Methodological extensions of meta-analysis with excess relative risk estimates: application to risk of second malignant neoplasms among childhood cancer survivors treated with radiotherapy

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Although radiotherapy is recognized as an established risk factor for second malignant neoplasms (SMNs), the dose response of SMNs following radiotherapy has not been well characterized. In our previous meta-analysis of the risks of SMNs occurring among children who have received radiotherapy, the small number of eligible studies precluded a detailed evaluation. Therefore, to increase the number of eligible studies, we developed a method of calculating excess relative risk (ERR) per Gy estimates from studies for which the relative risk estimates for several dose categories were available. Comparing the calculated ERR with that described in several original papers validated the proposed method. This enabled us to increase the number of studies, which we used to conduct a meta-analysis. The overall ERR per Gy estimate of radiotherapy over 26 relevant studies was 0.60 (95% CI: 0.30–1.20), which is smaller than the corresponding estimate for atomic bomb survivors exposed to radiation as young children (1.7; 95% CI: 1.1–2.5). A significant decrease in ERR per Gy with increase in age at exposure (0.85 times per annual increase) was observed in the meta-regression. Heterogeneity was suggested by Cochran’s Q statistic (P < 0.001), which may be partly accounted for by age at exposure.

Keywords: relative risk; ERR; childhood cancer; radiotherapy; second malignant neoplasm; meta-analysis

INTRODUCTION

Current multimodal treatments for cancer have greatly improved the survival rates of children with malignant diseases. Because of notable improvements in therapy and earlier stage diagnosis, children treated for cancer have become long-term survivors; ~80% survive for at least five years [1, 2]. Consequently, understanding the late effects of cancer treatment is important for continued medical care, and the risk of developing second malignant neoplasms (SMNs) after treatment is one such concern. Studies of long-term survivors of childhood malignant disease have demonstrated an increased risk of subsequent SMN development, even several decades after receiving radiotherapy.

Excess relative risk (ERR) is categorized as a relative excess measure [3] and is often used as an effect measure in the analyses of radiation epidemiological data [4, 5]. If ERR values have been derived from a linear dose–response analysis, they are often expressed as a relative increase in rates per unit dose, i.e. ERR per Gy. In this paper, we refer to ERR per Gy as ERR for simplicity.

Numerous studies have shown that the ERR of solid tumors per unit of radiation is much higher in children than in adults, meaning children are more sensitive to the carcinogenic effects of radiation than adults. The exceptions to this finding are cancers of certain sites [4, 6]. However, the dose–response relationship between radiation and the long-term effects of radiation in childhood are poorly quantified [7].
In addition, the small number of subjects in each study limits evaluation of the risk of SMNs after radiotherapy.

In a previous paper, we evaluated the risk of SMNs using a meta-analysis of nine studies in which ERR estimates were presented. However, the small number of eligible studies available restricted detailed quantitative evaluations. Additional studies, in which risk estimates were expressed in terms of relative risks (such as rate ratios, hazard ratios or odds ratios per several dose categories), were available; however, due to incomparability of data, these studies were not included in the meta-analysis.

The objective of this study was to develop a method of calculating ERR estimates from other forms of risk estimates. Using this new method, we conducted a meta-analysis of 26 studies and examined additional detailed evaluations of SMN risk according to study characteristics. We especially focused on age-related variability of radiation effects. In this report, we have described the details of the proposed method (not explained in the preliminary report) and evaluated its performance through simulation studies [8].

The paper is structured as follows. The Materials and Methods section outlines how ERR estimates were obtained, and how studies were identified and selected for inclusion in the meta-analysis. It also covers how data were extracted and analyzed. The Results section outlines the results of the study search, the validation and the analysis. The Discussion section considers these results and their relevance to the field of epidemiological radiation studies.

MATERIALS AND METHODS

Assumed data for estimating ERR

This paper proposes a method for estimating ERR from studies in which relative risk estimates (such as odds ratio, incidence rate ratio or hazard ratio) are calculated by dose category. The dataform assumed for the purpose of this study is described as follows.

Consider a study in which relative risk estimates for K dose categories (k = 1, 2, … K) are available (k = 0 represents the reference category). Let l_k and u_k represent the lower and upper limits, respectively, of the dose for a dose category k. For dose category k, the relative risk estimate \( \theta_k \) is available with confidence limits (CLs) from \( CL_U \) to \( CL_L \).

ERR calculation requires the use of a representative dose value for each dose category (d_k). Publications vary in the data provided about dose categories. If available, we used the median category value; if not, we used the mean. If neither were available, we calculated the value midway between the upper and lower limits of the dose category and used this for \( d_k \), i.e. we calculated the representative dose \( d_k \) using the following equation:

\[
d_k = (l_k + u_k)/2.
\]

In some studies, the upper limit of the largest dose category, \( K \), was unavailable. To estimate \( u_K \) in these instances, we used the upper limit of the subject’s dose range recorded in the patient characteristics. When no candidate values were available for \( u_K \), we assumed, for convenience, that the dose width for the largest dose category \( (u_K - l_K) \) was \( \tau \) times that of the second largest dose category \( (u_{K-1} - l_{K-1}) \). Therefore, \( u_K \) was calculated as follows:

\[
u_K = \tau \cdot (u_{K-1} - l_{K-1}) + l_K.
\]

In this equation, we adopted 2 as the \( \tau \) value.

In some studies, the dose in the reference category \( d_0 \) was not equal to zero, which may lead to underestimation of ERR estimates. To contend with the underestimation, we subtracted the reference category dose from doses in the other categories \( d_k = d_k - d_0 \), \( k = 1, 2, \ldots K \), and the adjusted value \( d_k \) was used as the central value for doses in each dose category.

To reiterate, we obtained the relative risk estimates with confidence limits \( \theta_k \), \( CL_U \), \( CL_L \), and representative dose \( d_k \) for each dose category. From the confidence limits \( CL_U \), \( CL_L \), the standard error (SE) of the relative risk estimate \( \theta_k \) was calculated using the width of the confidence interval (CI), which corresponds to \( CL_U - CL_L \). There are two options in calculating the SE: one is to assume the estimate has a normal distribution, and the other is to assume the estimate has a normal distribution with a logarithmic scale. The equations to obtain the SEs are explained further in the ‘Data extraction’ section.

Estimation of ERR from categorized data

When \( \theta_0 \) is the risk for unexposed individuals (e.g. incidence rate or odds ratio), and \( \theta_K \) is the risk for exposed individuals, ERR is calculated as \( (\theta_K - \theta_0)/\theta_0 \). Because ERR per Gy represents increased risk relative to the baseline per unit dose, it corresponds to the slope in a linear regression model. In this model, the response variable is the relative risk estimate; the covariate is dose, and the value of the intercept is 1. Our proposed estimation method is described below.

First, we fit the univariate linear regression model \( \theta_k = 1 + \beta \cdot d_k + \epsilon_k \), \( k = 1, \ldots, K \), in which \( \epsilon_k \) follows the normal distribution \( N(0, \text{var}(\theta_k)) \), and the estimate \( \beta \) corresponds to the estimated ERR. After obtaining an estimate for \( \beta \), we can calculate the CI of the estimated \( \beta \) for the meta-analysis. We propose a simulation-based method for the CI estimation.

The bootstrap is a method of estimating the distribution of sample estimates by random resampling with replacement. We used a bootstrap approach to estimate the distribution of calculated ERR estimates, from which we obtained the CIs. For example, after creating the bootstrap samples by resampling, the bootstrap estimates were obtained by analyzing each bootstrap sample as usual data. The bootstrap estimates can be regarded as the distribution of the estimates, and the
95% CLs of the estimate are obtained as the 2.5th and 97.5th percentile of the bootstrap estimates.

Alternatively, instead of resampling, the bootstrap samples can be created parametrically, which is known as a parametric bootstrap method [9]. Our method can be regarded, broadly, as a parametric bootstrap method. In the calculations, \( \hat{\theta}_k \) and its SE, \( \sqrt{\text{var}(\hat{\theta}_k)} \) are available for each K-dose category. We regard these K-relative risk estimates with the associated SE as data and generate B independent bootstrap samples, where B is the number of bootstrap samples used for the estimation. For our study, we chose 20,000 as the default value for B. For the b-th bootstrap sample \((b = 1, 2, \ldots, B)\), we generated a random number for a dose category k following the normal distribution with mean 0 and variance \( \text{var}(\hat{\theta}_k) \), and added this number to \( \hat{\theta}_k \). Let \( \hat{\theta}_k^b \) indicate the added-error estimate of \( \hat{\theta}_k \) \((\hat{\theta}_k^b = \hat{\theta}_k + U_b, \ U_b \sim N(0, \text{var}(\hat{\theta}_k))\) and repeat this procedure for all K dose categories. For the added-error estimate of each K dose category, we fit the following univariate linear regression model:

\[
\hat{\theta}_k^b = 1 + \beta_0 \cdot d_k + e_k, \ k = 1, \ldots, K.
\]

We obtained the estimate \( \hat{\beta}_0 \) as the result of fitting the above model to the b-th bootstrap sample. Finally, the CI for \( \beta_0 \) is constructed from the percentile of estimates from the B times bootstrap iteration, and the 100 \((1 - \alpha)\)% upper and lower limits are calculated as the 100(\( \alpha/2 \))th and 100(1 - \( \alpha/2 \))th percentiles. For example, \( \alpha \) is set at 0.05 to construct a 95% CI. This is known as the percentile method; however, there are several improved methods for constructing a bootstrap CI. Although we used the percentile method in our study, mainly for its simplicity, other methods can be applied if necessary [9].

There were several studies in which both ERR from the original articles and the calculated ERR were available. To validate the proposed method, we calculated the relative magnitude of the calculated ERR and concomitant SE and compared them with those available in the articles. The relative magnitude for ERR and SE was defined as the calculated value divided by the original value available in the articles.

Validation study
To evaluate the performance of the proposed method, a simulation study was conducted under a range of methodological options. We used hypothetical data generated from linear odds models, which are frequently employed in case-control studies of radiation epidemiology. After 5000 subjects had been generated in each study, ERR was estimated from the odds ratio estimates for several dose categories using the linear odds model shown in equation 4:

\[
p_i = \frac{\beta_0 \cdot (1 + \text{ERR} \cdot \text{dose}_i)}{1 + \beta_0 \cdot (1 + \text{ERR} \cdot \text{dose}_i)}, \quad (4)
\]

where \( \beta_0 \) controls the baseline probability (fixed at 0.05), and \( p_i \) is the probability of the i-th subject developing SMNs; the dose data (Gy) for the i-th subject \( \text{dose}_i \) was generated from a lognormal (the mean parameter in log-scale 0.9 and scale parameter 1.2 were selected for their similarity to the study by Nguyen [10]). The subjects were divided into five groups according to dose: subjects with \(<0.2 \text{ Gy} \) were regarded as the reference group, subjects with \(0.2–10 \text{ Gy} \) as Group 1, \(10–30 \text{ Gy} \) as Category 2, \(30–50 \text{ Gy} \) as Category 3, and \(50–100 \text{ Gy} \) as Category 4. After generating event data following the Bernoulli distribution with probability \( p_i \), the data were analyzed using linear odds models with categorical variables indicating each dose group. After obtaining odds ratios with CIs for each dose category (Categories 1, 2, 3 and 4) from the linear odds model, we applied the proposed method and obtained the ERR estimate with CLs.

There are two kinds of options in our method, and we compared the performance of each option. The first is the information on the representative dose for each dose category: mean, median or middle point of the category. The other is the scale option (assuming normal distribution with a logarithmic scale, or with the original scale): if we assume normality in a logarithmic scale, then the bootstrap procedure should also be conducted in the logarithmic scale, and vice versa for the original scale.

The combinations of these options for the proposed method were compared in terms of bias and coverage probability through 1000 iterations. Because ERR was fixed at 1, estimates equal to 1 indicate no bias, larger than 1 indicate overestimation, and smaller than 1 indicate underestimation. If the coverage probability of the 95% CI is near 0.95, it means that the estimation of standard error of the estimate has been successful.

Study identification in meta-analysis
Relevant studies were identified by a systematic search of the literature using the PubMed database (from 1950 to 2009). We used Medical Subject Headings (MeSH), a large controlled vocabulary developed for indexing journal articles and books on the life sciences, to retrieve studies indexed using the MeSH terms ‘neoplasms, second primary’ and ‘radiotherapy’. After performing the initial search using these MeSH terms, additional studies were retrieved with a standard keyword search using the terms ‘paediatric/pediatric’ or ‘childhood’. The computer search was supplemented by handsearching reference lists of already retrieved papers. The titles and abstracts of all studies were scanned to exclude irrelevant publications. This process was independently performed by two of the authors to avoid excluding relevant publications. The entire text of the remaining articles was then scanned to determine whether they fulfilled the inclusion criteria described below. If relevant articles (including abstracts without full text and unpublished studies) lacked the necessary information, we attempted to contact the authors.
To address articles published in languages other than English, titles from the PubMed search were scanned. Although many non-English articles have abstracts in English, we searched for articles without English abstracts using relevant titles. This process was also performed independently by two of the authors. In an attempt to include all available studies, we further scanned additional scientific literature, including review articles, books, and reports.

**Selection criteria**

The following inclusion criteria were used to determine the studies for the meta-analysis: (i) the endpoint of the study should be SMN risk among childhood cancer survivors, (ii) the study design should be either a cohort study or a case–control study, (iii) risk estimates should be expressed in terms of ERR (or ERR was calculable from category-specific risk estimates, including rate ratio, hazard ratio, and odds ratio), and (iv) sufficient data should be present in the publications to enable estimation of the SE of the ERR estimates. If the publication was an earlier report of data that was subsequently updated in another article, it was excluded from the analysis.

Generally, logistic regression analysis is utilized for case–control studies, and Poisson and Cox regression analyses are utilized for cohort studies; risk estimates obtained from these regression models are stated as an odds ratio, rate ratio or hazard ratio. Following our previous study that included randomized controlled trials (risk ratio), case–control studies (odds ratio) and cohort studies (rate ratio), we treated ERR estimates from odds ratios, rate ratios and hazard ratios equally and included them in the meta-analysis [11].

**Data extraction**

The following data were collected from each study: general study information (study population, study design, country, primary cancers, age at primary cancer, number of SMNs and number of follow-up years) and ERR-related information (site of SMNs, dosimetry site, effect measure, ERR, estimated ERR, and relative risk estimates for each dose category). When age at primary cancer diagnosis was not available, we attempted to calculate it from the age at SMN diagnosis and the span between the appearance of the primary cancer and that of the SMN.

We used ERR from the linear term of the linear quadratic models (LQ models) if estimates from both linear non-threshold models (LNT models) and LQ models were available. This is because ERR from LNT models may be underestimated by a cell-killing effect, i.e. a wider dose range may lead to a lower estimate.

We conducted the meta-analysis using a logarithmic scale, as conducted in previous studies [12, 13]. Using our method of calculating ERR from other risk estimates, ERR estimates and confidence limits were available for all studies. For the studies included in the meta-analysis, we calculated the SE of ERR estimates from the confidence limits. The SE in the logarithmic scale $\sigma_{\log}$ was obtained using the following equation:

$$\sigma_{\log} = (\log(C_L) - \log(CE))/2z_\alpha,$$

where $z_\alpha$ is the standardized normal deviate for a two-tailed area with probability $\alpha$. For example, we use $z_{0.05} = 1.96$ to calculate SE from a 95% CI. When $C_L$ was not available, the following equation was used:

$$\sigma_{\log} = (\log(CL) - \log(Est))/z_\alpha,$$

where $Est$ is the point estimate of ERR available in the article or is equal to $\hat{\beta}$ when ERR was estimated. The variance of ERR was calculated as the square of SE. When obtaining the SE in the original scale $\sigma$, we replaced $\log(C_L)$, $\log(C_L)$ and $Est$ with the original values, $C_L$, $C_L$ and $Est$, in the above equations.

**Statistical analysis**

On the basis of the ERR values available in the articles or estimated by the proposed method, the overall ERR was estimated using a random effects model. We did not use a fixed effects model because the study design, populations and other factors were expected to vary among individual studies. The difference between radiotherapy effects among studies is termed heterogeneity. The restricted maximum likelihood method was used for estimating variance components.

Because of the possibility of a negative estimate of a random effect variance, there were instances where we could not obtain the estimates from the random effects model. In these cases, we used a fixed effects model, because the results from each of the models have been deemed similar in such situations [14, 15].

Heterogeneity was tested using Cochran's Q statistic. If the $P$ value of Cochran’s Q statistic was less than 0.05, then we needed to explore the reason for the heterogeneity. To this end, we calculated overall estimates in a specific subgroup of studies according to the SMN site, study design (cohort or case–control study), geographical region (Europe, North America, and Europe and North America), and whether ERR was calculated by the proposed method. To examine the dependence of ERR on the age at which exposure occurred (we assumed that the age when the cancer first appeared was the age at exposure), a meta-regression was also conducted. Because we were interested in how the age of cancer onset affected ERR, we only included the initial age of onset as a covariate in the meta-regression. For the $i$-th study, $ERR_i$ and $age_i$ indicated the ERR estimate and the age at primary cancer diagnosis, respectively. The model is described as follows:

$$\log(ERR_i) = \alpha + \beta_{age} \cdot (age_i).$$
We also examined the effect of variations in age at first cancer diagnosis by adjusting other covariates in the meta-regression. However, we only added one additional covariate, i.e. the site of the SMN, because when only a moderate number of studies are used, the conventional recommendation is to use only one covariate in the meta-regression [15].

To assess publication bias in the articles we selected, we used a funnel plot as well as a statistical test for plot asymmetry, as proposed by Egger et al. [16]. This test performs a regression of the standardized effect size (ERR estimate divided by SE) against its precision (SE). A statistically significant difference of the slope from zero suggests the presence of publication bias. Most analyses were performed using SAS9.2 software (SAS for Windows release 9.2, SAS Institute Inc., Cary, NC). R statistical computing software (R for Windows release 2.12.1, R Development Core Team, Vienna, Austria) was also used for descriptive statistical calculations and validation study.

RESULTS

Search results
We selected 198 studies in the first step of the systematic literature search using MeSH terms and keywords. Of these, we excluded 180 studies that did not satisfy all of the inclusion criteria. We added 10 studies to the pool of eligible studies by conducting a handsearch. Two studies, one that used data reported earlier but included in a subsequent article and one that used identical data, were excluded. Eventually, we identified 26 epidemiological studies, summarized in Table 1.

A flow chart outlining the process used to select papers for the meta-analysis is shown in Fig. 1.

Among these studies, ERR estimates were available for 15 studies, and ERR estimates were calculable for 11. The studies included in the meta-analysis are summarized in Table 2.

We used ERR estimates for as many categories of SMNs as possible and tried to use a single ERR estimate per study, obtained by using all SMN cases in the analysis of individual studies. However, we could not obtain the individual ERR estimates that summarized all of the available data in the article. For example, in the study by de Vathaire et al., the risk estimates of both adenoma and carcinoma were available, but there was no single risk estimate of thyroid cancer including both adenoma and carcinoma [17]. Similarly, in the study by Lindberg et al., ERR estimates for both thyroid and cerebral SMNs were available, yet there was no ERR estimate that included both sites [18]. Separate estimates in one study were obtained by using different cases, that is, no cases were duplicated. We ultimately included 27 ERR estimates in the meta-analysis gleaned from the 26 eligible studies.

Validation study results
The results from a validation study are summarized (in terms of ERR estimate and coverage probability) in Table 3. In general, the performance of the proposed method with a logarithmic scale was better than with the original scale in terms of bias and coverage probability. The bias was smallest when the median was used for the representative dose for each category, and almost no bias was observed when the mean was used. When the middle category value was used, 10% underestimation was observed.

ERR calculation from dose category-specific risk data
We calculated ERR estimates from risk estimates by dose category; the estimates obtained are presented in Table 2. There were 22 studies in which ERR was calculable from dose category-specific risk data; however, both the ERR from the original article and the calculated ERR were available only for 11 studies. One article provided relative risk estimates for both adenoma and carcinoma; therefore, the number of calculated ERRs was 23. ERR values ranged from 0.004 to 2.24, with mean and median values of 0.62 and 0.38, respectively.

Comparison between estimated ERR and ERR from the original articles
There were 11 studies in which both ERR from the original articles and the calculated ERR were available. In these studies, the ratios of calculated estimates to available ones were calculated; the results are presented in Table 2. Relative ERR ranged from 0.24 to 1.19 with a mean value of 0.61, suggesting underestimation of the calculated ERR on the whole. The relative SE ranged from 0.17 to 1.34 with a mean value of 0.83.

Meta-analysis of the 26 studies
The overall ERR using the random effects model was 0.60 (95% CI: 0.30–1.20; n = 27). The ERR estimates and 95% CIs from the 26 studies, overall estimates, and those estimates from specific subgroups of studies are presented in Fig. 2. Cochran’s Q statistic was 351.48 (d.f. = 26, P < 0.001), indicating a significant heterogeneity among the studies. The test for plot asymmetry suggested the presence of publication bias (P < 0.001). The funnel plot is presented in Fig. 3, which shows that the shape of the plot was roughly symmetrical except for two extreme datapoints. One is an extremely small ERR value (Klein et al.) [19] and the other is a small ERR with extremely small SE (Wong et al.) [20]. The overall ERR when these two datapoints were omitted was 0.81 (95% CI: 0.44–1.49; n = 25).

The overall estimate of ERR from the cohort studies was 1.22 (95% CI: 0.45–3.33; n = 13), and that from the case–control studies was 0.60 (95% CI: 0.30–1.20; n = 27). The ERR estimates and 95% CIs from the 26 studies, overall estimates, and those estimates from specific subgroups of studies are presented in Fig. 2. Cochran’s Q statistic was 351.48 (d.f. = 26, P < 0.001), indicating a significant heterogeneity among the studies. The test for plot asymmetry suggested the presence of publication bias (P < 0.001). The funnel plot is presented in Fig. 3, which shows that the shape of the plot was roughly symmetrical except for two extreme datapoints. One is an extremely small ERR value (Klein et al.) [19] and the other is a small ERR with extremely small SE (Wong et al.) [20]. The overall ERR when these two datapoints were omitted was 0.81 (95% CI: 0.44–1.49; n = 25).
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Study population</th>
<th>Study design</th>
<th>Country</th>
<th>Primary cancer</th>
<th>Age at primary cancer</th>
<th>Treatment dose range</th>
<th>Number of SMNs (control)</th>
<th>Follow-up period</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Tucker 1991</td>
<td>The Late Effects Study Group</td>
<td>A total cohort of 9170 patients who survived any type of cancer in childhood for more than 2 years was constructed from the records of the 13 medical centers participating in the Late Effects Study Group</td>
<td>Nested case-control</td>
<td>USA, UK, Netherlands</td>
<td>all</td>
<td>Mean 7 years (0–18)</td>
<td>0–76 Gy (thyroid)</td>
<td>23 (89)</td>
<td>Mean 5.5 years 2–48</td>
<td>[21]</td>
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<tr>
<td>Vathaire 1992</td>
<td>Gustave–Roussy Institute IGR</td>
<td>A total of 592 children treated for a cancer at the Gustave–Roussy Institute (IGR) between 1942 and 1969 and who were alive and free of disease 5 years after diagnosis</td>
<td>Cohort</td>
<td>France</td>
<td>Neuroblastoma</td>
<td>Median 3 years (0–17)</td>
<td>0–41.92 Gy (thyroid)</td>
<td>24</td>
<td>Median 22 years 5–40</td>
<td>[22]</td>
</tr>
<tr>
<td>Hawkins 1992</td>
<td>Population-based National Register of Childhood Tumours in Britain</td>
<td>A case–control study of 26 secondary leukemias observed among survivors of childhood cancer diagnosed in Britain between 1940 and 1983, and 96 controls matched for sex, type of first cancer, age at first cancer, and interval to diagnosis of secondary leukemia</td>
<td>Case–control</td>
<td>UK</td>
<td>all</td>
<td>Not available</td>
<td>Not available</td>
<td>26 (96)</td>
<td>Mean 7.7 years</td>
<td>[23]</td>
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<td>Lundell 1994</td>
<td>Swedish Cancer Register</td>
<td>A total of 14 633 infants less than 18 months old received radiotherapy for skin hemangioma at Stockholm during the period 1920–1959</td>
<td>Cohort</td>
<td>Sweden</td>
<td>skin hemangioma</td>
<td>Mean 6.5 months</td>
<td>&lt;0.01–28.5 Gy (thyroid)</td>
<td>17</td>
<td>Mean 39 years (1–67)</td>
<td>[24]</td>
</tr>
<tr>
<td>Lindberg 1995</td>
<td>Swedish Cancer Registry</td>
<td>A total of 12 055 infants treated with radiouclides for hemangioma of the skin at the Sahlgrenska University Hospital, Sweden, between 1930 and 1965</td>
<td>Cohort</td>
<td>Sweden</td>
<td>skin hemangioma</td>
<td>Median 5 months</td>
<td>17–115 Gy (interquartile; thyroid), 7–97 Gy (interquartile; brain)</td>
<td>CNS 33, thyroid 15</td>
<td>Not available</td>
<td>[18]</td>
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<tr>
<td>Bhatia 1996</td>
<td>The Late Effects Study Group</td>
<td>A cohort of 1380 children with Hodgkin’s disease who received their primary treatment between 1955 and 1986</td>
<td>Cohort</td>
<td>USA, UK, Netherlands</td>
<td>Hodgkin</td>
<td>Median 11 years 1–16</td>
<td>0–52 Gy</td>
<td>17</td>
<td>Median 11.4 years 0.1–37</td>
<td>[25]</td>
</tr>
<tr>
<td>Hawkins 1996</td>
<td>Population-based National Registry of Childhood Tumours in Britain</td>
<td>A cohort study of 13 175 3-year survivors of childhood cancer diagnosed in Britain between 1940 and 1983 and who survived at least 3 years from the date of diagnosis</td>
<td>Nested case-control</td>
<td>UK</td>
<td>all</td>
<td>Not available</td>
<td>Not available</td>
<td>59 (220)</td>
<td>Mean 10.7 years</td>
<td>[26]</td>
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<td>Reference</td>
<td>Study Details</td>
<td>Source</td>
<td>Country</td>
<td>Disease</td>
<td>Mean Age</td>
<td>Median Dose</td>
<td>Reference Range</td>
<td>Follow-up</td>
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<td>Lundell 1996</td>
<td>Swedish Cancer Register</td>
<td>Cohort</td>
<td>Sweden</td>
<td>skin hemangioma</td>
<td>Mean 6.4 months</td>
<td>&lt;0.01–35.8 Gy (breast)</td>
<td>75</td>
<td>Mean 39 years (1–67)</td>
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<tr>
<td>Wong 1997</td>
<td>Massachusetts and New York cohort</td>
<td>Nested case-control</td>
<td>USA</td>
<td>retinoblastoma</td>
<td>Median 10 months for hereditary and median 23 months for nonhereditary</td>
<td>0–112 Gy (soft tissue), 0–212 Gy (bone)</td>
<td>Bone sarcoma 52, soft tissue 31 (89)</td>
<td>Median 20 years</td>
<td></td>
<td></td>
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<tr>
<td>Karlsson 1998</td>
<td>Swedish Cancer Register and Sahlgrenska University Hospital</td>
<td>Cohort</td>
<td>Sweden</td>
<td>skin hemangioma</td>
<td>Median 5 months</td>
<td>0–11.5 Gy (brain)</td>
<td>86</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Vu 1998</td>
<td>Children Cancer Research Group</td>
<td>Cohort study of 4400 3-year survivors of a first solid cancer diagnosed in France or the UK between 1942 and 1986</td>
<td>Nested case-control</td>
<td>France, UK</td>
<td>solid</td>
<td>Mean 71 months (0–201)</td>
<td>0–83 Gy</td>
<td>32 (160)</td>
<td>Mean 15 years (3–48)</td>
<td></td>
</tr>
<tr>
<td>Little 1998</td>
<td>French–British study</td>
<td>Nested case-control</td>
<td>France, UK</td>
<td>all except leukemia</td>
<td>Mean 6 years (0–16.9)</td>
<td>0–82.7 Gy (brain)</td>
<td>22 (not available)</td>
<td>Mean 15.1 years (2.2–45.8)</td>
<td></td>
<td></td>
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<tr>
<td>Vathaire 1999</td>
<td>French–British Study</td>
<td>Retrospective cohort</td>
<td>France, UK</td>
<td>all except retinoblastoma</td>
<td>Mean 6 years (0–16)</td>
<td>&lt;0.001–75 Gy (thyroid)</td>
<td>Adenoma 44, carcinoma 14</td>
<td>Mean 15 years 3–45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhatia 2002</td>
<td>Children’s Cancer Group</td>
<td>Cohort</td>
<td>USA, Canada</td>
<td>ALL acute lymphoblastic leukemia</td>
<td>Median 4.7 years 0–20.8</td>
<td>0–24 Gy</td>
<td>63</td>
<td>Median 5.5 years 0–16.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerin 2003</td>
<td>French–British Study and Nordic cohort</td>
<td>Nested case-control</td>
<td>France, UK, Denmark, Finland, Norway, Iceland, Sweden</td>
<td>all</td>
<td>Mean 8.6 years (0–19)</td>
<td>0–51 Gy</td>
<td>16 (45)</td>
<td>Mean 15 years 3–45 from other article</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Study population</th>
<th>Study design</th>
<th>Country</th>
<th>Primary cancer, Treatment dose range</th>
<th>Number of SMNs (control)</th>
<th>Follow-up period</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein 2003</td>
<td>The German Childhood Cancer Registry</td>
<td>A total of 24,203 patients with all malignancies, including SMN, diagnosed at age &lt;15 years among German residents from 1980 to 1998, and primary malignancies of patients with SMN in patients diagnosed at age &lt;25 years and residents of Switzerland, Austria, and the Netherlands</td>
<td>Nested case-control</td>
<td>Germany, Switzerland, Austria, Netherlands</td>
<td>all except retinoblastoma Not available</td>
<td>Not available</td>
<td>238 (450)</td>
<td>Median 6 years (0-18) [19]</td>
</tr>
<tr>
<td>Menu-Branthomme 2004</td>
<td>French-British study</td>
<td>A cohort of 4,400 3-year survivors treated for a solid cancer in eight centers in France and the UK was constituted by including all the children treated before 1985 for a solid cancer</td>
<td>Nested case-control</td>
<td>France, UK</td>
<td>solid Mean 77 months 0-61 Gy (soft tissue)</td>
<td>25 (121)</td>
<td>Mean 15 years (3-48) [33]</td>
<td></td>
</tr>
<tr>
<td>Guibout 2005</td>
<td>French-British study</td>
<td>A retrospective cohort of 4,400 children treated in eight large cancer treatment centers in France and the UK was constructed from 3-year survivors diagnosed before the age of 17 and before 1986</td>
<td>Cohort</td>
<td>France, UK</td>
<td>all except leukemia Median 5 years (0-16) 0-88 Gy (breast)</td>
<td>16</td>
<td>Mean 16 years 3-46 [34]</td>
<td></td>
</tr>
<tr>
<td>Sigurdson 2005</td>
<td>CCSS</td>
<td>A total of 14,054 5-year survivors of cancer during childhood from the Childhood Cancer Survivor Study cohort</td>
<td>Nested case-control</td>
<td>USA, Canada</td>
<td>all Not available 0.01–62.4 Gy (thyroid)</td>
<td>69 (265)</td>
<td>Not available [35]</td>
<td></td>
</tr>
<tr>
<td>Haddy 2006</td>
<td>French-British study</td>
<td>A cohort of 4,400 patients: 3-year survivors of childhood cancer treated before 16 years of age, between 1947 and 1986, in eight treatment centers in France and the UK, for all types of solid tumors, except retinoblastoma in the UK</td>
<td>Hospital-based cohort</td>
<td>France, UK</td>
<td>solid Median 5 years ( &lt;1-17) Unknown (possibly 14.99 Gy)</td>
<td>11</td>
<td>Median 13 years (3-46) [36]</td>
<td></td>
</tr>
<tr>
<td>Neglia 2006</td>
<td>CCSS</td>
<td>A cohort of 14,361 5-year survivors of childhood cancers treated for childhood cancer at any of the 26 collaborating institutions in the USA or Canada</td>
<td>Nested case-control</td>
<td>USA, Canada</td>
<td>all Median 7 years (calculated) Not available</td>
<td>116 (464)</td>
<td>Not available [37]</td>
<td></td>
</tr>
<tr>
<td>Svahn-Tapper 2006</td>
<td>Nordic population-based study</td>
<td>A total of 25,120 individuals diagnosed before the age of 20 years with a malignant neoplasm notified to one of the five Nordic national cancer registries during the years 1960 through 1987</td>
<td>Nested case-control</td>
<td>Denmark, Finland, Norway, Iceland, Sweden</td>
<td>all Mean 11.7 years Not available</td>
<td>196 (567)</td>
<td>Not available [38]</td>
<td></td>
</tr>
</tbody>
</table>
studies was 0.30 (95% CI: 0.12–0.73; n = 14). The overall estimate of ERR from European studies was 0.74 (95% CI: 0.30–1.83; n = 20), from the North American studies was 0.28 (95% CI: 0.07–1.17; n = 5), and from both European and North American studies was 0.46 (95% CI: 0.06–3.10; n = 2). The overall estimate of ERR according to SMN sites are as follows: thyroid, 3.01 (95% CI: 1.09–8.35; n = 7); bone and soft tissue, 0.48 (95% CI: 0.03–2.35; n = 4); brain, 1.51 (95% CI: 0.10–23.09; n = 4); and leukemia, 0.38 (95% CI: 0.16–0.99; n = 4). The overall estimate of ERR according to SMN sites was 0.28 (95% CI: 0.07–1.17; n = 5). The meta-analysis, which included the age at primary cancer diagnosis as a covariate of main interest, the age at primary cancer diagnosis also revealed a trend of decreasing ERR with increasing age at primary cancer diagnosis (0.85 times [95% CI: 0.78–0.91] per year); however, this trend was not statistically significant.

In the meta-regression model, which included age at primary cancer diagnosis as a covariate of main interest, the regression coefficient was -0.159 (95% CI: -0.29–0.0241). The analysis of ERR by the proposed method was 0.25 (95% CI: 0.08–0.84; n = 11). The analysis of ERR by the proposed method was 0.25 (95% CI: 0.08–0.84; n = 11).
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Site of SMNs</th>
<th>Dosimetry site</th>
<th>Effect measure</th>
<th>ERR in the original paper*</th>
<th>Estimated ERR(^a)</th>
<th>Relative ERR, SE(b)</th>
<th>Reference category</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
<th>Category 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucker 1991</td>
<td>The Late Effects Study Group</td>
<td>Thyroid</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>Not available</td>
<td>0.38 (0.08–3.89)</td>
<td>&lt;2 Gy</td>
<td>2.9–9.99 Gy: 13.1 (1.5–144)</td>
<td>10–29.99 Gy: 12.1 (1.3–117)</td>
<td>&gt;30 Gy: 17.6 (1.4–226)</td>
<td></td>
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</tr>
<tr>
<td>Vathaire 1992</td>
<td>Gustave–Roussy Institute IGR</td>
<td>Thyroid</td>
<td>SMN site</td>
<td>Rate ratio</td>
<td>Not available</td>
<td>2.25 (0.67–11.74)</td>
<td>0 Gy</td>
<td>0.001–0.50 Gy: 6.6 (1.1–40)</td>
<td>0.51–1 Gy: 5.2 (0.5–50)</td>
<td>1.01–5.00 Gy: 9.5 (2–59)</td>
<td></td>
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</tr>
<tr>
<td>Hawkins 1992</td>
<td>Population-based National Register of Childhood Tumours in Britain</td>
<td>Leukemia</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>Not available</td>
<td>0.73 (0.23–5.51)</td>
<td>0 Gy</td>
<td>0.01–4.99 Gy: 2.1 (1.1–3.9)</td>
<td>5.9–9.99 Gy: 4.4 (1.3–15.0)</td>
<td>10–14.99 Gy: 9.4 (1.5–58.0)</td>
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<tr>
<td>Lundell 1994</td>
<td>Swedish Cancer Register</td>
<td>Thyroid</td>
<td>SMN site</td>
<td>Incidence rate ratio</td>
<td>4.92 (1.26–10.2)</td>
<td>0.41 (0.95)</td>
<td>&lt;0.01 Gy (mean 0.0024)</td>
<td>0.02–1.0 Gy: 11.1 (0.35–3.71)</td>
<td>&gt;1.0 Gy (mean 4.49 Gy)</td>
<td>10:1 (2.5–40.4)</td>
<td></td>
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</tr>
<tr>
<td>Lindberg 1995</td>
<td>Swedish Cancer Registry</td>
<td>Thyroid, cerebral</td>
<td>SMN site</td>
<td>Incidence rate ratio</td>
<td>7.5 (0.4–18.1) for thyroid, 10.9 (3.6–20.5) for cerebral</td>
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<tr>
<td>Bhatta 1996</td>
<td>The Late Effects Study Group</td>
<td>Breast</td>
<td>Irradiated site</td>
<td>Hazard ratio</td>
<td>Not available</td>
<td>0.52 (0.11–3.19)</td>
<td>&lt;20 Gy</td>
<td>20–40 Gy: 5.9 (1.2–30.3)</td>
<td>&gt;40 Gy: 23.7 (3.7–152.3)</td>
<td></td>
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<tr>
<td>Hawkins 1996</td>
<td>Population-based National Registry of Childhood Tumours in Britain</td>
<td>Bone</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>Not available</td>
<td>1.24 (0.27–15.48)</td>
<td>0 Gy</td>
<td>0.01–9.99 Gy: 0.7 (0.2–2.2)</td>
<td>10–29.99 Gy: 12.4 (0.9–163.3)</td>
<td>30–49.99 Gy: 93.4 (6.8–1285.4)</td>
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<tr>
<td>Lundell 1996</td>
<td>Swedish Cancer Register</td>
<td>Breast</td>
<td>SMN site</td>
<td>Incidence rate ratio</td>
<td>0.38 (0.09–0.85)</td>
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</tr>
<tr>
<td>Wong 1997</td>
<td>Massachusetts and New York cohort</td>
<td>Bone and soft tissue sarcoma</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>Not available</td>
<td>0.10 (0.08–0.13)</td>
<td>0–4.9 Gy (median 1.7)</td>
<td>5.0–9.9 Gy (median 7.2): 1.9 (1.4–2.6)</td>
<td>10.0–29.9 Gy (median 19.6): 3.7 (2.8–4.5)</td>
<td>30.0–59.99 Gy (median 40.1): 4.5 (3.7–5.6)</td>
<td></td>
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</tr>
<tr>
<td>Karlsson 1998</td>
<td>Swedish Cancer Registry and Sahlgrenska University Hospital</td>
<td>Intracranial</td>
<td>SMN site</td>
<td>Incidence rate ratio</td>
<td>2.7 (1.0–5.6)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Yu 1998</td>
<td>Children Cancer Research Group</td>
<td>Osteosarcoma</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>3.1SE: 4.5</td>
<td>1.70 (0.39–18.95)</td>
<td>0.55 (1.05)</td>
<td>0.1–0 Gy (mean 0.1) 10–10 Gy (mean 3.2): 7.8 (0.97–165.16)</td>
<td>10–30 Gy (mean 20.6): 24.2 (3.0–517.86)</td>
<td>30–50 Gy (mean 40.8): 183.7 (22.8–4485.90)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Little 1998</td>
<td>French–British study</td>
<td>Brain</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.19 (0.03–0.85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vathaire 1999</td>
<td>French–British Study</td>
<td>Thyroid</td>
<td>(carcinoma, adenoma)</td>
<td>Incidence rate ratio</td>
<td>0.63 (0.11–7.67) for carcinoma, 1.15 (0.41–3.93) for adenoma</td>
<td>0–&lt;0.25 Gy (mean 0.04)</td>
<td>0.25–&lt;1.00 Gy (mean 0.52) [Car]: 4.0 (0.7–44.0) [Ade]: 2.3 (0.7–8.6)</td>
<td>1.00–&lt;1.00 Gy (mean 3.60) [Car]: 11.0 (2.3–123.0) [Ade]: 9.2 (3.5–31.0)</td>
<td>10.00–&lt;30.00 Gy (mean 20.00) [Car]: 15 (2.2–141.0) [Ade]: 25 (9.2–84.0)</td>
<td>300.00 Gy (mean 41.00) [Car]: 26.0 (3.4–308.0) [Ade]: 47.0 (16.0–164.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhatta 2002</td>
<td>Children’s Cancer Group</td>
<td>All</td>
<td>Irradiated site</td>
<td>Hazard ratio</td>
<td>Not available</td>
<td>0.11 (0.02–0.35)</td>
<td>0 Gy</td>
<td>0–18 Gy: 1.5 (0.9–2.6)</td>
<td>24 Gy: 3.9 (1.4–11.2)</td>
<td></td>
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</tr>
</tbody>
</table>

<sup>Table 2. Risk estimates and related measures included in the meta-analysis</sup>
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Site</th>
<th>Irradiated site</th>
<th>Odds ratio</th>
<th>0 Gy</th>
<th>0–1 Gy (mean)</th>
<th>1 Gy–15 Gy (mean)</th>
<th>&gt;15 Gy (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerin 2003</td>
<td>French-British Study and Nordic cohort</td>
<td>Melanoma</td>
<td>Irradiated site</td>
<td>Not available</td>
<td>0.42 (0.009–6.07)</td>
<td>0 Gy</td>
<td>0–1 Gy (mean 0.16; 1.4 (0.28–7.0)</td>
<td>1–15 Gy (mean 1.4; 3.2 (0.37–27.0)</td>
</tr>
<tr>
<td>Klein 2003</td>
<td>The German Childhood Cancer Registry</td>
<td>All</td>
<td>Irradiated site</td>
<td>Not available</td>
<td>0.004 (–0.005–0.02)</td>
<td>0 Gy</td>
<td>0–18 Gy: 11.1 (0.6–1.8)</td>
<td>18–35 Gy: 1.1 (0.6–1.9)</td>
</tr>
<tr>
<td>Menu-Branthome 2004</td>
<td>French-British study</td>
<td>Soft tissue sarcoma</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>Not available</td>
<td>0.04 (0.01–0.125)</td>
<td>0 Gy</td>
<td>0–1 Gy (mean 0.2; 0.9 (0.1–5.8)</td>
</tr>
<tr>
<td>Guibout 2005</td>
<td>French-British study</td>
<td>Breast</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.13 (0.0–0.75)</td>
<td>0.41 (0.84)</td>
<td>0 Gy</td>
<td>&gt;0–&lt;1 Gy: 1.3 (0.3–6.3)</td>
</tr>
<tr>
<td>Sigurdson 2005</td>
<td>CCSS</td>
<td>Thyroid</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>1.32 (0.44–4.06, 0.51 LNT)</td>
<td>0.25 (NA)</td>
<td>0 Gy</td>
<td>0–&lt;10 Gy: 1.1 (0.4–3.3)</td>
</tr>
<tr>
<td>Haddy 2006</td>
<td>French-British study</td>
<td>Leukemia</td>
<td>SMN site</td>
<td>Incidence rate ratio, Hazard ratio</td>
<td>0.31 (–0.32–0.94)</td>
<td>0.61 (1.06)</td>
<td>0 Gy</td>
<td>0–3 Gy: 0.6 (0.05–6.3)</td>
</tr>
<tr>
<td>Neglia 2006</td>
<td>CCSS</td>
<td>CNS</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.69 (0.25–2.23)</td>
<td>0.82 (0.40–2.28)</td>
<td>1.19 (0.95)</td>
<td>&lt;1 Gy (mean 0.1)</td>
</tr>
<tr>
<td>Svanh-Tapper 2006</td>
<td>Nordic population-based study</td>
<td>Solid</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.28 (0.13–0.59)</td>
<td>0.32 (0.14–0.76)</td>
<td>1.15 (1.34)</td>
<td>0 Gy</td>
</tr>
<tr>
<td>Guerin 2007</td>
<td>French-British study</td>
<td>All</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.17 (0.03–0.40)</td>
<td>0.08 (0.04–0.18)</td>
<td>0.65 (0.71)</td>
<td>0 Gy</td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>French-British study</td>
<td>All</td>
<td>SMN site</td>
<td>Hazard ratio, Incidence rate ratio (ERR)</td>
<td>0.48 (–0.04–0.99)</td>
<td>0.20 (0.09–0.40)</td>
<td>0.41 (0.30)</td>
<td>0 Gy</td>
</tr>
<tr>
<td>Haddy 2009</td>
<td>Gustave­–Roussy Institute IGR</td>
<td>Thyroid</td>
<td>SMN site</td>
<td>Incidence rate ratio</td>
<td>10.2 (1.7–18.6)</td>
<td>5.7 (0.7–19.4)</td>
<td>1.02 (0.21–3.01)</td>
<td>0 Gy</td>
</tr>
<tr>
<td>Inskip 2009</td>
<td>CCSS</td>
<td>Breast</td>
<td>SMN site</td>
<td>Odds ratio</td>
<td>0.27 (0.10–0.67)</td>
<td>0.26 (0.11–0.64)</td>
<td>0.96 (0.92)</td>
<td>0 Gy</td>
</tr>
</tbody>
</table>

*The underlined values are included in the meta-analysis. "Relative ERR is calculated as the calculated ERR value divided by ERR available in the original articles. Car = Carcinoma, Ade = Adenoma."
DISCUSSION

**Proposed methods for calculating ERR from dose category-specific risk data**

This paper proposed a method for calculating ERR estimates from dose category-specific risk estimates. Using this method, the number of studies included in the meta-analysis was increased from 15 to 26, thus enabling us to perform a separate analysis based on type of SMN. We could also quantify the dependence of ERR on the age at primary cancer diagnosis.

To our knowledge, our previous study was the first meta-analysis that estimated SMN risk among childhood cancer survivors in relation to radiation dose [13], and the current study is the first meta-analysis presenting separate ERR estimates for each type of SMN.

To validate the proposed method, we calculated the relative magnitude of calculated ERR compared with the ERR available in the articles used in the meta-analysis. The mean value of the relative magnitude was 0.61, suggesting that the ERR estimate may have been somewhat underestimated. We explore possible explanations for the underestimation in the following discussion.

With our proposed method, ERR values were calculated from relative risks for several dose categories. To apply our method, a central dose value for each dose category is required in addition to a relative risk estimate, with confidence limits for each dose category. As described earlier, we regarded the middle value of the upper and lower limits as the central dose when this information was not available. While we believe that the most reasonable value was obtained from only the upper and lower limits, the true central value, such as mean or median dose, deviates from the middle value. In regression models, covariate measurement errors often result in underestimation, which is known as attenuation [42]. Especially when the dose range is wide, deviation of the true central value becomes larger, resulting in more severe underestimation. The validation study confirmed that the underestimation was observed when we used the middle value of the dose categories for the central dose.

With regard to the relative SE of the calculated ERR, the mean value of the relative SE was 0.83, suggesting a small underestimation. When excluding two outlying values (0.30 reported by Nguyen, 2008 and 0.17 by Haddy, 2009) [10, 40], the remainders ranged from 0.71 to 1.34 with a mean of 0.98. When exploring the reason for these two outlying values, we found that two different models had been used for the available ERR (Poisson regression models) and relative risks (Cox regression models) in the study by Nguyen (2008) [10]. In the other study by Haddy (2009) [40], the dose category for the largest dose was small (0.1 Gy) compared with the maximum dose for the thyroid (5.42 Gy) without any central doses. This may lead to incompatibility between calculated SE and available SE in the thesis. The low coverage probability in the validation study also suggested that the SE was underestimated. In estimation of SEs, we employed the bootstrap procedure, which required a huge number of iterations. Though profile-based CIs are easy to use in Epicure [43] (statistical software commonly used in the analysis of radiation epidemiology), we used Wald-based CIs for computation time.

There are three studies (Hawks 1992, Hawks 1996, and Klein 2003) in which no candidate values were available for the highest dose category, and the category width was extrapolated from the second highest dose category [18, 22, 31]. Because the highest dose category can strongly affect the dose response, we calculated ERR estimates from these studies without using the highest dose category. The estimates changed from 0.732 (95% CI: 0.223–5.555) to 0.574 (95% CI: 0.159–2.800), from 1.240 (95% CI: 0.267–15.341) to 1.854 (95% CI: 0.209–23.798), and from 0.004 (95% CI: −0.005–0.020) to 0.005 (95% CI: −0.013–0.035), respectively. The overall estimate was 0.604 (95% CI: 0.302–1.209) when we used the above estimates in the three studies, suggesting a very restrictive influence on the overall results.

In essence, the lack of information—such as the central doses of dose categories and dose range (used for the upper limit of the largest dose category)—is the main cause of incompatibilities between the calculated ERR and its SE. We will therefore be able to obtain more compatible ERR estimates from our method when we obtain more information. Though our proposed method can be refined further, we demonstrated that it works well for meta-analysis, especially when relatively few applicable studies are available.

This method was initially proposed to increase the number of studies included in the meta-analysis; however, the application of this method is not restricted to data on childhood cancer survivors. As we have described earlier, the results of radiation epidemiological data are often presented in terms of ERR, and we can use our proposed method to calculate ERR estimates from studies in which only the relative risks for dose categories are available. For example, our method is applicable to data from nuclear worker, radon and lung cancer studies [44, 45]. While ERR estimates are available in some of the aforementioned studies, there remain many other studies in which only relative risk estimates per dose categories are available. Using our method, we can compare more studies using the same measure, namely ERR.

**Meta-analysis of the 26 available studies**

The overall ERR estimate from the random effects model was 0.60 (95% CI: 0.30–1.20). This result is similar to those from our previous meta-analysis (0.53; 95% CI: 0.22–1.31) [9], but much smaller than the sex-averaged ERR estimate of solid cancer incidence in atomic bomb survivors who are 50 years old and were exposed as children (1.7; 95% CI: 1.1–2.5) [46], which suggests an underestimation in our meta-analysis. In atomic bomb survivors, however, the total
irradiation dose is much smaller and delivered at one time, without fractionation, compared with childhood cancer survivors (total dose is typically more than several times larger and divided into several, smaller doses). With all these differences, ERR estimates for atomic bomb survivors are compared with results from a variety of radiation research because they are from one of the most reliable, large-scaled epidemiological studies in the world. Possible explanations for the lower risk estimates in our meta-analysis are as follows.

As we noted in the previous meta-analysis, the cell-killing effect, the site of dosimetry, and dose fractionation partly account for this underestimation. Compared with the doses in atomic bomb survivors, the radiation dose to target organs is generally much higher in radiotherapy, and a downturn curve in the dose–response relationship is often observed in the high-dose range (referred to as the cell-killing effect). One possibility is that this effect accounts for the discrepancy between these two estimates [47]. We found three studies in which dosimetry was performed for the irradiated site of target organs; if a patient subsequently developed breast cancer when the original cancer for which radiotherapy was administered was of the central nervous system (CNS), the actual dose to the breast was much lower than the dose to the head. The overestimation of the actual dose likely leads to the lower estimates. In the context of radiobiology, fractionation of the radiation dose produces, in most cases, better

<table>
<thead>
<tr>
<th>Scale</th>
<th>Central dose in categories</th>
<th>ERR estimate</th>
<th>Coverage Probability</th>
</tr>
</thead>
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<tr>
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<td>0.948</td>
<td>0.775</td>
</tr>
<tr>
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<td>median</td>
<td>1.011</td>
<td>0.747</td>
</tr>
<tr>
<td>log</td>
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<td>0.779</td>
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<td>median</td>
<td>0.828</td>
<td>0.078</td>
</tr>
<tr>
<td>original</td>
<td>middle</td>
<td>0.682</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Fig. 2. Excess relative risk estimates and 95% confidence intervals from 26 studies, with overall estimates obtained by the random effects model.
tumor control for a given level of normal tissue toxicity compared with a single large dose [48]. Therefore, irradiation in radiotherapy is necessarily fractionated, which results in small ERR values.

The increased number of studies included in the meta-analysis enabled us to evaluate the separate estimate for each type of SMN. The risk estimates of childhood thyroid cancer exposed to radioiodine after the Chernobyl accident are 1.91 (95% CI: 0.43–6.34) [49], 2.15 (95% CI: 0.81–5.47) [50], and varied from 5.5 (95% CI: 3.1–9.5) to 8.4 (95% CI: 4.1–17.3), depending on the risk model [51]. The pooled risk estimate from five cohort studies of childhood thyroid cancer, including studies of atomic bomb survivors and medically irradiated children, is 7.7 (95% CI: 2.1–28.7) [52]. In our study, the overall estimate for thyroid SMN was 3.01 (95% CI: 1.09–8.35; n = 7), and compatible with these studies.

We used ERR from LQ models if available because ERR from LNT models may be underestimated by the cell-killing effect. This is the situation where the coefficient of the quadratic term in the model is negative, and will cause overestimation when the coefficient is positive. The negative quadratic coefficient can be seen for radiation-related leukemia among atomic bomb survivors (Richardson 2009) [53], in which the dose range is relatively lower than in radiotherapy studies. Therefore, it is reasonable to expect the coefficient to be negative in situations where studies include subjects with a high dose, and the wider dose range may lead to lower estimates. Nevertheless, in our proposed method, we fitted a univariate linear regression model (including LNT models) to calculate ERR. When information about the central dose for each dose category is not certain (e.g. the mean or median value of dose for each dose category is not available), the calculated ERR would be unstable if we were to use LQ models to obtain ERR. Although a limitation of using the LNT model seems negligible compared with the merit of increasing the number of studies available for the meta-analysis, caution should be exercised in the interpretation of results.

Of the 26 studies included in the meta-analysis, two studies have extremely small ERR estimates along with a narrow CI compared with other studies (Klein 2003, Wong 1997) [19, 20], as seen in the funnel plot (Fig. 3). Because studies with narrower CIs have a larger influence in a meta-analysis, the overall ERR estimate may be intensely influenced by these values, which in turn leads to smaller values. We therefore investigated any unique aspects of these studies that may account for the low ERR values. In the study by Wong et al. [20], participants included patients with retinoblastoma; the risk of developing SMN among retinoblastoma patients is high even when they are not irradiated, and the higher baseline risk is often associated with lower ERR estimates [54, 55]. In the study by Klein (2003) [19],
the dosimetry was performed for the irradiated site of the target organs rather than the SMN sites, which may explain the lower ERR estimates as described above. There are four studies in which the dosimetry was performed for the irradiated site. If we omitted these four studies, the overall ERR estimate was increased to 0.81 (95% CI: 0.42–1.58).

The meta-regression suggested that ERR was multiplied by 0.85, i.e. 15% decrease for a 1-year increase in the age at primary cancer diagnosis. Compared with the attained-age dependence in the Life Span Study solid cancer incidence data (attained-age specific ERR decreased by ~17% per decade, with an increase in age at exposure), it was suggested that the effect of a 1-year increase in childhood age on the ERR corresponded to the effect of a decade increase in adult age. Though this may indicate higher age dependence in childhood exposure, other factors may also explain this result, such as confounding factors caused by the correlation between the type of primary cancer and the age at primary cancer diagnosis. There were six studies in which the first cancer was skin hemangioma, and the overall ERR among these studies was 3.91 (95% CI: 1.01–15.13; n = 6) with a mean value of 0.64 for the age at first cancer diagnosis. In this subgroup, a higher ERR estimate with a lower age at primary cancer diagnosis was observed, and this may partly explain the age dependence in the meta-regression.

In the cohort studies, it is possible that risk may change according to the follow-up period. To explore the risk dependence on the follow-up length, we conducted an additional meta-regression including follow-up years as a covariate. It was suggested that ERR was multiplied by 1.08 (95% CI: 1.01–1.17) with a 1-year longer follow-up. In contrast, the ERR for solid cancers among atomic bomb survivors decreases when attained age increases [46, 56]. The discrepancy in ERR dependence on attained age might suggest that radiotherapy studies with a short follow-up period are likely to result in underestimation as a result of inability to ascertain SMNs occurring in the latent period. However, we should be careful in interpreting the results because 10 studies included in this meta-regression differ in aspects other than follow-up length.

Comparison with a relevant study and suggestions for further studies
Little (2001) also proposed a method for calculating ERR estimates from relative risk estimates in each dose category [47]. His method is similar to ours in terms of the point estimate of ERR, and it is expected that the difference between the two values will not be large. Although the method used for calculating the SE of the calculated ERR is different from ours, his method was based on the profile likelihood. On the other hand, our method calculated the SE using pseudo data, which may be validated within the framework of the parametric bootstrap. Furthermore, our method has been validated using hypothetical data. Although there are two studies in which the SE differed substantially, the remaining studies were generally consistent. This may be due to discrepancies in the data available in the published manuscripts, and not to a methodological defect.

Another advantage of our method is that it can be applied using standard numerical software, such as SAS, R and MATLAB. Our ERR estimation procedure is composed of generating random numbers and fitting linear regression models. A disadvantage of our method is that underestimation is seen when information on the representative dose such as median or mean dose is not available for a dose category. Though it may be possible to refine our method by using additional information available in the published papers about dose distributions, the procedure for incorporating the information will be much more complicated and requires the imposition of further assumptions.

With the methods developed to calculate ERR, we have conducted a meta-analysis that includes a greater number of studies about SMN risk among childhood cancer survivors than was previously possible. From the detailed evaluation, some factors that may explain heterogeneity were suggested, such as age at which the cancer is first diagnosed. For further evaluation of how the age of diagnosis affects ERR, further studies should include patients who have been irradiated in adulthood in addition to childhood.

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