
</tr>
<tr>
<td>ANTH alone</td>
<td>5,415</td>
<td>16,094</td>
<td>16,219</td>
<td>5</td>
</tr>
<tr>
<td>BLEO alone</td>
<td>13</td>
<td>44</td>
<td>42,869</td>
<td>1</td>
</tr>
<tr>
<td>ALKY alone</td>
<td>10,202</td>
<td>29,329</td>
<td>140</td>
<td>1</td>
</tr>
<tr>
<td>ALKY + BLEO</td>
<td>196</td>
<td>223</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>ANTH + BLEO</td>
<td>106</td>
<td>384</td>
<td>595</td>
<td>1</td>
</tr>
<tr>
<td>ANTH + ALKY</td>
<td>15,567</td>
<td>44,272</td>
<td>47,091</td>
<td>1</td>
</tr>
<tr>
<td>ANTH + ALKY + BLEO</td>
<td>4,095</td>
<td>5,947</td>
<td>8,156</td>
<td>1</td>
</tr>
<tr>
<td>P-value</td>
<td>0.05</td>
<td>0.97</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>

NB: Four patients with missing thyroid radiation dose were excluded in this analysis. Significant associations are shown in bold print.

Abbreviations: RR, relative risk; PYR, person-year; TC, thyroid cancer cases; BLEO, bleomycin; ALKY, alkylating agents; ANTH, anthracyclines.

<sup>a</sup>A non-significant 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 (Hodgkin lymphoma, leukemia and others)

<sup>c</sup>RR adjusted for sex, natural logarithm of attained age, type of first cancer (Hodgkin lymphoma, 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 (Hodgkin lymphoma, 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 zero; 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)
\(g\) Cumulative dose of anthracyclins could not be estimated among 380 patients (4 cases).

\(h\) Not exposed category means not exposed to alkylating agents or anthracyclines or bleomycin, but could have been treated with other types of drugs.