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A Pooled Analysis of Thyroid Cancer Incidence Following Radiotherapy for Childhood Cancer

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Abstract

Childhood cancer five-year survival now exceeds 70–80%. Childhood exposure to radiation is a known thyroid carcinogen; however, data are limited for the evaluation of radiation dose-response at high doses, modifiers of the dose-response relationship and joint effects of radiotherapy and chemotherapy. To address these issues, we pooled two cohort and two nested case-control studies of childhood cancer survivors including 16,757 patients, with 187 developing primary thyroid cancer. Relative risks (RR) with 95% confidence intervals (CI) for thyroid cancer by treatment with alkylating agents, anthracyclines or bleomycin were 3.25 (0.9–14.9), 4.5 (1.4–17.8) and 3.2 (0.8–10.4), respectively, in patients without radiotherapy, and declined with greater radiation dose (RR trends, $P = 0.02$, 0.12 and 0.01, respectively). Radiation dose-related RRs increased approximately linearly for <10 Gy, leveled off at 10–15-fold for 10–30 Gy and then declined, but

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remained elevated for doses >50 Gy. The fitted RR at 10 Gy was 13.7 (95% CI: 8.0–24.0). Dose-related excess RRs increased with decreasing age at exposure ($P < 0.01$), but did not vary with attained age or time-since-exposure, remaining elevated 25+ years after exposure. Gender and number of treatments did not modify radiation effects. Thyroid cancer risks remained elevated many decades following radiotherapy, highlighting the need for continued follow up of childhood cancer survivors.

INTRODUCTION

In the 1950s and early 1960s, the first publications appeared that associated external radiation exposure during childhood with cancer of the thyroid gland (1–3). Research has since shown that the young thyroid gland is particularly radiosensitive, that radiation-related risk increases with dose up to several Gray (Gy), then appears to level off and possibly decreases at doses in the 2–20 Gy range. Depending on the study, both external and internal radiation can induce benign and malignant thyroid tumors, radiation-related effects may last 30 and more years after exposure, and papillary thyroid cancer is the main radiation-related histologic type of thyroid cancer (4–7). In 1995, Ron *et al.* published a pooled analysis of seven studies of thyroid cancer and external radiation that quantified the excess relative risk (ERR) per Gy and demonstrated that the strength of the association between thyroid cancer and radiation decreased with increasing age at exposure and that a radiogenic effect persisted for 30 years and more after exposure (5). The Ron *et al.* analysis included only one high-dose study of childhood cancer survivors, which limited the ability to evaluate the dose-response at high doses among children.

Due to improved treatments, survival from childhood cancers has increased appreciably, with 70–80% of childhood cancer patients in the U.S. and other countries now surviving at least 5 years (8–12). However, it is now clear these survivors have an increased risk of developing a variety of treatment-related diseases and conditions, including radiotherapy-related cancer of the thyroid (7, 13). In 2005, over 325,000 childhood cancer survivors were living in the U.S. (14), with about half over age 30 years, an age when thyroid cancer becomes more prevalent. To increase understanding of treatment-related primary thyroid cancer following childhood cancer, we analyzed pooled data from four childhood cancer survivor studies that had individual thyroid radiation dose estimates and information on specific chemotherapeutic agents. This information allowed for detailed assessment of the shape of the radiation dose-response at high doses and to investigate the relationship between radiotherapy and chemotherapy on the risk of thyroid cancer.

METHODS

Study Populations

We conducted a MEDLINE search, reviewed references and queried colleagues to identify all childhood cancer studies of radiation-related thyroid cancer. For the current analysis, we included studies with 10 thyroid cancer cases or more that were diagnosed as a second primary malignancy after treatment for a first childhood malignancy and with individual estimates of thyroid radiation dose. Four studies, two retrospective cohort studies and two nested case-control studies, met these criteria.

Study participants received radiotherapy at high doses and high dose rates, mainly from orthovoltage beams as high voltage X or γ rays. Because survivors had a variety of first cancers and therefore received many different radiotherapy regimens, there was a broad range of radiation doses to the thyroid gland. In addition, most patients had been treated concurrently or subsequently with chemotherapy. Each study investigator provided

estimated thyroid doses based on recorded treatment parameters and phantom measurements and detailed chemotherapy information. For all studies, we included microscopically confirmed cases only and all histologic types. A brief summary of each study is presented below and in Table 1.

United States Childhood Cancer Survivors Study (CCSS-US) (7)

This cohort study included 12,547 five-year survivors of childhood cancer treated before age 21 between 1970 and 1986 at 25 medical centers in the U.S. and Canada. From 1975 to 2005, there were 119 incident thyroid cancers among study participants, with 111 identified as second malignancies and 8 as third malignancies. In contrast to previous reports (7, 15), we only included cases who had thyroid cancer as their second malignancy. We excluded 34 patients who developed a second cancer within five years of the initial cancer diagnosis, leaving 12,064 patients. For each patient, we summed doses from all radiation treatments over the 10 years from the first cancer diagnosis. Thyroid doses ranged from 0 to 67 Gy, with a mean dose among exposed of 11.3 Gy. We excluded 449 patients, including 4 thyroid cancer cases, for which thyroid doses were not estimable. We analyzed 107 second primary thyroid cancer cases that were diagnosed and pathologically confirmed through the end of follow-up in 2005.

France and United Kingdom Childhood Cancer Survivors Study (CCSS-Fr/UK) (16)

The original cohort included 4,096 three-year cancer survivors who were diagnosed before age 15 between 1942 and 1986 at eight centers in France and the UK, with follow-up through 1991. For this pooling, we used substantially extended data, including childhood cancer survivors treated between 1942 and 2000, 179 newly identified patients, 267 patients with newly estimated thyroid radiation doses (176 patients with recovered radiotherapy records and 91 patients treated with brachytherapy for whom we assumed equal doses) and an additional 18 years of follow-up (1992–2009). We excluded one patient without a dose estimate, resulting in 4,541 patients. Thyroid doses ranged from 0 to 72 Gy, with a mean dose among exposed patients of 5.9 Gy. Analyses included 45 thyroid cancer cases.

Late Effects Study Group (LESG) (17)

This was a case-control study nested in a cohort of 9,170 two-year childhood cancer survivors treated before age 18 between 1936–1979 at 13 medical centers throughout the U.S., Canada and Western Europe. The study included 23 second primary thyroid cancers and 89 controls, matched on type of tumor and age at first tumor, duration of follow-up, gender and race. One case and seven controls were excluded due to insufficient information to estimate dose, leaving 22 cases and 82 controls. Radiation doses ranged from 0 to 76 Gy, with a mean dose of 12.5 Gy. Some thyroid cancer cases could potentially have appeared in both the LESG and CCSS-US studies. Although we could not specifically link case patients, filtering subjects using various study variables revealed that duplication could have involved at most three cases, and therefore any overlap of cases would have minimal impact on results.

Nordic Countries Childhood Cancer Survivor Study (CCSS-Nordic) (18)

This is a case-control study nested in a cohort of 25,120 childhood cancer survivors who were identified through the five Nordic population-based cancer registries. Patients were diagnosed before age 20 between 1960 and 1981. The original study included 14 pathologically confirmed second primary thyroid cancer cases and 41 controls, matched on age and calendar year of first tumor and duration of follow-up. We excluded one case and two controls without dose estimates and three controls that were treated for thyroid cancer as

their first cancer. The analysis included 13 confirmed second thyroid cancer cases and 36 matched controls. Estimated thyroid doses ranged from 0 to 55 Gy, with a mean of 10 Gy.

Organization of Data

Due to different inclusion criteria, numbers of patients and thyroid cancer cases for individual studies may differ slightly from original publications. In addition, CCSS-US and CCSS-FR/UK studies considered patients not exposed and assigned a zero dose if their thyroid dose estimate was below the detection limit (DL) under the dosimetry method. In the pooled data, 326 (2.8%) exposed patients [33 (0.4%) in the CCSS-US and 293 (9%) in the CCSS-Fr/UK] had radiation measurements below DLs. Since relatively few patients had estimates below the DL and since we were estimating relative risk (RR) patterns at dose levels that are only minimally influenced by low doses (19, 20), we inserted DL/ 2 as the thyroid dose estimate for these patients. This approach was less biased than inserting a dose of zero or equal to the DL, and was simpler than undertaking a complex imputation (21).

Dose fractionation can be defined in a variety of ways. We analyzed dose fractionation using number of radiation treatments, where one treatment was all radiation doses received within six months. Data harmonization requirements made this definition necessary. This resulted in the large majority of patients receiving one radiation “treatment”, which was similar by case status (88.6% and 87.4% among non-cases and cases, respectively) and across the individual studies. We considered radiation treatments following a pause of six months or more as a separate treatment.

We classified chemotherapy drugs into five groups: alkylating agents, anthracyclines, epipodophyllotoxins, platinum compounds and bleomycin. We computed the RR for patients who received a drug group relative to patients who did not receive a drug group if there were 10+ cases in the group. Chemotherapy often involved drug combinations. However, data were insufficient to differentiate RRs in patients receiving combination chemotherapies from those receiving a single group only. In addition, due to the different approaches used to estimate chemotherapy doses in each study, we could not assign consistent scores representing chemotherapy doses across the studies.

For the cohort studies, accrual of person-time started five years (CCSS-US) or three years (CCSS-Fr/UK) after first cancer and continued until death, loss to follow-up, occurrence of a second primary cancer or end of study, whichever occurred earliest. We cross-tabulated person-years (PY) by gender, age at exposure (<1, 1–4, 5–9, 10–14, 15 years), calendar year of follow-up (<1970, 1970–1974, ..., 1995–1999, 2000), time since exposure (<5, 5–9, 10–14, 15–19, 20–24, 25 years), attained age (<10, 10–14, 15–19, ..., 65–69, 70 years), any chemotherapy treatments (yes/no), exposure to individual chemotherapy groups (yes/no) and thyroid radiation dose (0, >0–1, 2–4, 5–9, 10–19, 20–29, 30–39, 40 Gy). We also computed person-years weighted means within each cell of the cross-tabulation for continuous variables. We used Poisson regression to model disease risk.

Since case-control data were limited, we enlarged categories for study-specific analysis: age at exposure (<1, 1–4, 5–9, 10 years), time since exposure (<10, 10 years), attained age (<20, 20 years) and thyroid radiation dose (0–1, 2–9, 10–29 and 30 Gy), with the lowest dose category as the referent for dose-response analysis. We used unconditional likelihood regression for binary (Bernoulli) outcomes for analysis.

For pooled analyses, we used a likelihood function that combined binomial and Bernoulli probabilities. For small disease rates, a binomial distribution closely approximates a Poisson distribution. For each cell of the person-years cross-tabulation, we assumed a binomial distribution, where the number of cases represented the “successes” from person-time

“trials”. The likelihood was then the product of cell-specific binomial and case-control subject-specific Bernoulli probabilities.

The pooled and the case-control analyses estimated odds ratios (OR), while the Poisson regression of cohort data estimated RRs. Since thyroid cancer is rare, these measures will be similar and we use RRs throughout for simplicity.

Risk Models

Initial analyses for either the binomial or Poisson regressions used a standard log-linear model for the RR i.e., $RR = \exp(\theta x)$, where x was a vector of explanatory variables that varied by analysis but generally included gender, attained age, year of birth, age at and type of first cancer diagnosis, chemotherapy and other factors, as well as categories of radiation dose and where θ was the associated vector of parameters.

We further examined the radiation dose-response relationship using both an excess relative risk (ERR) model:

$$\lambda(x, z, d) = \lambda_0(x) \{1 + ERR(d, z)\} \quad (1)$$

and, for the cohort studies only, an excess absolute risk (EAR) model:

$$\lambda(x, z, d) = \lambda_0(x) + EAR(d, z) \quad (2)$$

where $ERR(d, z)$ and $EAR(d, z)$ represented the excess relative risk and excess absolute risk, respectively, in terms of radiation dose, d , and other factors, z , and where $\lambda_0(x) = \exp(\theta x)$ described the thyroid cancer incidence rate among non-radiation exposed patients in terms of covariates x . We based hypothesis tests on likelihood ratios and 95% CIs for dose-response parameters on a profile likelihood.

For the ERR (and EAR) we used the general linear-exponential (linear-quadratic) form:

$$ERR(d) = \beta d \exp(\gamma_1 d + \gamma_2 d^2) \quad (3)$$

which included the linear model, $\gamma_1 = \gamma_2 = 0$, the linear-exponential (linear) model $\gamma_2 = 0$, and the linear-exponential (quadratic) model, $\gamma_1 = 0$. We also considered the extension whereby $(\beta_1 d + \beta_2 d^2)$ replaced βd , but found no additional improvement in fit. For the pooled data, the best fitting model was the linear-exponential (linear) model with β and γ_1 .

Using model (3), we evaluated a categorical effect modifier, z , in relationship to either the linear factor or the exponential factor or both using likelihood ratio tests. For an effect modifier, z , with J levels and in relationship to the linear component of the ERR (or EAR), we replaced βd with $(\sum_j \beta_j z_j d)$, where z_j was a zero/one indicator variable and β_j was the ERR/Gy for the j th category. The global test of no effect modification, i.e., $\beta_1 = \dots = \beta_J$, had $J-1$ degrees of freedom (df). We fitted model (3) with $\beta d \times \exp(\theta z)$ for the test of no trend ($\theta = 0$) with continuous z . We assessed effect modification with the nonlinear component of model (3) by replacing $\gamma_1 d$ with $(\sum_j \gamma_{1,j} z_j d)$ or $\gamma_2 d^2$ with $(\sum_j \gamma_{2,j} z_j d^2)$, as well as effect modification with both the linear and non-linear components. Power was limited and none of these latter tests were rejected. We evaluated the effect of categories of gender, age at exposure, attained age, time since exposure, number of radiation treatments, type of first cancer and chemotherapy as potential modifiers of the ERR and EAR. We considered a chemotherapy group only if more than 10 thyroid cancer patients had received that treatment for their first cancer.

Analyses used the EPICURE program, with the AMFIT module for Poisson regression and the GEMBO module for regression for the case-control analyses and for the Bernoulli/binomial regression of pooled data (22).

RESULTS

Characteristics of the Study Populations

The pooled data included 16,757 childhood cancer survivors, 288,660 person-years of follow-up and 187 patients who developed thyroid cancer (Table 1). Distributions of first cancer differed among the studies. In the CCSS-US cohort, leukemia (33.9%), Hodgkin lymphoma (13.2%) and cancer of the central nervous system (CNS) (12.9%) were the most frequent first cancers, while in the CCSS-Fr/UK study, which did not enroll leukemia patients, kidney cancer (19.5%), CNS cancer (17.2%) and neuroblastoma (13.2%) were the most frequent. In the LESG study, neuroblastoma (32.6%) was the most common first malignancy followed by kidney cancer (24.0%). In the CCSS-Nordic study, 18.3% had leukemia, while 30.6% of the patients had other cancers. In the combined data, leukemia and CNS patients represented 24.5% and 14.0% of first cancers, respectively.

Thyroid Cancer Risk by Chemotherapy and Other Factors

The case-control studies were matched on gender and age at first cancer and thus RRs for these factors were not estimable (Table 2). After adjustment for radiation dose and other variables, RRs in the cohort studies were about twofold in females and increased with attained age. RRs were significantly higher at younger ages at first cancer in the CCSS-US study, but showed no significant variation in the CCSS-Fr/UK study.

There was a non-significantly higher RR for children who received chemotherapy in the CCSS-US and CCSS-Nordic studies, but no effect in the LESG and CCSS-Fr/UK studies.

For all data combined, RRs of thyroid cancer were higher in females (RR = 2.2, 95% CI: 1.6–3.1), decreased with greater age at first cancer ($P < 0.01$) and increased with greater attained age ($P < 0.01$), but were not related to type of first cancer ($P = 0.23$). RRs were increased in patients treated with radiation (RR = 5.5, 95% CI: 3.1–9.7) and in patients treated with chemotherapy (RR = 1.4, 95% CI: 0.9–2.0), although the latter was not statistically significant.

In non-radiation treated patients, RRs and 95% CIs for thyroid cancer by any chemotherapy, alkylating agents, anthracyclines, or bleomycin were 2.4 (0.6–16.9), 3.2 (0.9–14.9), 4.5 (1.4–17.8) and 3.2 (0.8–10.4), respectively, and decreased with increasing radiation dose category for any chemotherapy ($P = 0.21$), alkylating agents ($P = 0.02$), anthracyclines ($P = 0.12$) and bleomycin ($P = 0.01$) to about 1.0 for patients receiving >20 Gy (Table 3). Using all data and adjusting for continuous radiation dose with model (3), the estimated RRs in non-radiation treated patients agreed closely with estimated chemotherapy RRs of 2.1 (0.7–6.9), 4.1 (1.4–11.7), 3.2 (1.3–8.3) and 4.6 (1.7–12.0), respectively.

Patients were often treated with multiple chemotherapeutic agents. Among 143 thyroid cancer cases receiving chemotherapy, 46 received alkylating agents only, 38 received alkylating agents and anthracyclines, 12 received alkylating agents, anthracyclines, and bleomycin, while 9 cases received other combinations and 38 cases received other types of chemotherapy or could not be classified unambiguously. For ≥ 20 Gy, RRs for alkylating agents alone, alkylating agents and anthracyclines, and alkylating agents, anthracyclines and bleomycin were 1.3 (0.7–2.5), 1.7 (1.0–3.0) and 3.2 (1.4–7.4), respectively, and slightly higher in those with combination therapies, although homogeneity was not rejected (not shown).

Radiation Dose-Response Relationships

For all data, RRs increased with radiation dose through 10 Gy, reached a plateau, then declined above 30 Gy (Table 4 and Fig. 1). Individual studies exhibited similar patterns, although maxima occurred at slightly different doses: 5–10 Gy for CCSS-Fr/UK, 2–30 Gy for LESG, 10–30 Gy for CCSS-Nordic and 20–30 Gy for CCSS-US.

A linear model did not describe RR trends for any study, although linearity was not rejected for the CCSS-Nordic data ($P = 0.18$) (Table 5). Comparing deviances, a measure of model fit, the linear-exponential (quadratic) model provided the best fit to the CCSS-US data, while for the other studies and for all data combined, the linear-exponential (linear) model provided the best fit. The fitted RR at 10 Gy was 13.7 (95% CI: 8.0–24.0) for all data, with individual fitted estimates ranging from 6.8 in the CCSS-Fr/UK study to 12.9 in the CCSS-Nordic study.

Modification of the Radiation Dose-Response Relationship

We used the linear-exponential (linear) model for the pooled data and for each study, except the CCSS-US study for which we used the linear-exponential (quadratic) model, to evaluate modification of the ERR/Gy (Table 6). In the pooled data, the ERR/Gy increased significantly with decreasing age at exposure ($P < 0.01$). The ERR/Gy increased with time since exposure with an apparent peak 15–19 years after first exposure, but remained elevated 25 years and more after exposure. Results were not appreciably changed after further adjusting for age at exposure as an effect modifier of dose (not shown).

We also observed a consistent elevation in ERR/Gy with increasing attained age, which remained after adjustment for age at exposure (not shown). The ERR/Gy was significantly lower for Hodgkin lymphoma patients ($P < 0.01$), even after further adjustment for age at exposure ($P = 0.05$). Gender and number of treatments did not modify the ERR/Gy estimate, although multiple radiation treatments increased the ERR/Gy in the CCSS-Fr/UK study ($P = 0.05$).

Consistent with Table 3, we observed significant effect modification of radiation dose for treatment with alkylating agents ($P = 0.01$), anthracyclines ($P = 0.01$) and bleomycin ($P = 0.02$). Additional detailed analyses suggested that the reduced radiation effects for treatment with alkylating agents and anthracyclines derived from a reduced strength of association (i.e., different β 's) and not from changes in curvatures (i.e., similar γ_1 's) (see Supplementary Material Table S1, <http://dx.doi.org/10.1667/RR2889.1.S1>).

We evaluated the influence of each study on the estimated RR at 10 Gy by omitting each study in turn and found only slight changes in point estimates (see Supplementary Material Fig. S1, <http://dx.doi.org/10.1667/RR2889.1.S1>). Using a linear-exponential (linear) model, there was homogeneity of radiation effects across studies ($P = 0.57$) (see Supplementary Material Table S2, <http://dx.doi.org/10.1667/RR2889.1.S1>). However, under a linear-exponential (linear-quadratic) model, there was heterogeneity ($P = 0.01$), due entirely to the CCSS-US study, with the other three studies exhibiting homogeneity of dose effects ($P = 0.53$).

Estimation of the EAR

We fitted EAR models to the two cohort studies. The pooled estimate of the EAR at 10 Gy times 10^4 PY was 12.4 (95% CI: 9.3–16.8), and differed for the CCSS-US (12.7, 95% CI: 8.9–18.1) and CCSS-Fr/UK (8.2, 95% CI: 4.3–15.4) studies ($P < 0.01$) (see Supplementary Material Tables S3 and S4, <http://dx.doi.org/10.1667/RR2889.1.S1>).

At 10 Gy, the pooled EAR estimate was twofold in females compared to males ($P = 0.01$) and increased with age at radiation exposure under age 15 years, time since radiation exposure, calendar year of diagnosis and attained age (see Supplementary Material Table S5, <http://dx.doi.org/10.1667/RR2889.1.S1>). We observed similar EAR patterns in the CCSS-US and CCSS-Fr/UK studies, except gender which did not modify the EAR in the CCSS-Fr/UK study ($P = 0.91$).

ERR and EAR models are not nested and therefore not directly able to be compared. However, differences in deviances suggested that data were more simply described with the ERR model than with the EAR model (not shown).

Histology-Specific Results

Among 165 thyroid cancer cases with histology information, 133 cases (80.6%) were papillary tumors, and results restricted to those tumors were similar to results for all thyroid cancer (see Supplementary Material Table S6, <http://dx.doi.org/10.1667/RR2889.1.S1>). There were too few cases ($n = 32$) of others histologies to evaluate in detail. However, they also appeared to be radiogenic ($P < 0.01$).

DISCUSSION

Childhood exposure to radiation is a well known cause of thyroid cancer, but until recently there were limited data at the high doses used to treat childhood cancers (5). The improvement in childhood cancer survival (8–12, 23) and relatively high risk for developing subsequent treatment-related thyroid cancers (7, 13, 15, 24) highlighted the need to better understand the role of radiotherapy and the joint effects of radiotherapy and chemotherapy in the development of thyroid cancer. Our pooling used original data from the four studies that had individual thyroid dose estimates and information on chemotherapy. The CCSS-US was the largest individual study, with 57% of all thyroid cancers. However, the inclusion of the LESG, CCSS-Fr/UK and CCSS-Nordic studies increased our ability to evaluate patterns of radiation and chemotherapy risks and interactions between treatment types over a range of time periods (1936 to 2000) and populations (North American and European) beyond those demonstrated in the CCSS-US study alone (7, 15).

In this first pooled analysis of childhood cancer survivors, which included 187 thyroid cancer cases, we observed an approximately linear increase in RR of thyroid cancer with dose through about 10 Gy. Above 10 Gy, RRs leveled, then declined above 30 Gy. Study-specific RR estimates at 10 Gy ranged from 6.8 to 12.9. For the pooled data, the best fitting ERR model was linear exponential (linear) with an estimated RR at 10 Gy of 13.7 (95% CI: 8.0–24.0). The maximum fitted RR was 14.9 (95% CI: 8.2–24.5), which occurred at 15.9 Gy.

At 1 Gy, our estimated RR was 3.2 (95% CI: 2.2–5.3), which was lower than the estimated 8.7 at 1 Gy (95% CI: 3.1, 29.7) from the pooled analysis of five cohort studies of populations irradiated primarily at low to moderate doses (5). However, after adjustment for (non-significant) differences between exposed and non-exposed subjects, the Ron *et al.* estimate was 4.8 (95% CI: 2.4, 11.7) and very similar to our estimate.

While the leveling and downturn of the ERR at high doses likely reflected cell killing, it is noteworthy that the ERR remained elevated even above 40 Gy. For lung and breast cancer risks after high-dose radiotherapy for Hodgkin lymphoma, Sachs and Brenner proposed that stem cell repopulation during and after fractionated exposure can compensate for cell killing (25). They suggested that accelerated repopulation can explain why risks for solid cancer

after radiotherapy remains substantially greater than predictions based solely on initiation and cell-killing mechanisms.

Both the ERR and EAR increased with decreasing age at exposure and showed no diminution with time since exposure. Although risks remained elevated throughout the follow-up period, risks appeared to peak 15–19 years after exposure in both the ERR and EAR models. As in previous studies, we found that gender modified the EAR/PY-Gy, with females having double the risk of males, but not the ERR/Gy. This agreed with the pooled analysis of Ron *et al.*, where females had a higher ERR/Gy, but the difference was not statistically significant and individual studies were inconsistent (5). Attained age and calendar year of diagnosis both modified the EAR, with risk increasing with increasing age and calendar period of incidence. These results generally were similar to those reported for the CCSS-US study as it was the larger study in the EAR analysis. We found that the effect modification by number of treatments differed by study, with a statistically significantly higher ERR/Gy with greater number of treatments for the CCSS-Fr/UK study, and a non-statistically significantly lower ERR/Gy in the CCSS-US and CCSS-Nordic studies. These findings were consistent with dose rate having only a weak effect on thyroid cell line survival (26) and were compatible with risk estimates from studies of persons receiving external radiation, or I-131 radiation from Chernobyl during childhood (27). Finally, we observed lower ERR/Gy estimates among Hodgkin lymphoma patients compared with “other” first cancers (Table 6). The lower ERR/Gy persisted for Hodgkin lymphoma patients after including age at exposure as a modifier in the model. The reason for this difference was unknown. Radiation dosimetry would have accounted for treatment-related dose, and our evaluation of ERR/Gy did not vary by tumor size, which suggested comparable rates of thyroid screening among Hodgkin lymphoma patients.

A particularly interesting finding was the joint radiotherapy and chemotherapy relationship. Veiga *et al.* recently reported that chemotherapy increased the risk of developing a secondary thyroid cancer after a childhood cancer only if the radiotherapy dose to the thyroid was less than 20 Gy (15). While overall results were similar, our pooling expanded that case group by 80% and allowed a more detailed examination of RRs for chemotherapy with increasing radiation dose. We observed RRs of thyroid cancer of 3.2 to 4.5 for patients with chemotherapy (alkylating agents, anthracyclines and bleomycin) relative to those without chemotherapy, among those who received no radiation, RRs of 1.4 to 2.6 among those who received doses up to 5 Gy, RRs of 1.1 to 2.4 among those who received doses between 5 to 20 Gy, and no excess RRs among those who received doses >20 Gy. For both alkylating agents and bleomycin, decreasing trends were statistically significant as radiation dose increased, with a similar but non-significant pattern for anthracyclines. Consistent with Veiga *et al.*, among patients who did not have chemotherapy, we observed enhanced radiation effects in the two cohort studies. However, we did not find a similar pattern in the CCSS-Nordic case-control study, which included only 13 thyroid cancer patients.

Combinations of chemotherapies were common, and data were insufficient to disentangle the effects of individual drugs or of differences in the radiation and chemotherapy interactions. While observed RRs were slightly greater in patients with multiple chemotherapies, differences were nonsignificant. These results were consistent with Veiga *et al.*, who found little evidence of differential RRs for treatment combinations, either overall or > 20 Gy (15). Although we could not harmonize a consistent metric for drug dose across studies, Veiga *et al.* found increased RRs with increasing drug score for alkylating agents.

As in all second cancer studies, we were evaluating older treatment regimens because the occurrence of a second cancer required a minimum follow-up period. With the majority of treatments occurring before 1985, we could not evaluate conformal radiotherapy, intensity-

modulated radiation therapy (IMRT) and proton therapy. While these new techniques offer a great advantage in delivering the radiation to a more concentrated target volume and thereby minimize dose to nearby normal tissue, the larger total body dose may increase risk of second cancers due to increased leakage radiation and exposure of a larger tissue volume (28).

The treatment of childhood cancer patients is one of oncology's greatest successes, but second cancer risks from high-dose radiotherapy remain a concern. From this perspective, the ideal treatment plan would give a very high dose to the tumor while minimizing radiation dose to surrounding and distant normal tissue and thus second cancer risks. A better understanding of the shape of the dose-response relationship for radiation-induced cancers potentially allows optimization of treatment plans to minimize second cancer risks from radiotherapy. Our pooled analysis of thyroid cancer adds to the growing literature showing that certain chemotherapeutic agents can increase risks of solid tumors, but may interact with radiotherapy in complex ways. We also show that, while risks decline after high-dose radiotherapy, elevated risks continue for potentially many decades and therefore indicates the need for continued follow up of childhood cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1. Relative Risks (RR) and 95% confidence intervals for categories of radiation dose and fitted dose-response models for each study and for all data combined. Category-specific RRs for LESG and CCSS-Nordic Studies adjusted using the fitted linear-exponential (linear) model to reflect a referent of zero dose.

TABLE 1

Characteristics of Patients for Each Study and for All Pooled Data Combined

Study characteristics	LESG	CCSS-Nordic	CCSS-US	CCSS-Fr/UK
Study design	Case-control	Case-control	Cohort	Cohort
Thyroid cancer patients	22	13	107	45
Papillary tumors (%)	86.9 ^a	81.6	81.3	82.2
Non-thyroid cancer patients	82	36	11,957	4,495
Person-years	—	—	193,206	81,904
Year of treatment	1936–1979	1957–1981	1970–1986	1942–2000
Follow-up period ^b	1938–1984	1960–1991	1975–2006	1946–2009
Age at first cancer ^c (range)	5.2 (0–18.7)	10.7 (2.0–19.0)	8.2 (0–20.9)	6.2 (0–17.1)
Years since exposure ^c (range)	12.5 (3.4–26.4)	14.3 (5.0–27.0)	14.2 (5.0–34.0)	15.6 (3.0–55.6)
Age at thyroid cancer diagnosis ^c (range)	19.2 (3.7–29.6)	25.6 (11.3–40.9)	29.1 (11.5–46.2)	28.3 (11.5–46.2)
Thyroid dose (Gy) ^d				
Mean	12.8	7.0	11.3	5.9
Median	3.3	0.8	1.1	0.6
Range	0.1–64	0.06–49	0.0035–67.3	0.0007–72.1
Number of treatments (%) ^e				
1	NA ^f	24 (82.8)	7,502 (88.2)	2,830 (87.0)
2+		5 (17.2)	926 (10.9)	315 (9.7)
Missing		0	79 (0.9)	107 (3.3)
Type of first cancer (%)				
Bone	4 (3.8)	4 (8.1)	1,013 (8.4)	290 (6.4)
Central nervous system	4 (3.8)	7 (14.2)	1,560 (12.9)	780 (17.2)
Hodgkin lymphoma	20 (19.2)	6 (12.2)	1,595 (13.2)	385 (8.5)
Kidney (Wilm's tumor)	25 (24.0)	3 (6.1)	1,049 (8.7)	887 (19.5)
Leukemia	NA	9 (18.3)	4,100 (33.9)	NA
Non-Hodgkin lymphoma	7 (6.7)	2 (4.0)	888 (7.4)	479 (10.6)
Neuroblastoma	34 (32.6)	1 (2.0)	814 (6.7)	598 (13.2)
Soft tissue sarcoma	4 (3.8)	2 (4.0)	1,045 (8.7)	584 (12.9)
Other	6 (5.7)	15 (30.6)	NA	537 (11.8)
Type of treatment (%) ^g				
No radiotherapy, no chemotherapy	6 (5.8)	11 (22.4)	923 (7.7)	386 (8.5)
Chemotherapy, no radiotherapy	5 (4.8)	9 (18.4)	1,416 (11.9)	902 (19.9)
Radiotherapy, no chemotherapy	44 (42.3)	13 (26.5)	3,079 (25.9)	1,040 (22.9)
Radiotherapy + chemotherapy	49 (47.1)	16 (32.6)	6,477 (54.5)	2,212 (48.7)

Note. NA, not applicable, category of type of first cancer was missing or not included in the study.

^aFrom Tucker *et al.* (17), since histology information was not available in the dataset.

^bFollow-up period for cohort studies or case ascertainment period for the case-control studies.

^cYears. For cohort studies, entries are person-years weighted means for age at first cancer and years since exposure.

^d Among exposed subjects for cohort studies and among exposed controls for the case-control studies.

^e One treatment defined as all radiation given within a six-month interval.

^f NA, information not available or missing.

^g Treatment may also include surgery.

TABLE 2
Relative Risk (RR) of Thyroid Cancer after Treatment for Childhood Cancer by Selected Variables for each Study and for All Data Combined

	LESG		CCSS-Nordic		CCSS-US		CCSS-Fr/UK		Pooled data	
	N ^a	RR ^b (95% CI)	N	RR ^b (95% CI)	N	RR ^c (95% CI)	N	RR ^c (95% CI)	N	RR ^d (95% CI)
Gender										
Male	8 (28)	NA ^e	3 (9)	NA	34 (100,377)	1.0	19 (44,371)	1.0	64 (144,796)	1.0
Female	14 (54)		10 (27)		73 (92,829)	2.6 (1.7–3.8)	26 (37,533)	1.6 (0.9–2.9)	123 (130,467)	2.0 (1.5–2.8)
<i>p</i> <i>f</i>						0.01		0.11		<0.01
Age at first cancer (years)										
<1	4 (18)	NA	–	NA	6 (14,503)	1.0	2 (12,892)	1.0	12 (27,417)	1.0
1–4	7 (33)		3 (12)		23 (64,362)	0.5 (0.2–1.1)	11 (30,588)	1.3 (0.3–5.9)	44 (95,005)	0.7 (0.3–1.3)
5–9	5 (15)		2 (6)		23 (42,267)	0.4 (0.2–1.1)	16 (19,730)	1.6 (0.3–7.3)	46 (62,025)	0.6 (0.3–1.3)
10–14	4 (11)		2 (4)		40 (38,665)	0.5 (0.2–1.3)	16 (16,120) ^g	1.6 (0.3–7.5)	62 (54,806)	0.7 (0.3–1.4)
15	2 (5)		6 (14)		15 (33,411)	0.2 (0.05–0.6)	–		23 (36,010)	0.3 (0.1–0.6)
<i>p</i> <i>f</i>						0.02		0.23		<0.01
Years since first cancer										
<15	15 (60)	NA	8 (21)	NA	30 (112,597)	1.0	7 (44,174)	1.0	60 (156,875)	1.0
15–19	4 (11)		3 (7)		42 (47,714)	2.0 (1.1–3.7)	14 (13,442)	2.6 (0.9–7.6)	63 (61,183)	2.4 (1.4–4.0)
20–24	3 (11)		2 (8)		19 (21,700)	1.7 (0.8–3.6)	11 (10,900)	1.7 (0.5–6.4)	32 (32,610)	1.9 (1.0–3.5)
25					16 (11,194)	2.5 (1.1–5.9)	13 (13,387)	1.2 (0.3–5.9)	32 (24,596)	2.3 (1.1–4.9)
<i>p</i> <i>f</i>						0.08		0.14		0.01
Attained age (years)										
<20	12 (52)	NA	3 (9)	NA	16 (80,931)	1.0	4 (40,721)	1.0	35 (121,728)	1.0
20–29	10 (30)		5 (17)		42 (74,640)	2.5 (0.9–6.8)	22 (25,302)	8.4 (2.9–24.6)	79 (100,003)	3.5 (2.3–5.5)
30–34	–		5 (10)		31 (21,488)	6.6 (1.6–26.9)	11 (7,620)	15.0 (4.7–48.4)	46 (29,116)	8.9 (5.2–15.2)
35	–				18 (16,152)	6.7 (1.2–36.7)	8 (8,261)	12.7 (1.0–2.4)	27 (24,413)	9.0 (4.7–17.2)
<i>p</i> <i>f</i>						0.03		<0.01		<0.01
Type of primary cancer										
Kidney (Wilm's)	4 (21)		1 (2)	1.0	2 (17,550)	1.0	8 (18,880)	1.0	15 (36,458)	1.0
Bone cancer	0 (4)		1 (3)	0.7 (0.01–43.4)	10 (16,174)	4.5 (0.9–21.4)	1 (4,721)	0.4 (0.05–3.4)	12 (20,903)	1.6 (0.7–3.7)

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	LESG		CCSS-Nordic		CCSS-US		CCSS-Fr/UK		Pooled data	
	N ^a	RR ^b (95% CI)	N	RR ^b (95% CI)	N	RR ^c (95% CI)	N	RR ^c (95% CI)	N	RR ^d (95% CI)
Central nervous system	1 (3)	NA	0 (7)	–	13 (23,618)	2.2 (0.5–10.6)	2 (12,683)	0.3 (0.05–1.3)	16 (36,312)	0.7 (0.3–1.6)
Hodgkin lymphoma	5 (15)		5 (1)	4.6 (0.09–209.7)	34 (26,283)	2.3 (0.5–10.8)	15 (5,950)	2.1 (0.7–5.9)	59 (32,259)	1.3 (0.6–2.6)
Leukemia	–		2 (7)	0.5 (0.01–16.5)	26 (63,790)	1.9 (0.4–8.4)	–	–	28 (63,799)	1.0 (0.5–2.0)
Non-Hodgkin lymphoma	2 (5)		1 (1)	1.7 (0.03–99.9)	6 (14,493)	1.4 (0.3–7.2)	6 (7,843)	1.6 (0.6–4.7)	15 (22,345)	1.0 (0.5–2.2)
Neuroblastoma	7 (27)		0 (1)	–	8 (13,802)	4.0 (0.8–19.4)	7 (11,373)	1.4 (0.5–4.2)	22 (25,210)	1.9 (0.9–3.8)
Soft tissue sarcoma	1 (3)		0 (2)	–	8 (17,497)	2.7 (0.6–13.20)	3 (9,931)	0.6 (0.2–2.4)	12 (27,434)	1.0 (0.5–2.3)
Others	2 (4)		3 (12)	0.5 (0.01–16.2)	–	–	3 (10,522)	0.7 (0.2–2.7)	8 (10,544)	1.0 (0.4–3.1)
<i>P^f</i>						0.19		0.05		0.28
Radiation treatment										
No	0 (11)	–∞	1 (19)	1.0	10 (62,705)	1.0	3 (22,753)	1.0	14 (85,489)	1.0
Yes	22 (71)	1.0	12 (17)	14.8 (1.7–130)	97 (130,501)	4.5 (2.2–8.8)	42 (59,151)	4.0 (1.2–13.2)	173 (189,774)	5.5 (3.1–9.7)
<i>P^f</i>		0.01		<0.01		<0.01		<0.01		<0.01
Chemotherapy										
No	10 (40)	1.0	4 (20)	1.0	18 (40,200)	1.0	12 (30,025)	1.0	44 (70,299)	1.0
Yes	12 (42)	1.0 (0.4–2.9)	9 (16)	2.6 (0.4–15.2)	89 (153,006)	1.5 (0.9–2.7)	33 (51,879)	1.1 (0.5–2.3)	143 (204,964)	1.4 (0.9–2.0)
<i>P^f</i>		0.96		0.29		0.13		0.90		0.09

^aN denotes counts of cases (controls) for case-control studies (LESG and CCSS-Nordic), cases (person-years) for cohort studies (CCSS-US and CCSS-Fr/UK) and cases (trials) for pooled data, with trials equal to the sum of controls and person-years.

^bRRs computed using unconditional logistic regression with adjustment for gender and attained age.

^cRRs computed using Poisson regression with adjustment for gender, attained age, first cancer (Wilm's, Hodgkin lymphoma and others), chemotherapy, radiation dose categories and year of birth, excluding the respective risk factor according to the analysis.

^dRRs computed using unconditional logistic regression with adjustment for study, gender, attained age, first cancer (Wilm's, Hodgkin lymphoma and others), chemotherapy, radiation dose categories and year of birth, excluding the respective risk factor according to the analysis.

^eNA, "Not applicable" since cases and controls were matched for gender and age at first cancer. For LESG study, also matched for type of first cancer.

^f*P*-value for likelihood ratio test of homogeneity of risk across categories.

^gCategory merges all higher categories.

TABLE 3
Relative Risk^a (RR) of Thyroid Cancer and Use of Chemotherapy by Categories of Thyroid Radiation Dose for All Data Combined

Treatment	Levels	Thyroid radiation dose									
		0 Gy		> 0 and 5 Gy		> 5 and 20 Gy		> 20 Gy		P ^c	P ^e
		N ^b	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)		
Chemotherapy	No	2 (23,482)	1.0	11 (29,499)	1.0	9 (3,444)	1.0	22 (13,875)	1.0		
	Yes	12 (62,008)	2.4 (0.5–12.3)	34 (96,999)	2.5 (1.1–5.9)	45 (19,294)	1.1 (0.5–2.8)	52 (26,663)	1.3 (0.7–2.1)	0.11	
	<i>P</i> ^d		0.24		0.02		0.75		0.35		
Alkylating agents	No	4 (46,695)	1.0	21 (71,297)	1.0	24 (9,650)	1.0	33 (17,168)	1.0		
	Yes	10 (38,697)	3.2 (0.8–12.8)	24 (55,141)	2.5 (1.2–5.3)	33 (14,538)	1.3 (0.7–2.5)	41 (23,326)	0.9 (0.5–1.4)	0.01	
	<i>P</i> ^d		0.08		0.01		0.44		0.58		
Anthracyclines ^e	No	4 (54,844)	1.0	25 (82,192)	1.0	24 (13,214)	1.0	56 (33,671)	1.0		
	Yes	10 (30,537)	4.5 (1.3–15.7)	14 (44,203)	1.4 (0.7–2.9)	21 (9,497)	1.2 (0.7–2.4)	11 (76,798)	0.8 (0.4–1.6)	0.12	
	<i>P</i> ^d		0.01		0.33		0.49		0.59		
Bleomycin ^e	No	10 (79,499)	1.0	37 (124,636)	1.0	40 (21,745)	1.0	62 (36,760)	1.0		
	Yes	4 (5,882)	3.1 (0.9–10.9)	2 (1,759)	2.0 (0.4–9.9)	5 (966)	2.4 (0.8–7.7)	5 (3,708)	0.6 (0.2–1.6)	0.01	
	<i>P</i> ^d		0.09		0.41		0.16		0.30		

^aRRs adjusted for study, gender, attained age, type of first cancer (Wilm's, Hodgkin lymphoma and others) and year of birth. Analysis omitted patients with missing data on use of alkylating agents, anthracyclines or bleomycin.

^bN denotes counts of cases (trials), where for pooled data trials equaled the sum of controls and person-years.

^cP-value for trend in RRs for treatment across dose categories.

^dP-value for test of no treatment effect within category of radiation dose.

^eLESG study did not have information on anthracycline and bleomycin administration and was omitted.

TABLE 4
Relative Risk^a (RR) of Thyroid Cancer by Radiation Dose Categories for Each Study and for All Data Combined

	Radiation dose (Gy)								
	0	>0-1	2-4	5-9	10-19	20-29	30-39	40	Total
Pooled data									
Cases	14	32	13	18	36	38	21	15	187
Trials	85,490	116,208	10,199	7,305	15,523	14,595	12,405	13,538	275,263
Mean ^b	0	0.5	3.2	7.3	14.8	24.3	35.5	46.1	9.3
RR 95% CI	1.0	1.9 (1.0-3.7)	7.4 (3.3-16.4)	14.9 (7.1-31.4)	14.8 (7.8-28.3)	15.2 (7.8-28.4)	9.3 (4.3-20.3)	5.1 (2.2-11.9)	<0.01 ^c
Cohort study: CCSS-US									
Cases	10	14	3	5	23	27	16	9	107
Person-years	62,705	76,425	5,039	3,444	11,478	11,190	10,706	12,219	193,206
Mean ^b	0	0.6	3.1	7.4	14.7	24.3	35.5	45.7	11.2
RR 95% CI	1.0	1.2 (0.5-2.7)	4.0 (1.1-14.7)	9.0 (3.1-26.4)	12.1 (5.7-25.6)	14.3 (6.7-30.4)	8.9 (3.6-22.0)	4.3 (1.5-12.2)	<0.01 ^c
Cohort study: CCSS-Fr/UK									
Cases	3	11	5	9	5	7	3	2	45
Person-years	22,752	39,736	5,145	3,847	4,030	3,392	1,691	1,307	81,904
Mean ^b	0	0.4	3.2	7.2	15	24.4	35.5	49.6	5.6
RR 95% CI	1.0	2.0 (0.6-7.4)	6.9 (1.6-29.1)	13.9 (3.6-53.5)	5.9 (1.3-26.3)	8.6 (2.0-36.6)	7.3 (1.3-39.9)	6.6 (1.0-43.2)	<0.01 ^c
Case-Control study: LESG									
Cases	3	7	7	5	22				
Controls	40	17	14	11	82				
Mean ^b	0.71	5.8	20.2	45.7	11.1				
OR (95% CI)	1.0	6.1 (1.4-27.2)	6.1 (1.4-27.2)	5.4 (1.1-27.2)	0.02 ^c				
Case-Control study: CCSS-Nordic									
Cases	5	2	5	1	13				
Controls	31	2	2	1	36				

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	Radiation dose (Gy)			
	0-1	2-9	10-29	30
Mean ^b	0.26	4.9	24.1	48.9
OR (95% CI)	1.0	4.0 (0.4-43.1)	9.3 (1.1-76.7)	3.1 (0.07-149.1)
				0.18 ^c

^aRRs estimated for cohort studies based on Poisson regression, adjusting for gender, attained age, chemotherapy, first cancer (Wilm's, Hodgkin lymphoma and others) and year of birth, and for case-control and pooled data based on unconditional logistic regression adjusting for gender and attained age (LESG), or gender attained age and first cancer (CCSS-Nordic) or gender, attained age, chemotherapy, first cancer, study and year of birth (pooled data).

^bMean dose among exposed patients weighted by person-years (cohort studies) or by trials (pooled data, see text) or mean dose among all controls (case-control studies).

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

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TABLE 5
Parameter Estimates for the Best Fitting Model^a for the Relative Risk (RR) for Each Study and for All Data Combined

Study	Model	Linear slope, β (95% CI)	Curvature	P^b	RR _{10 Gy} ^c (95% CI)
CCSS-Nordic ^d	Linear-exponential (linear)	2.47 (0.0–18)	–0.0731	0.18	12.9 (1.3–499.7)
LESG ^e	Linear-exponential (linear)	1.49 (0.1–44.1)	–0.0498	0.05	9.9 (1.4–220.7)
CCSS-Fr/UK ^f	Linear-exponential (linear)	1.05 (0.3–3.4)	–0.0599	<0.01	6.8 (2.9–17.8)
CCSS-US ^f	Linear-exponential (quadratic)	1.44 (0.7–3.0)	–0.0013	<0.01	12.8 (0.6–26.2)
Pooled data ^{f,g}	Linear-exponential (linear)	2.38 (1.2–4.6)	–0.0628	<0.01	13.7 (8.0–24.0)

^aModels for the excess RR with radiation dose, d, include: linear-exponential (linear): $RR(d) = [1 + \beta \cdot d \exp(\gamma_1 d)]$; and linear-exponential (quadratic): $RR(d) = [1 + \beta \cdot d \exp(\gamma_2 d^2)]$, with β defining the linear slope parameter and γ_1 or γ_2 defining the curvature.

^bP-value for test of no departure from linearity ($\gamma_1 = 0$ or $\gamma_2 = 0$).

^cFitted relative risk at 10 Gy.

^dFor the CCSS-Nordic study, model fitting inserted the mean dose (0.26 Gy) for all doses <2 Gy and used unconditional likelihood regression adjusted for gender, attained age and first cancer. The test of departure from a linear model, $RR(d) = [1 + \beta \cdot d]$, was not rejected ($P = 0.18$); the estimated β and the estimated RR_{10Gy} with 95% CIs were 0.26 (0.02–2.86) and 3.6 (1.2–29.6), respectively. For consistency, analyses used the linear-exponential (linear) form.

^eModel fitting inserted the mean dose (0.71 Gy) for all doses <2 Gy and used unconditional likelihood regression adjusted for gender, attained age and first cancer.

^fModels adjusted for gender, attained age, chemotherapy, first cancer (Wilm’s, Hodgkin lymphoma and others) and year of birth.

^gModel additionally adjusted for study.

TABLE 6

Variable	LESG		CCSS-Nordic		CCSS-Fr/UK		CCSS-US		Pooled data	
	β_j	γ_1	β_j	γ_1	β_j	γ_1	β_j	γ_2	β_j	γ_1
Gender										
Male	∞	-0.0570	NA		1.94	-0.0574	2.02	-0.00124	2.85	-0.0627
Female	0.96				0.77		1.24		2.17	
P^c	0.67				0.38		0.48		0.99	
Age at exposure (years)										
<5	2.19	-0.0488	6.88	-0.06032	1.27	-0.0476	1.79	-0.00112	2.88	-0.0561
5-9	1.60		0.24		0.74		1.35		1.98	
10-14	1.48 ^d		15.9		0.54 ^d		1.51		1.93	
15	-		6.64				0.40		0.51	
P^c	0.93		0.25		0.42		0.01		<0.01	
P_{trend}^e	0.32		0.18		0.10		0.01		<0.01	
Year since first exposure										
<15	1.09	-0.0378	3.67	-0.07214	0.50	-0.0647	0.84	-0.00125	1.30	-0.0623
15-19	3.43 ^d		1.19 ^d		2.03		1.95		3.67	
20-24	-				1.09		1.58		2.48	
>25	-				0.94		1.82		2.75	
P^c	0.20		0.65		0.22		0.11		<0.01	
P_{trend}^e	0.20		0.45		0.96		0.23		0.16	
Attained age (years)										
<20	1.59	-0.0517	1.82	-0.0842	0.91	-0.0547	1.24	-0.00124	1.90	-0.0627
20-24	1.43 ^d		24.4 ^d		1.55		1.40		2.35	
25-29					1.26		1.23		2.24	
30-34					1.31		2.06		3.44	
35					0.28		1.31		2.00	
P^c	0.92		0.24		0.29		0.55		0.34	

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Variable	LESG		CCSS-Nordic		CCSS-Fr/UK		CCSS-US		Pooled data		
	β_j	γ_1	β_j	γ_1	β_j	γ_1	β_j	γ_2	β_j	γ_1	$RR_{10\ GY}^b$
<i>P</i> -trend ^e	0.59		0.56		0.33		0.14			<0.01	
Type of first cancer											
Others	1.61	-0.0471	NA ^f		1.58	-0.0635	1.48	-0.00124	2.96	-0.0600	17.2
Hodgkin lymphoma	0.81				0.05		0.31		0.23		2.3
<i>P</i> ^c	0.47				0.06		0.14		<0.01		
Number of treatments ^g											
1	NA	-	1.61	-0.09507	1.03	-0.0711	1.67	-0.00116	3.13	-0.0623	17.5
2+			0.44		3.18		0.98		3.42		19.0
<i>P</i> ^c			0.73		0.05		0.21		0.78		
Chemotherapy											
No	NA		-0.08	-0.02805	2.42	-0.0565	3.78	-0.00128	3.85	-0.0632	21.5
Yes			2.19		0.77		1.27		2.16		12.49
<i>P</i> ^c			0.06		0.32		0.27		0.41		
Alkylating agents											
No	1.38	-0.0526	9.5	-0.1014	5.59	-0.0596	3.04	-0.00129	5.62	-0.0632	30.8
Yes	1.35		38.5		0.43		0.90		1.37		7.3
<i>P</i> ^c	0.99		0.26		0.02		0.07		0.01		
Anthracyclines											
No	NA		NA		2.16	-0.0598	3.05	-0.00133	4.91	-0.0656	26.5
Yes					0.45		0.83		1.21		7.39
<i>P</i> ^c					0.13		0.05		0.01		
Bleomycin											
No	NA		NA		0.97	-0.0531	2.13	-0.00140	3.00	-0.0648	16.7
Yes					1.40		0.09		0.44		3.3
<i>P</i> ^c					0.81		0.01		0.02		

^aModels for radiation dose, d, include: linear-exponential (linear): $RR(d) = [1 + \beta d \exp(\gamma_1 d)]$ for LESG, CCSS-Nordic, CCSS-Fr/UK and pooled data; and linear-exponential (quadratic): $RR(d) = [1 + \beta d \exp(\gamma_1^2 d^2)]$ for CCSS-US, with β defining the slope parameter and γ_1 or γ_2 defining the curvature. For modifiers, βd was replaced by $(\sum_j \beta_j z_j d)$, where z_j was a zero/one indicator variable for the j th category and β_j represented the linear component of the dose response relationship within the j th category. Models adjusted for gender, attained age, chemotherapy, first cancer (Wilm's, Hodgkin lymphoma and others) and year of birth and additionally adjusted by study for pooled data.

- h Fitted relative risk at 10 Gy.
- c P value for $J-1$ degrees of freedom likelihood ratio test of homogeneity of β_j across categories, i.e., $\beta_1 = \dots = \beta_J$.
- d Category merges all higher categories.
- e P value for linear trend using continuous variable.
- f NA, “not applicable” or <10 case patients.
- g Sum of radiation treatments, where one treatment included all radiation doses received within six months.