

# Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review

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Although exposure to moderate-to-high doses of ionizing radiation is the only established environmental risk factor for brain and CNS tumors, it is not clear whether this relationship differs across tumor subtypes, by sex or age at exposure, or at the low-to-moderate range of exposure. This systematic review summarizes the epidemiologic evidence on the association between ionizing radiation exposure and risk of brain/CNS tumors. Articles included in this review estimated radiation exposure doses to the brain and reported excess relative risk (ERR) estimates for brain/CNS tumors. Eight cohorts were eligible for inclusion in the analysis. Average age at exposure ranged from 8 months to 26 years. Mean dose to the brain ranged from 0.07 to 10 Gy. Elevated risks for brain/CNS tumors were consistently observed in relation to ionizing radiation exposure, but the strength of this association varied across cohorts. Generally, ionizing radiation was more strongly associated with risk for meningioma compared with glioma. The positive association between ionizing radiation exposure and risk for glioma was stronger for younger vs older ages at exposure. We did not observe an effect modification on the risk for meningioma by sex, age at exposure, time since exposure, or attained age. The etiologic role of ionizing radiation in the development of brain/CNS tumors needs to be clarified further through additional studies that quantify the association between ionizing radiation and risk for brain/CNS tumors at low-to-moderate doses, examine risks across tumor subtypes, and account for potential effect modifiers.

**Keywords:** brain cancer, brain tumors, glioma, ionizing radiation, meningioma.

Moderate-to-high-dose ionizing radiation (IR) is the only established environmental risk factor for brain/CNS tumors (B/CNSTs),<sup>1,2</sup> as confirmed by studies of atomic bomb survivors<sup>3–6</sup> and children irradiated for benign medical conditions<sup>7–14</sup> and first primary tumors.<sup>15–20</sup> However, the precise nature of the IR–B/CNST relationship, particularly at lower-level exposures, is not well characterized. Additionally, clarification is needed regarding the role of potential modifiers of this relationship—such as sex, age at exposure, attained age, and time since first exposure.

The risk for B/CNSTs after exposure to radiation is known to differ by histologic subtype. Brain tumor subtypes are heterogeneous and differ in etiology, biological behavior, clinical course, pathology, and morphology. Gliomas, meningiomas, and schwannomas are the 3 most prevalent subtypes of B/CNSTs; however, even within these histologic classifications, subtypes can differ considerably.<sup>22,23</sup> Gliomas can range in behavior from slow-growing and benign (eg, pilocytic astrocytomas) to aggressive and malignant (eg, glioblastomas). Meningiomas and schwannomas, on the other hand, are primarily benign.<sup>2</sup> Given this marked heterogeneity, it is important to evaluate potential risk factors for B/CNSTs by histologic subtype.

Several articles have reviewed the epidemiology and etiology of brain tumors in general,<sup>1,24–28</sup> with some articles focusing on subtypes such as gliomas<sup>29,30</sup> and meningiomas.<sup>31–33</sup> None of these articles have comprehensively and systematically reviewed the evidence on exposure to IR and risk for B/CNSTs. In this systematic review, we summarize the published evidence from studies that have quantified the relationship between IR and risk for B/CNSTs and tumor subtypes.

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## Materials and Methods

### Literature Search and Data Abstraction

PubMed was searched for potentially relevant articles up to August 3, 2011 by using the search phrase “ionizing radiation” AND “brain tumor” OR “brain cancer” OR “glioma” OR “meningioma” OR “brain neoplasm.” All published articles related to IR and brain tumors and relevant references within these articles were assessed for inclusion. Articles were excluded if they were case reports, did not present original data, were in a language other than English, or analyzed only non-IR effects. Only studies that had dose-response information on the IR–B/CNST relationship and that calculated an excess relative risk (ERR) estimate for all B/CNSTs or tumor subtypes (eg, glioma, meningioma) or behavior (eg, malignant, benign) were included in the review. ERR is generally used as a measure of the cancer risk associated with radiation when dose information is available, and restricting to studies using this effect measure allowed for comparability of results across studies. The general form of the ERR model is

$$\lambda_0(\cdot)[1 + \text{ERR}(d, e, s, a)],$$

where  $\lambda_0(\cdot)$  is the background B/CNST incidence rate, and the function  $\text{ERR}(d, e, s, a)$  represents the relative change in rates associated with a dose,  $d$ , taking into account the effects of age at exposure ( $e$ ), sex ( $s$ ), and attained age ( $a$ ).<sup>5</sup>

ERR estimates quantify the risk for B/CNSTs per dose of IR. In this review, ERR estimates describe the excess risk per Gray.

### Statistical Analysis

We extracted information on sample size, number of people exposed, total cases, composition of study population by sex, method of tumor ascertainment, dosage, fractionation, age at exposure, age at diagnosis, and ERR estimates from each of the studies. We reviewed the populations, tumor definitions, and ERR estimates for each of the studies to determine the feasibility of calculating a weighted ERR estimate. If calculating a weighted risk estimate was deemed both feasible and appropriate based on comparability of studies, we tested the heterogeneity across the study-specific risk estimates using the  $I^2$  statistic.<sup>34</sup> We then calculated a weighted, summary ERR estimate using a random effects meta-analysis. If there was heterogeneity across studies, we sequentially dropped individual studies from the meta-analysis in order to determine the source of the heterogeneity. All meta-analyses were performed using Stata/SE 11.0.

## Results

Among the 413 articles found using PubMed, 11<sup>3–5,8–12,15–17</sup> met study inclusion criteria. These articles

described and analyzed data from 8 different cohorts. Since 3 articles<sup>8–10</sup> pertained to the Gothenburg Skin Hemangioma cohort, we used data from the most recently published article,<sup>8</sup> a pooled analysis of the Gothenburg and Stockholm Skin Hemangioma cohorts. For the Life Span Study, 3 articles<sup>3–5</sup> were located. Again, results from the most recently published article<sup>5</sup> were primarily included. The other 2 articles<sup>3,4</sup> were used when pertinent information—ie, dose, age at exposure, and ERR estimates stratified by sex—was not specified in the most recently published article.<sup>5</sup>

The 8 cohorts differed considerably with respect to characteristics of the study population, dose to the brain, and B/CNST outcome definition. As shown in Table 1, study populations varied by country of origin, by sex, by age at exposure, by age at diagnosis, and by source of radiation. Included studies were conducted in Japan, Sweden, Israel, the United States, France, and the United Kingdom. The proportion of women in the cohorts ranged from 13%<sup>12</sup> to 67%.<sup>8</sup> Average age at exposure was as young as 8 months (range, 0.8–50) in the pooled Skin Hemangioma cohorts<sup>8</sup> to as old as 26 years in the Life Span Study.<sup>5</sup> The mean age of cancer diagnosis ranged from 20.5 years (range, 5–40) in the US Childhood Cancer Survivor Study (USCCSS)<sup>15</sup> to 62.6 years in the Life Span Study.<sup>5</sup> Seven<sup>8,11,12,15–17</sup> of the 8 cohorts were exposed to radiation therapy in a medical setting. The Life Span Study<sup>5</sup> population was based on a one-time exposure to atomic bomb radiation. The range of mean dose to the brain was 0.07<sup>8</sup>–10 Gy.<sup>15,17</sup>

The definition of “all B/CNSTs” differed considerably across studies, with some restricting B/CNST ERR estimates to intracranial tumors and others including spinal tumors (Table 2). The all B/CNSTs category also included subtypes such as glioma and meningioma, which are known to differ biologically, morphologically, and pathologically. Without consistent outcome definitions, it is difficult to compare all B/CNST ERR estimates across studies.

All studies included in the analysis reported an elevated risk for all B/CNSTs postexposure to IR, but the strength of the association varied across studies. The ERR estimates for all B/CNSTs ranged per Gy from 0.19 (95% confidence interval [CI]: 0.03, 0.85)<sup>16</sup> to 5.6 (95% CI: 3.0, 9.4)<sup>12</sup> (Fig. 1). There was significant heterogeneity across studies ( $I^2 = 74.7\%$ ,  $P = .003$ ). Most examined the effect modification of the IR–B/CNST association by sex, age at exposure, time since first exposure, and attained age (Table 3); therefore, the results may be informative of the extent to which these factors contributed to the heterogeneity of study ERR estimates. Generally, the IR–all B/CNST association was attenuated with increasing age at exposure. Stronger associations were generally observed among men. Since the results for all B/CNSTs varied substantially by sex, age at exposure, and attained age<sup>5,8,15</sup> and since B/CNST definitions differed across studies, we did not calculate a summary ERR.

We examined the risk for B/CNSTs by histologic subtype based on results from 4 relevant studies.<sup>5,11,15,17</sup> Three studies<sup>5,15,17</sup> reported an ERR estimate for

**Table 1.** Study population, methods of tumor ascertainment, and dose exposures

Study	Location	N	Total Cases	Female	Method of Tumor Ascertainment	Dose to Brain, Gy, mean (range)	Fractionation, mean (range)	Age at Exposure, mean (range)	Age at Diagnosis, mean/median (range)
Pooled Skin Hemangioma cohorts <sup>8–10</sup>	Sweden	28 008	86	67%	Cancer registry, medical records	0.07 (0–11.5)	1.4 (Gothenburg) 1.5 (Stockholm) (1–37)	8 months (0.8–50 months)	33 y (4–56)
Life Span Study <sup>3,4,5</sup>	Japan	80 180	281	59%	Tumor registries, medical records, death certificates	0.266 <sup>c</sup>	1	26.6 y <sup>c</sup>	62.6 y
NYC Tinea Capitis cohort <sup>12</sup>	NYC	3604	17	13% <sup>a</sup> , 21% <sup>b</sup>	Questionnaire, medical records	1.4 (0.75–1.7)	NS	7.8 y (1–15)	NS
Israel Tinea Capitis cohort <sup>11</sup>	Israel	10 834	125	51.1% <sup>a</sup>	Cancer registry, medical records	1.5 (0.98–6.0)	(5–20)	7.1 y (<1–15)	NS
Childhood Cancer cohort <sup>16</sup>	France, UK	4199	22	44.6%	Medical records	6.2 (0–82.7)	NS	6.0 y (0.0–16.9)	22.1 y (8.0–41.2)
U.S. Childhood Cancer Survivor Study <sup>15</sup>	U.S.	14 361	116	46.6%	Medical records, questionnaires, death certificates, institutional records	10 (glioma) 9 (meningioma)	NS	(0–20)	20.5 y (5–40)
British Childhood Cancer Survivor Study <sup>17</sup>	UK	17 980	247	45%	Cancer registries, questionnaires, medical records	10 (glioma/PNET)	NS	(0–14)	NS

Abbreviations: NS, not specified; PNET, primitive neuroectodermal tumor.

<sup>a</sup>Exposed group only.

<sup>b</sup>Nonexposed group only.

<sup>c</sup>From Thompson et al. 1994.<sup>3</sup>

**Table 2.** ERR estimates for the main brain tumor subtypes and categories

Study	Outcome for Overall Brain/CNS	Overall Brain/CNS ERR per Gy (CI)	Cases	Glioma ERR per Gy (CI)	Cases	Meningioma ERR per Gy (CI)	Cases	Schwannoma ERR per Gy (CI)	Cases	Malignant Brain Tumors ERR per Gy (CI)	Cases	Benign or Unspecified ERR per Gy (CI)	Cases
Pooled Skin Hemangioma cohorts	ICD-7: 193.0, 193.2–193.9, 195.3	2.7 (1.0, 5.6)	86	NA	35	NA	20	NA	10	NA		NA	
Life Span Study	ICD-10: C70-C72	0.62 (0.21, 1.17)	281	0.56 (–0.2, 2.0)	56	0.64 (–0.01, 1.8)	110	4.5 (1.9, 9.2)	64	NA	76	NA	205
NYC Tinea Capitis cohort	Intracranial tumors	5.6 (3.0, 9.4)	17	NA		NA	4	NA	6	1.1 (0.1, 2.8)	7	NA	10
Israel Tinea Capitis cohort	NA	NA	125	NA		5.01 (2.66, 9.80)	86	NA		1.98 (0.73, 4.69)	44	4.63 (2.43, 9.12)	81
Childhood Cancer cohort	ICD-9: 8000, 88903, 94000, 94003, 94013, 94303, 94403, 94503, 95300, 95310, 95370; 1911–1913, 1916–1917, 1919, 1921, 2150, 2250, 2252	0.19 (0.03, 0.85)	22	NA		NA		NA		0.07 (<0, 0.62)	12	>1000 (0.25, >1000) <sup>a</sup>	10
U.S. Childhood Cancer Survivor Study	ICD-O-2: 9380–9523, 9530–9539	0.69 (0.25, 2.23)	116	0.33 (0.07, 1.71)	40	1.06 (0.21, 8.15)	66	NA		NA		NA	
British Childhood Cancer Survivor Study	ICD-O-3: C70.0–72.9, C75.1–75.3; 9380–9523, 9530–9539, 9560–9561	NA		0.079 <sup>b</sup> (0.021, 0.229)	73	5.1 (0.7, 107.7)	137	NA		NA		NA	

Abbreviations: ICD, International Classification of Diseases; NA, not available.

<sup>a</sup> Did not converge.<sup>b</sup> Includes primitive neuroectodermal tumor in addition to glioma.

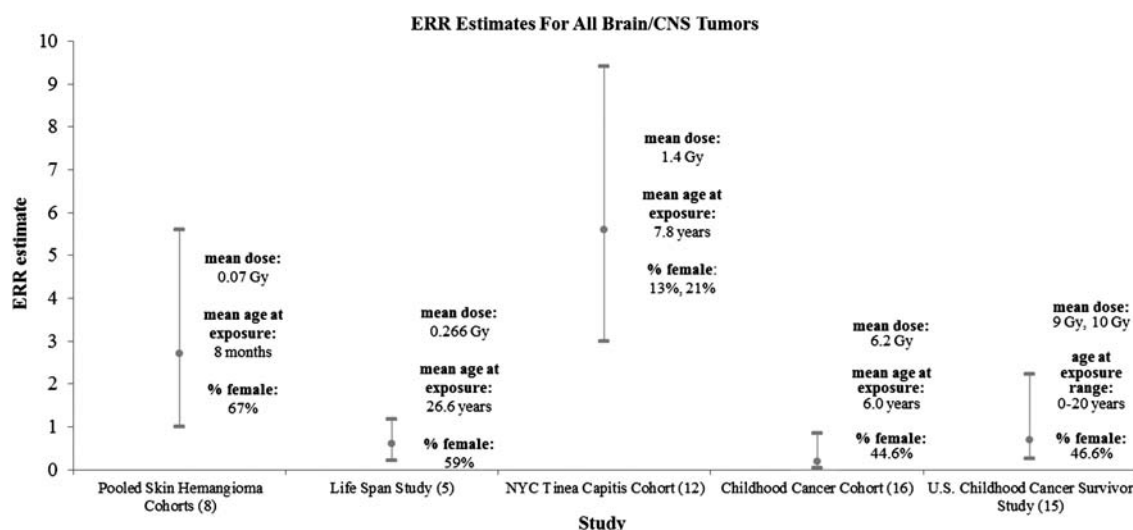


Fig. 1. Cohort-specific ERRs (95% CIs) for all brain/CNS tumors. The dots represent ERRs and the vertical lines correspond to CIs. Note that the definition of all brain/CNS varied across studies.

glioma that ranged per Gy from 0.079 (95% CI: 0.021, 0.229) to 0.56 (95% CI: -0.2, 2.0) (Fig. 2). The British Childhood Cancer Survivor Study (BCCSS)<sup>17</sup> and the USCCSS<sup>15</sup> observed that the association was stronger for patients exposed at younger ages than those exposed at older ages. The populations in the USCCSS15 and the BCCSS17, both exposed to a mean dose of 10 Gy, were composed of similar proportions of females (46.6% USCCSS, 45% BCCSS) and had similar ranges for age at exposure (0–20 years, USCCSS; 0–14 years, BCCSS). Despite stronger ERRs for glioma in men vs women, this difference was not statistically significant. Although there was no evidence of heterogeneity across studies of glioma ( $I^2 = 0.0\%$ ,  $P = 0.586$ ), we chose not to calculate a summary ERR for glioma because of study differences in the range of ages at exposure, which appeared to modify the relationship between IR exposure and glioma risk in these studies.

Four studies<sup>5,11,15,17</sup> provided an estimate for meningioma, with ERRs ranging per Gy from 0.64 (95% CI: -0.01, 1.8) to 5.1 (95% CI: 0.7, 107.7) (Fig. 3). The studies reported an elevated risk for meningioma post-exposure to radiation, but the strength of the association varied across studies. The Life Span Study<sup>5</sup> showed the weakest positive association between radiation dose and risk for meningioma (ERR = 0.64; 95% CI: -0.01, 1.8), possibly because this population had the lowest mean dose exposure, the highest average age at exposure, and the highest proportion of females relative to the other 3 studies. No study reported significant interactions by age at exposure, sex, time since first exposure, or attained age; therefore, we calculated a summary ERR per Gy across the 4 studies of 1.81 (95% CI: -0.51, 4.14) ( $I^2 = 44.8\%$ ,  $P = 0.142$ ) (Fig. 4). Stratifying by dose produced summary ERR estimates for studies of high and low-to-moderate doses per Gy of 1.08 (95% CI: -2.88, 5.04) ( $I^2 = 0.0\%$ ,  $P = 0.883$ ) and 2.47 (95% CI: -1.76, 6.70) ( $I^2 = 81.5\%$ ,  $P = 0.020$ ), respectively. CIs for the 2 strata

overlapped considerably, suggesting that ERR estimates for high- and low-dose studies were consistent with each other. When stratified by sex, the summary ERR estimates per Gy for meningioma were 2.45 (95% CI: -0.64, 5.54) ( $I^2 = 0.0\%$ ,  $P = 0.353$ ) in men and 0.54 (95% CI: -0.32, 1.40) ( $I^2 = 29.3\%$ ,  $P = 0.243$ ) in women. When we sequentially removed individual studies, we found that dropping the Israel Tinea Capitis cohort<sup>11</sup> decreased heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.967$ ), and the summary ERR estimate for the remaining studies was 0.66 (95% CI: -0.22, 1.54).

Only the Life Span Study reported an ERR estimate for schwannoma: 4.5 (95% CI: 1.9, 9.2) per Gy.<sup>5</sup> The association between radiation exposure and schwannoma risk was stronger for men (ERR = 8.0 per Gy) than for women (ERR = 2.3 per Gy). The association was also stronger for people exposed at ages younger than 20 years (ERR = 6.0 per Gy) compared with those exposed at ages 20 years or older.

## Discussion

To our knowledge, this is the first detailed, systematic review focused on the relationship between IR dose and risk for B/CNSTs. We reviewed the characteristics of the study population, dose information, and results from 8 distinct cohorts. Across all studies, there was an elevated risk for all B/CNSTs, gliomas, and meningiomas post-exposure to radiation, but the strength of the association varied across studies. Differences in the mean dose to the brain, average age at exposure, proportion of females, and age at diagnosis across study populations may account for the study variations in ERR estimates.

Several of the studies reported ERRs by brain tumor subtype<sup>5,11,15,17</sup> or behavior.<sup>11,12,16</sup> Overall, IR appeared to have a greater impact on the risk for meningioma compared with glioma, with ERR ranges per Gy of

**Table 3.** Study-specific results according to age at exposure, sex, attained age, time since first exposure, and other factors

Study	Sex	Age at Exposure (y)	Time since First Exposure/Attained Age (y)	Other
Pooled Skin Hemangioma cohorts	Not significant for intracranial tumors	↓ Risk of intracranial tumors with ↑ age at exposure <sup>a</sup>	Not significant time since exposure for intracranial tumors	Dose, treatment decade
Life Span Study	All brain/CNS <sup>c</sup> : 1.4 (M), 0.1 (F) <sup>b</sup> Meningioma: 1.6 (M), 0.4 (F) <sup>b</sup> Schwannoma: 8.0 (M), 2.3 (F) <sup>b</sup>	All brain/CNS <sup>c</sup> : 1.2 (<20), 0.3 (20–39), 0.1 (≥40) <sup>b</sup> Meningioma: 1.3 (<20), 0.5 (20–39), 0.3 (≥40) <sup>b</sup> Schwannoma: 6.0 (<20), 2.6 (20–39), 3.3 (≥40) <sup>b</sup>	All brain/CNS <sup>c</sup> : 0.6 (<50), 0.6 (50–69), 0.8 (≥70) <sup>b</sup> Meningioma: 2.0 (<50), 0.5 (50–69), 0.7 (≥70) <sup>b</sup> Schwannoma: 8.4 (<50), 3.0 (50–69), 3.0 (≥70) <sup>b</sup>	
NYC Tinea Capitis cohort	Not significant for intracranial tumors	Not significant for intracranial tumors	Not significant time since exposure for intracranial tumors	Race
Israel Tinea Capitis cohort	Malignant tumors: 2.11 (M), 1.79 (F) Benign meningioma: 4.97 (M), 4.37 (F)	Malignant tumors: 3.56 (<5), 2.24 (5–9), 0.47 (10+) Benign meningioma: 4.48 (<5), 5.03 (5–9), 4.11 (10+)	Malignant tumors: 2.94 (<20 latent), 1.21 (20–29 latent), 2.05 (30+ latent) Benign meningioma: 4.46 (<20 latent), 3.29 (20–29 latent), 5.21 (30+ latent)	Malignant tumors: 1.40 (Middle East), 2.16 (North Africa), 2.14 (Israel) Benign meningioma: 6.27 (Middle East), 4.00 (North Africa), 3.97 (Israel)
Childhood Cancer cohort	Not significant for all brain/CNS tumors	Not significant for all brain/CNS tumors	Not significant time Since exposure for all brain/CNS tumors	Country, fractionation, first CNS tumor, first tumor, malignant vs. benign/other, <sup>a</sup> neurofibromatosis, genetic syndrome
U.S. Childhood Cancer Survivor Study	All brain/CNS: 1.46 (M), 0.41 (F) Glioma: 0.48 (M), 0.23 (F) Meningioma: 3.99 (M), 0.41 (F)	All brain/CNS: 0.71 (<5), 0.78 (5–9), 0.59 (10–20) Glioma: 0.64 (<5), 0.10 (5–9), 0.15 (10–20) Meningioma: 0.75 (<5), 1.99 (5–9), 1.36 (10–20)	All brain/CNS: 0.39 (5–9 y latent), 0.45 (10–14 y latent), 2.07 (≥15 y latent) Glioma: 0.45 (5–9 y latent), 0.18 (10–14 y latent), n/a <sup>d</sup> (≥15 y latent) Meningioma: 0.05 (5–9 y latent), n/a <sup>d</sup> (10–14 y latent), n/a <sup>d</sup> (≥15 y latent)	
British Childhood Cancer Survivor Study	Not analyzed	↓ Risk of glioma/PNET with ↑ age at exposure <sup>a</sup>	Not significant for glioma/PNET and meningioma	↑ Risk for glioma/PNET for genetic susceptibility, <sup>a</sup> chemotherapy

Abbreviation: PNET, primitive neuroectodermal tumor.

<sup>a</sup> Significant at  $P < 0.05$ .<sup>b</sup> From Preston et al. 2002.<sup>4</sup><sup>c</sup> Excludes schwannoma.<sup>d</sup> Model did not converge.



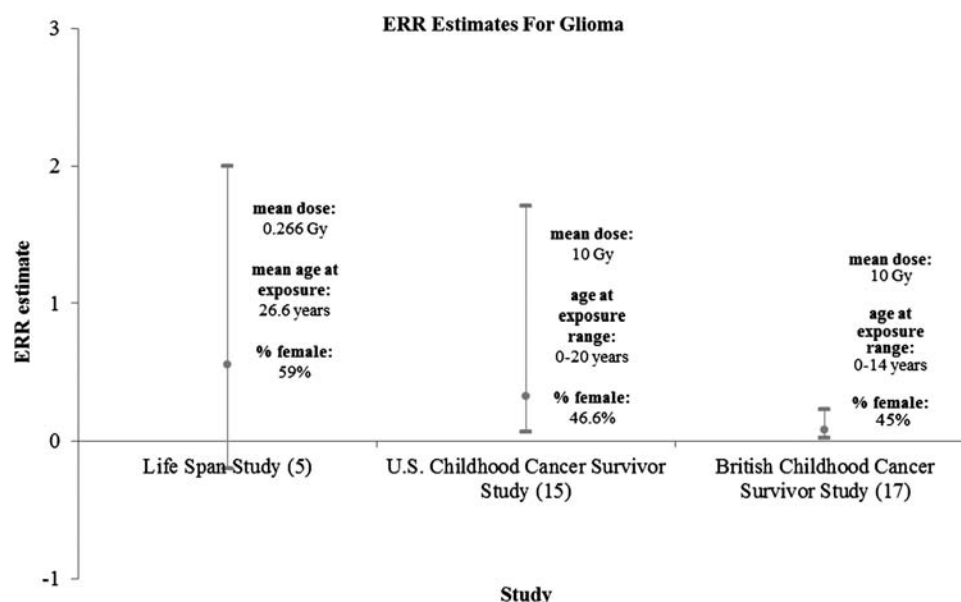


Fig. 2. Cohort-specific ERRs (95% CIs) for glioma. The dots represent ERRs and the vertical lines correspond to CIs.

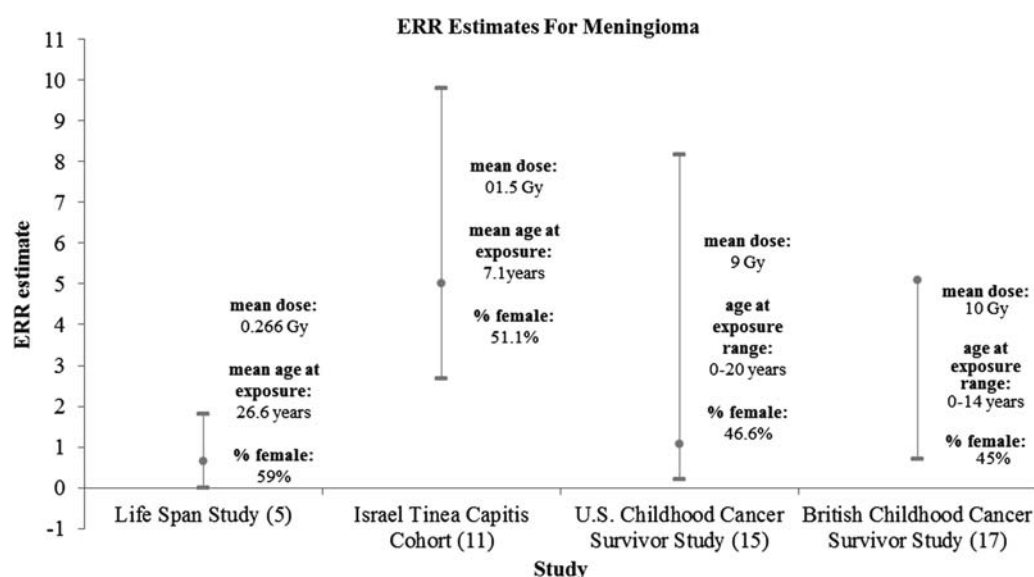


Fig. 3. Cohort-specific ERRs (95% CIs) for meningioma. The dots represent ERRs and the vertical lines correspond to CIs. Note that the upper range for the British Childhood Cancer Survivor Study (17) is 107.7 and is not shown.

0.079<sup>17</sup>–0.56<sup>5</sup> for glioma and 0.64<sup>5</sup>–5.1 for meningioma.<sup>17</sup> While we did not observe an effect modification on the risk for meningioma by sex, age at exposure, time since exposure, or attained age, it is possible that the sample size was too small to detect variation in these factor risks. None of the previous studies on this topic examined risk by glioma subtype (eg, glioblastoma), which may differ with regard to etiology. Despite the strong positive association between IR exposure and risk for schwannoma observed in the Life Span Study,<sup>5</sup> no other study with detailed information on organ dose examined risk for this subtype, most likely due to the lack of registry information on schwannomas, which are primarily benign.<sup>8</sup> Since the evidence suggests

that the role of IR in the etiology of brain tumors varies according to different tumor characteristics, future studies should investigate these associations separately for glioma and glioma subtypes and for meningioma and schwannoma.

Our analysis included several cohorts of varying mean doses to the brain, facilitating comparison of the differential risks for B/CNSTs across a wide range of exposures to IR. The Life Span Study<sup>3</sup> population and the pooled Skin Hemangioma cohorts<sup>8</sup> were exposed to an average dose of <0.3 Gy. However, with increasing concern over the effects of frequent, low-dose exposures to medical and dental radiation, it is important to analyze these studies and characterize the IR–B/CNST

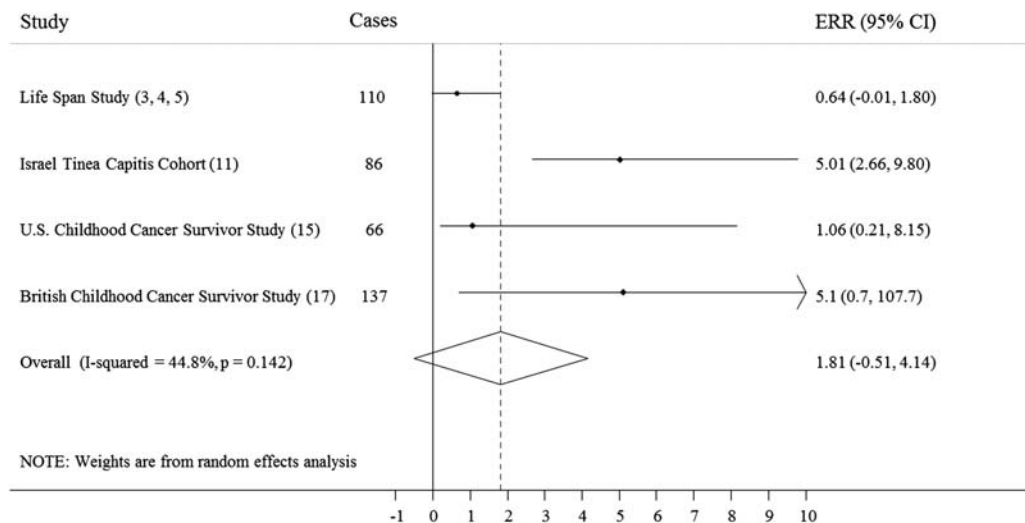


Fig. 4. Cohort-specific and summary ERRs (95% CIs) for meningioma.

relationship at even lower doses. Human epidemiologic studies examining the relationship between low-dose diagnostic exposures and brain tumors have yielded conflicting results. A population-based case-control study observed an elevated risk for meningioma in males exposed to dental X rays but an unexplainable decreased risk for glioma.<sup>35</sup> Davis et al.<sup>36</sup> observed an elevated risk for glioma after 3 or more cumulative exposures to CT scans to the head and neck, but only in cases of family history of cancer. Another population-based case-control study<sup>37</sup> found a significant 2-fold increased risk for meningioma after 6 or more full-mouth series of dental X rays over a lifetime but did not detect a dose-response relationship; the study also did not find an elevated risk with bitewing, lateral cephalometric, or panoramic radiographs. Recently, Claus et al.<sup>38</sup> reported an increased risk for meningioma with frequent annual exposure to bitewing and panorex films, especially at younger ages.

On the other hand, both of the low-dose studies<sup>5,8</sup> reported an increased risk for all B/CNSTs. One reason for the conflicting results may be that case-control studies that rely on self-reported exposure data may have difficulty obtaining accurate information on exposure to medical and dental radiation. These studies can be susceptible to information bias because the exposure data depend on study participants' ability to recall lifetime exposures to medical, dental, and other types of radiation. Study participants may be more likely to report exposure to dental and medical radiation than less-publicized sources (eg, radiation during air travel). Differential recall bias can also be an issue because cases are more likely than controls to report exposure to radiation; therefore, the IR-B/CNST association appears more positive than it actually is. Given that current evidence on the low-dose IR-B/CNST association is limited and inconsistent, additional prospective studies are needed to assess fully the B/CNST risk post-exposure to low-to-moderate doses of radiation.

The main limitation of this review was the heterogeneity of tumor definitions and of study population characteristics, which precluded comparison of ERR estimates across studies and calculation of summary ERR estimates for all B/CNSTs and glioma using meta-analysis. Only one study<sup>5</sup> reported an ERR estimate for schwannoma; therefore, we could not calculate a summary risk estimate. In addition, younger ages at exposure for most of the studies may limit the generalizability of the results of our review, which consisted primarily of studies of children who had undergone radiation for medical conditions, with only the Life Span Study<sup>5</sup> assessing exposure in adulthood.

Given that IR is the only known modifiable risk factor for B/CNSTs, clarifying the IR-B/CNST relationship is important for providing etiologic clues and implementing preventative strategies. Generally, we found that exposure to radiation was associated with an increased risk for all B/CNSTs, gliomas, and meningiomas and that radiation had a greater effect on the risk for meningioma compared with glioma. A future pooled analysis of ERR estimates from the original data could be useful for expanding our understanding of this complex relationship in that a standardized definition of all B/CNSTs may be applied across studies and important differences accounted for in the analysis. More studies, preferably large prospective studies that estimate the dose-response relationship between radiation exposure and risk for specific B/CNST subtypes, taking into account potential effect modifiers, will be key for expanding our knowledge of radiation-induced B/CNSTs.

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