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Risk Factors of Subsequent Central Nervous System Tumors after Childhood and Adolescent Cancers: Findings from the French Childhood Cancer Survivor Study

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ABSTRACT

Background: Childhood or adolescent cancer survivors are at increased risks of subsequent primary neoplasms (SPN) of the central nervous system (CNS) after cranial irradiation. In a large multicentric cohort, we investigated clinical and therapeutic factors associated with the long-term risk of CNS SPN, and quantified the dose–response relationships.

Methods: We selected all CNS SPN cases diagnosed up to 2016 among members of the French Childhood Cancer Survivor Study at least 5 years after first cancer diagnosis in 1946–2000. Four controls per case were randomly selected within the cohort and matched by sex, year of/age at first cancer diagnosis, and follow-up time. On the basis of medical and radiological reports, cumulative radiation doses received to the SPN or matched location were retrospectively estimated using mathematical phantoms. We computed conditional logistic regression models.

Results: Meningioma risk significantly increased with higher radiation doses [excess OR per Gy (EOR/Gy) = 1.377; $P < 0.001$; 86 cases; median latency time = 30 years], after adjustment for reported genetic syndromes and first CNS tumor. It was higher among youngest individuals at first cancer diagnosis, but did not vary with follow-up time. On the opposite, radiation-related glioma risk (EOR/Gy = 0.049; $P = 0.11$; 47 cases; median latency time = 17 years) decreased over time (P for time effect = 0.05). There was a significant association between meningioma risk and cumulative doses of alkylating agents, but no association with growth hormone therapy.

Conclusions: The surveillance of patients with cranial irradiation should continue beyond 30 years after treatment.

Impact: The identified risk factors may inform long-term surveillance strategies.

Introduction

Each year, 15.6/100,000 children and adolescents (0–19 years of age) are diagnosed with cancer worldwide, of whom 18% are diagnosed with a tumor of the central nervous system (CNS; ref. 1). With improvements in cancer detection, treatment, and supportive care, survival rates of patients with childhood and adolescent cancer have considerably increased over the past decades. Consequently, the number of long-term survivors is increasing, it is estimated to be 300,000–500,000 currently in Europe (2), as does the burden of disease and treatment late sequelae. These individuals have indeed substantially higher risks of developing severe morbidity, including subsequent primary neoplasms (SPN), compared with the general population, and the absolute excess risks increase with attained age (3).

The cumulative incidence of CNS SPN is estimated to be 3.6% after 40 years of follow-up since childhood or adolescent cancer diagnosis (4). After cranial irradiation, this risk is 10–500 times higher compared with survivors who did not receive cranial irradiation (5–8), with median latency times of 10–25 years (4, 5, 8). Previous studies consistently reported a linear increase of risk with higher radiation doses, but widely varying magnitudes of risks across the populations (4, 5, 8, 9). The factors explaining this heterogeneity remain unknown. Age at exposure and follow-up time are potential explaining factors, but trends in radiation-related risks with age and time were inconsistent across studies (4, 5, 8). Some studies reported associations between risk of meningioma and treatment with intrathecal methotrexate (4) or platinum agents (8, 10), but none of these results were replicated in another study.

Hence, providing a better understanding of the risk factors of potentially disabling, life-threatening CNS SPN is crucial to define

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guidelines for long-term surveillance of childhood and adolescent cancer survivors, improve early detection, and, possibly, better prevent these events. In a large multicentric cohort, the French Childhood Cancer Survivor Study (FCCSS), we investigated clinical and therapeutic factors associated with the long-term risk of CNS SPN, including the type of first cancer, genetic syndromes, and treatment modalities (radiotherapy, chemotherapy, and growth hormone). More specifically, we quantified the radiation dose–response relationship for different SPN histology, and investigated whether clinical and therapeutic factors modify these associations.

Material and Methods

Source population

We conducted a case–control study nested within the FCCSS cohort (https://fccss.fr/), which has included 7,670 individuals diagnosed in 1946–2000 with a solid cancer or lymphoma before the age of 21 years. These individuals had been treated at one of the five participating French university hospitals and had survived at least 5 years after their first cancer diagnosis. The FCCSS has been approved by a regional committee on ethics and the French national agency regulating data protection (Commission Nationale Informatique et Liberté, agreements no., 902287 and no., 12038829), with an exemption from obtaining individual consent from the participants for retrospective data collection. The study was conducted in accordance with the applicable French laws and requirements, European authorities, and the Declaration of Helsinki.

For each cohort member, detailed information on clinical characteristics and treatments (radiotherapy, chemotherapy, and hormonal treatments) received for first cancer occurrence, relapse/progression, or SPN was collected. Twenty genetic syndromes are recorded in the FCCSS as evaluated in routine practice. We considered the following as being potentially associated with CNS SPN risk: neurofibromatosis types 1 and 2, Turcot, Gorlin, Li-Fraumeni, Klinefelter, Rubinstein–Taybi, Turner, or Bloom syndrome, tuberous sclerosis, polyposis coli, and also considered bilateral or familial retinoblastoma (likely reflecting RB1 mutation). Subsequent mortality and morbidity events were identified through medical records at the treatment centers (including a long-term follow-up clinic since 2012), patient/proxy-reported questionnaires since 2005 (response rate up to 2016: 50.9%), and cohort linkage with the national healthcare data system (data available since 2006) and the national registries of vital status and causes of death (virtually exhaustive since 1968). SPNs were identified through these different sources, and all were subsequently validated by a trained and experienced nurse on the basis of medical, pathology, or radiological reports obtained from the treating centers or from referring doctors, regardless of the data source used for first identification.

Selection of cases and controls

We included all malignant and benign CNS SPN validated cases that occurred at least first 5 years after the first cancer diagnosis until December 31, 2016, among the FCCSS cohort members who had complete radiation dosimetry at the time of the analyses (97.1% of the cohort). These cases were classified according to the 2016 World Health Organization Classification of CNS tumors (ref. 11; Supplementary Table S1). Patients who were diagnosed with CNS SPN at different dates (≥6 months after a previous diagnosis) accounted for several cases, whether the histology was identical or not. The different histologic types were grouped as meningioma, glioma, and other/unspecified. Four controls per case were randomly selected among the FCCSS cohort members with complete radiation dosimetry, and matched by sex (male and female), year of first cancer diagnosis (±5 years), age at first cancer diagnosis (±2 years), and follow-up time (≥ the interval between first cancer diagnosis and diagnosis of CNS SPN of the matched case). Individuals who developed CNS SPN could serve as controls for other individuals diagnosed with CNS SPN at an earlier time after their first primary cancer diagnosis.

Radiation doses

All treatment data were abstracted from medical and radiology records at the participating centers, which also included partial information from nonparticipating centers if the patients were treated at several places. For external beam radiotherapy and/or brachytherapy, radiation dose distributions to the brain were retrospectively reconstructed on the basis of the treatment information (treatment machine, type of radiation, beam energy, irradiation technique, field size and shape, gantry and collimator angles, use of accessories, target volume location, and total delivered dose), mathematical gender- and age-specific phantoms modeling patient's anatomy in treatment position, and validated particle transport simulation models (12). This dose reconstruction system allowed estimating doses to 2-mm voxels for the whole body. For each individual, we averaged the estimated dose within the border of delineated CNS SPN for cases (or matched location for controls). Cumulative radiation exposure to the SPN location was defined as total doses from all treatments of initial cancer or non-CNS SPN from first cancer diagnosis up to 5 years (presumed latency time between irradiation and potentially induced CNS SPN) before CNS SPN diagnosis for cases, or index date for controls (control's first cancer diagnosis + matched case's follow-up time until SPN diagnosis). CNS SPN locations were delineated on phantoms by a radiation oncologist (W. Zrafi) based on radiological and medical records. When information was not retrieved on the SPN location (26% of cases), we considered the mean dose to the cerebral lobe where the SPN occurred when this information was recorded, or the whole brain. If multiple SPN locations (e.g., diffuse meningioma) were reported on a given diagnosis date, we considered the mean dose to all locations.

Chemotherapy exposures

The abstracted information on chemotherapy included drug names, delivered doses (in milligrams per square of the body surface area), administration routes, and dates of each treatment, for initial cancer or SPN. Exposures to chemotherapy were ascertained as: (i) receipt (or not) of any chemotherapy agent, alkylating (including platinum) agents, anthracyclines, antibiotics, antimetabolites, epipodophyllotoxins, or vinca alkaloids and (ii) cumulative doses for each chemotherapy class from first cancer diagnosis up to 1 year before the exit date (date of SPN diagnosis for cases or index date for controls). The 1-year period of exclusion was applied to avoid reverse causation by considering CNS SPN treatments started before the diagnosis was histologically confirmed, while we hypothesized that the latency time between chemotherapy exposure and potential SPN occurrence was longer than 1 year. We also considered exposures to specific drugs having the ability to cross the blood–brain barrier (Supplementary Table S2), when the number of exposed individuals was ≥10. For methotrexate, we considered cumulative doses by administration route (intrathecal, oral, intravenous, and unknown/multiple) to evaluate whether we could replicate the findings of a previous study reporting an increased risk of meningioma with intrathecal administration only (4). Finally, we considered reported treatment with growth hormone, and its total duration.

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Statistical analyses

ORs of CNS SPN for cases versus matched controls were estimated according to clinical (reported genetic syndrome, yes/no and first CNS tumor, yes/no) and therapeutic (reported growth hormone, yes/no; cumulative radiation doses, no radiotherapy/0 to <5/5 to <20/20 to <40/≥40 Gy; and chemotherapy classes or agents, yes/no) factors, using conditional logistic regression models. We also evaluated associations between cumulative radiation and chemotherapy doses, and duration of growth hormone treatment (i.e., continuous variables), as linear and exponential dose–response functions with risk of CNS SPN. For radiation doses, linear functions were preferred to model excess ORs per Gy (EOR/Gy), because it provided a much better fit than the more commonly used exponential model. Departure from linearity in dose–response relationships was assessed by comparing the goodness-of-fit of linear versus nonlinear (linear-quadratic, linear-exponential, linear-quadratic-exponential, quadratic, and quadratic-exponential) models. These models were compared using likelihood ratio tests for nested models, and the Akaike information criterion (AIC) otherwise.

Radiation exposure–related risks were estimated with adjustment for first CNS tumor and reported genetic syndromes (except otherwise stated). The adjustment for first CNS tumor aimed to control for a potential indication bias, while treatment modalities depend on the tumor treated, and CNS first tumor may reflect a particular genetic background for developing CNS tumors, where the available information on genetic syndromes was probably incomplete. Indeed, not all patients were tested for known genetic factors, and the genetic background of CNS tumors is not yet fully understood and characterized. Routine surveillance strategies of asymptomatic individuals may also differ for CNS and non-CNS cancers. The analyses investigating the main effects of chemotherapy and growth hormone therapy were adjusted for first CNS tumor (except otherwise stated), reported genetic syndromes, and radiation dose as a continuous variable. Our main hypotheses regarding the interconnections between the variables of interest are detailed in Supplementary Fig. S1.

Interactions between therapeutic factors were tested on multiplicative and additive scales. Modification of the effect of radiation exposures by host characteristics and time since exposure was assessed by likelihood ratio tests for nested models ($P_{heterogeneity}$ of EOR/Gy across population subgroups), and interactions between radiation dose and potential effect modifiers were considered as continuous variables (P_{trend}). All analyses were performed using the PECAN module of Epicure v.1.81 software (13). Except otherwise stated, two-sided P values and 95% confidence intervals (CI) were based on the likelihood-ratio statistic.

Results

This study included 152 cases (meningioma, 86; glioma, 47; and other/unspecified histology, 19) and 604 controls (**Table 1**). Among cases, the mean age at diagnosis of first and subsequent CNS neoplasm was 6 years (meningioma, 6.2; glioma, 5.6; and others, 5.9 years) and 29 years (meningioma, 31.8; glioma, 20.8; and others, 31.0 years), respectively. The median time between first cancer diagnosis and SPN diagnosis was 30.2, 17.3, and 26.5 years for meningioma, glioma, and unspecified/other histology, respectively (Supplementary Table S3). A total of 98 (64.5%) SPNs occurred after a first CNS tumor, and 40 (26.3%) among individuals with reported genetic syndromes (neurofibromatosis type 1, $n = 25$; Gorlin, $n = 8$; Li-Fraumeni, $n = 3$; bilateral or familial retinoblastoma, $n = 3$; and Turcot, $n = 1$). The majority (65%) of meningioma cases occurred in regions irradiated with ≥20 Gy; 22% of cases occurred in regions exposed to <5 Gy or in nonirradiated individuals. Almost half of glioma and other/unspecified cases occurred in regions exposed to <5 Gy or in nonirradiated individuals.

Meningioma

The risk of subsequent meningioma was 16 times higher among CNS tumor survivors compared with other cancer survivors (**Table 2**). Adjusting for radiation dose substantially reduced the OR for first CNS tumor, while the OR for genetic syndromes remained unchanged. We estimated ORs of 9.2 (95% CI, 2.4–42.2), 27.9 (95% CI, 7.8–124.0), and 17.8 (95% CI, 3.6–103.0) for radiation doses of 5–<20, 20–<40, and ≥40 Gy, respectively, after adjustment for genetic syndromes and first CNS tumor. The EOR/Gy was 1.377 (95% CI, 0.416–5.058; $P < 0.001$) with no significant departure from linearity, even though there was a suggestion of a downward curvature at doses >25–30 Gy (**Fig. 1A**). The EOR/Gy significantly increased with lower age at first cancer diagnosis ($P_{trend} < 0.05$), and was nonsignificantly higher among non-CNS tumor survivors compared with CNS tumor survivors ($P_{heterogeneity} = 0.08$; **Table 3**). The EOR/Gy remained stable over time since first cancer diagnosis, and did not vary with other host characteristics. There was a modest, but significantly, elevated risk with increasing cumulative doses of alkylating agents, all drugs combined (OR per 1,000 mg/m^2, 1.06; 95% CI, 1.02–1.09; $P = 0.03$), but no significant association with any single alkylating drug (Supplementary Tables S4 and S5). We found no association with other chemotherapy agents or growth hormone therapy, and no additive or multiplicative interaction between radiation, chemotherapy, and growth hormone therapy.

Glioma

Genetic syndrome and first CNS tumor were each associated with a 10 times higher risk of subsequent glioma (**Table 2**). There was no or a moderate reduction in these risks after adjustment for cumulative radiation dose, suggesting that they were little driven by radiotherapy. There was no significant association between radiation dose and glioma risk overall after adjustment for genetic syndrome and first CNS tumor (EOR/Gy, 0.049; 95% CI, −0.005–0.301; $P = 0.11$; **Fig. 1B**). However, the EOR/Gy significantly increased among older individuals at the time of first cancer diagnosis ($P_{trend} < 0.05$) and with a shorter follow-up time ($P_{trend} = 0.05$; **Table 3**). The risk of glioma was also significantly elevated among individuals who received epipodophyllotoxins compared with those who did not receive these drugs (OR, 3.7; $P = 1.0$–14.6; 11 cases among the exposed), but there was no dose–response relationship (Supplementary Table S4). We found no significant association with other chemotherapy class or agent and no interaction between chemotherapy and radiation exposures. The sample size was too small to investigate risks associated with growth hormone.

Other/unspecified histology

The risk of CNS SPN with unspecified/other histology increased with higher radiation doses (**Table 2**). The EOR/Gy adjusted for genetic syndrome and first CNS tumor was 0.402 (95% CI, <−0.177–11.61; $P = 0.002$), with no significant departure from linearity (**Fig. 1C**). We found no association with alkylating agents (there were too few cases to investigate associations with other chemotherapy class or growth hormone exposures; Supplementary Table S4), and no interaction between these drugs and radiation exposures on the risk of other/unspecified CNS SPN.

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Table 1. Numbers of cases and controls (%) by demographic, clinical, and therapeutic factors.

			Cases		
		Controls	Meningioma	Glioma	Other/ unspecified
Overall		604 (100.0)	86 (100.0)	47 (100.0)	19 (100.0)
Sex	Male	232 (38.4)	26 (30.2)	23 (48.9)	9 (47.4)
	Female	372 (61.6)	60 (69.8)	24 (51.1)	10 (52.6)
Year of 1st cancer diagnosis	<1970	117 (19.4)	17 (19.8)	9 (19.1)	4 (21.1)
	1970–1979	177 (29.3)	28 (32.6)	8 (17.0)	4 (21.1)
	1980–1989	215 (35.6)	33 (38.4)	20 (42.6)	8 (42.1)
	1990–2000	95 (15.7)	8 (9.3)	10 (21.3)	3 (15.8)
Age at 1st cancer diagnosis, in years	<2	128 (21.2)	10 (11.6)	9 (19.1)	3 (15.8)
	2–<5	170 (28.1)	28 (32.6)	15 (31.9)	6 (31.6)
	5–<10	192 (31.8)	33 (38.4)	14 (29.8)	7 (36.8)
	10–21	114 (18.9)	15 (17.4)	9 (19.1)	3 (15.8)
ICCC-3 code of the 1st cancer diagnosis	II. Lymphomas	101 (16.7)	15 (17.4)	1 (2.1)	4 (21.1)
	III. CNS, miscellaneous intracranial and intraspinal tumors	73 (12.1)	57 (66.3)	34 (72.3)	7 (36.8)
	III.b Astrocytomas	26 (4.3)	8 (9.3)	19 (40.4)	4 (21.1)
	III.c Embryonal tumors[a]	28 (4.6)	37 (43.0)	5 (10.6)	3 (15.8)
	IV. Peripheral nervous cell tumors	73 (12.1)	4 (4.7)	1 (2.1)	2 (10.5)
	V. Retinoblastoma	34 (5.6)	1 (1.2)	2 (4.3)	1 (5.3)
	VI. Renal tumors	155 (25.7)	3 (3.5)	1 (2.1)	2 (10.5)
	VIII. Bone tumors	41 (6.8)	1 (1.2)	2 (4.3)	0 (0.0)
	IX. Soft tissue sarcoma	68 (11.3)	2 (2.3)	6 (12.8)	0 (0.0)
	X. Germ cell tumors, neoplasms of gonads	31 (5.1)	2 (2.3)	0 (0.0)	2 (10.5)
	VII, XI–XII. Others, unspecified tumors	28 (4.7)	1 (1.2)	0 (0.0)	1 (5.3)
Genetic syndrome	Not reported	574 (95.0)	71 (82.6)	26 (55.3)	15 (78.9)
	Yes	30 (5.0)	15 (17.4)	21 (44.7)	4 (21.1)
Radiotherapy	No	260 (43.0)	5 (5.8)	14 (29.8)	1 (5.3)
	Yes	344 (57.0)	81 (94.2)	33 (70.2)	18 (94.7)
Chemotherapy agents	None	135 (22.4)	32 (37.2)	28 (59.6)	6 (31.6)
	Any chemotherapy agents	455 (75.3)	53 (61.6)	19 (40.4)	12 (63.2)
	Alkylating agents	304 (50.3)	47 (54.7)	15 (31.9)	10 (52.6)
	Anthracyclines	213 (35.3)	13 (15.1)	5 (10.6)	4 (21.1)
	Epipodophyllotoxins	66 (10.9)	7 (8.1)	11 (23.4)	5 (26.3)
	Vinca alkaloids	362 (59.9)	46 (53.5)	9 (19.1)	8 (42.1)
	Antimetabolites	100 (16.6)	19 (22.1)	5 (10.6)	3 (13.0)
	Antimetabolites: methotrexate	89 (14.7)	16 (18.6)	5 (10.6)	3 (15.8)
	Methotrexate, intrathecal route	45 (7.5)	7 (8.1)	1 (2.1)	2 (10.5)
	Antibiotics	250 (41.4)	7 (8.1)	6 (12.8)	4 (17.4)
	Others	37 (6.1)	5 (5.8)	1 (1.8)	1 (5.3)
	Unknown	14 (2.3)	1 (1.2)	0 (0.0)	1 (5.3)
Growth hormone	Not reported	558 (92.4)	51 (59.3)	38 (80.9)	16 (84.2)
	Yes	46 (7.6)	35 (40.7)	9 (19.1)	3 (15.8)
Availability of information on CNS SPN location	No	N/A	11 (27.5)	18 (19.4)	11 (57.9)
	Yes		29 (72.5)	75 (80.6)	8 (42.1)

Abbreviations: ICCC-3, International Classification of Childhood Cancer, 3rd edition; N/A, not applicable; all, but four cases, had each four matched controls; the remaining four cases had three matched controls only.
[a]All first cancer diagnoses, but for two controls, are medulloblastomas.

Discussion

On the basis of the long-term follow-up of a large cohort of childhood or adolescent cancer survivors, this study showed that the risk of subsequent meningioma was strongly associated with cumulative radiation doses, with significantly increased risks at doses as low as 5–20 Gy, and to a lesser extent, with reported genetic syndromes and first CNS tumor, independently of radiation exposure. The radiation-related risk of meningioma remained elevated after ≥25 years of follow-up. For glioma, however, it decreased over time, suggesting that, over a long follow-up time (>10–20 years after treatment), the risk of subsequent glioma would be mostly attributable to genetic background and/or other first tumor–related factors.

Three previous large studies have investigated the radiation dose–response relationship for CNS SPN risks, and also found a strong association with cumulative radiation doses for meningioma (refs. 4, 5, 8; Supplementary Table S6). The EOR/Gy estimated in this study was nevertheless higher than in the U.S. cohort (5), which may be attributable to a longer follow-up time (median latency time = 30.2 vs. 17 years in the U.S. cohort; ref. 5) because both studies found (nonsignificantly) lower radiation-related risks during the first 10–15 years of follow-up (**Table 3**). The French and the U.S. studies

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Table 2. OR of SPN of the CNS associated with reported genetic syndromes predisposing to CNS tumors, type of first cancer, and radiation dose categories.

	Cases/controls, *n*	Model with clinical factors only OR (95% CI)	Model with therapeutic factors only OR (95% CI)	Model with clinical + therapeutic factors OR (95% CI)
Meningioma				
Genetic syndrome				
No	71/326	1.0 (Ref.)	—	1.0 (Ref.)
Yes	15/14	3.5 (1.4–9.4†)	—	4.0 (1.3–12.9†)
First cancer type				
Non-CNS tumor	29/301	1.0 (Ref.)	—	1.0 (Ref.)
CNS tumor	57/39	15.7 (8.2–33.2)	—	3.4 (1.5–8.3)
Radiation dose, in Gy				
0 (no radiotherapy)	5/138	—	1.0 (Ref.)	1.0 (Ref.)
0–<5 (mean: 0.8)	14/153	—	2.2 (0.8–6.5†)	1.43 (0.5–4.7)
5 to <20 (mean: 12.1)	11/15	—	20.7 (5.6–82.8†)	9.24 (2.4–42.2)
20 to <40 (mean: 29.1)	42/25	—	68.8 (22.1–241.5†)	27.86 (7.8–124.0)
≥40 (mean: 48.2)	14/9	—	61.1 (15.2–269.1†)	17.80 (3.6–103.0)
Glioma				
Genetic syndrome				
No	26/179	1.0 (Ref.)	—	1.0 (Ref.)
Yes	21/9	10.5 (3.1–39.4†)	—	11.0 (3.1–43.5)
First cancer type				
Non-CNS tumor	13/166	1.0 (Ref.)	—	1.0 (Ref.)
CNS tumor	34/22	10.0 (4.1†–26.2)	—	6.7 (2.2†–20.0†)
Radiation dose, in Gy				
0 (no radiotherapy)	14/89	—	1.0 (Ref.)	1.0 (Ref.)
0 to <5 (mean: 0.7)	7/73	—	0.6 (0.2†–1.7†)	0.9 (0.2–3.7)
5 to <20 (mean: 11.3)	11/8	—	9.3 (2.8–32.5†)	1.2 (0.2–7.5)
20 to <40 (mean: 28.3)	5/13	—	3.2 (0.8–12.0†)	1.7 (0.3–9.0)
≥40 (mean: 50.1)	10/5	—	11.9 (3.5–43.9†)	4.3 (0.7–31.1)
Other/unspecified histology				
Genetic syndrome				
No	15/69	1.0 (Ref.)	—	1.0 (Ref.)
Yes	4/7	2.7 (0.4–4.2)	—	3.4 (0.5–5.3†)
First cancer type				
Non-CNS tumor	12/64	1.0 (Ref.)	—	1.0 (Ref.)
CNS tumor	7/12	2.8 (0.8–10.3)	—	1.3 (0.2–6.5)
Radiation dose, in Gy[a]				
0 to <5 (mean: 0.4)	8/62	—	1.0 (Ref.)	1.0 (Ref.)
5 to <30 (mean: 18.7)	7/11	—	8.7 (1.9–45.3†)	9.2 (1.9–71.9)
≥30 (mean: 38.7)	4/3	—	16.5 (2.5–124.7†)	14.2 (1.8–162.8)

Note: CI estimated using the likelihood profiles, except for the bounds noted as "†," which were estimated using the Wald method (the likelihood profile method did not converge).

[a]Different radiation dose categorization was used for "other/unspecified histology" due to the small number of cases by dose categories.

consistently reported a nonsignificant downward curvature in the radiation dose–risk relationship, with highest risks at doses of 20–40 and 30–45 Gy, respectively, and lower excess risks for exposures above these dose ranges. The United Kingdom study, however, reported a highest RR at doses ≥40 Gy, and a much higher EOR/Gy (5.1; 95% CI, 0.7–107.7) over the full dose range (4). *Ad hoc* analyses of the FCCSS with various adjustment factors (Supplementary Table S6A) show that the higher EOR/Gy estimated in the United Kingdom study can likely be explained by the absence of adjustment for first tumor type in that study and the report of a radiation dose effect among individuals without exposure to methotrexate (according to the modeling method used). The Dutch study reported a much lower EOR of 0.30 per Gy (8), but the use of prescribed total doses in that study (instead of doses to the SPN/matched location as in this study and others; refs. 4, 5) probably makes the risk estimates not comparable, especially for individuals with focal or boost irradiation to the head, which is associated with high-dose gradients at the edge of the radiation field.

In the FCCSS, the radiation-related risk of glioma during the first 15 years of follow-up (EOR/Gy, 0.45; **Table 3**) was similar to that found in the U.S. cohort with a median follow-up of 9 years after adjustment for first cancer type (EOR/Gy, 0.33; Supplementary Table S6B). Unlike that study (5), the absence of a significantly increased risk overall in the FCCSS was thus, probably due to a longer follow-up time, because the EOR/Gy decreased over time (**Table 3**). Compared with the United Kingdom study (4), we found a higher EOR/Gy based on the same median follow-up time (17 years) and a risk model adjusted for genetic conditions only in both studies (Supplementary Table S6B). This difference was unlikely due to the higher proportion of individuals with reported genetic syndromes in the FCCSS (which could be related to the noninclusion of patients with leukemia as first cancer and/or a higher completeness rate of this information in the FCCSS) because

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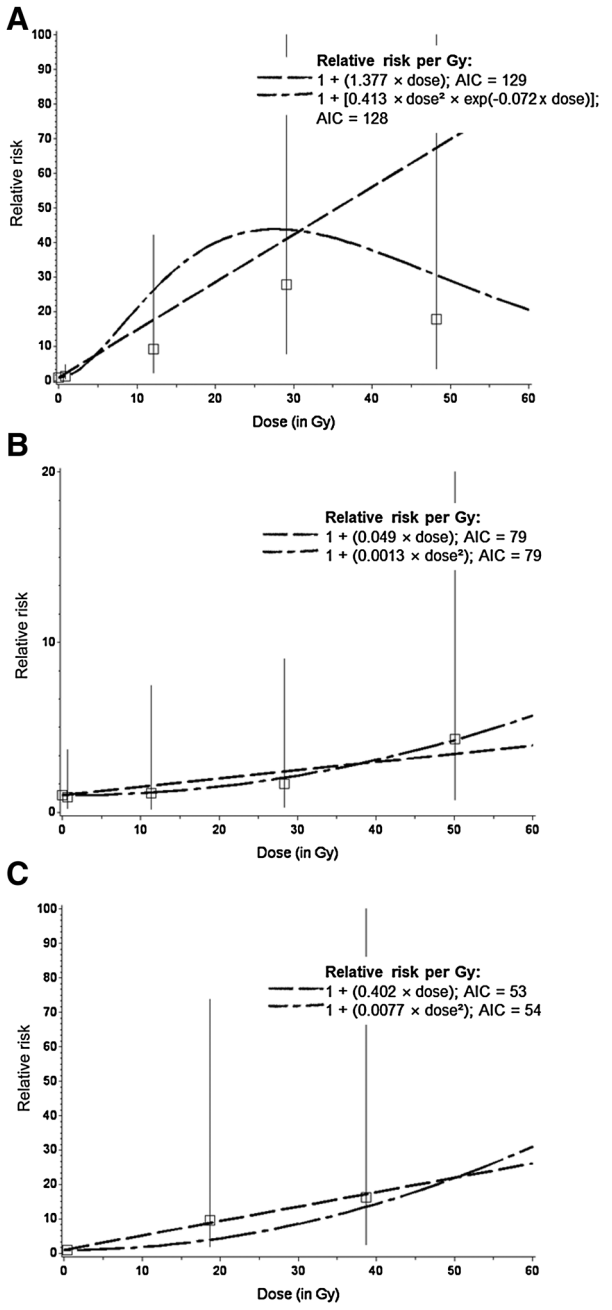

Figure 1.

Radiation dose–response relationship for risks of second primary tumors of the CNS. The figure displays fitted risk values from the two dose risk models with the lowest AIC values among all evaluated models, for meningioma (**A**), glioma (**B**), and tumors with other/unspecified histology (**C**). It also reports RRs by dose category (squares, which are placed at the mean dose value of the dose category) and 95% CIs (vertical lines).

adjustment for this factor slightly reduced the risk estimate. The inclusion of other neuroepithelial neoplasms and primitive neuroectodermal neoplasms (4) in the "glioma" category in the United Kingdom study, instead of the more restricted definition used here (11), is also unlikely to be an explanatory factor, because we also report a higher risk of tumors with other/unspecified histology (**Table 2**). In this category, the histology was nevertheless unknown for 10 (52%) cases, which makes the interpretation of these results difficult.

The characterization of time factors and host characteristics by which the risks of CNS SPN differ is important, not only to understand why the risk estimates vary across study populations, but also to identify patient subgroups who have higher risks of treatment sequelae. As it has been already suggested (4, 5, 8, 14), the risk of meningioma subsequent to radiation exposure increased from 15 years of follow-up onwards, and remained elevated after ≥25 years of follow-up with no signs of a decreased risk over time (**Table 3**). On the contrary, our results suggest that the radiation-related risk of glioma decreased over time, with an excess risk that would be restricted to the first years after exposure. This study reports no variation of radiation-related risks by sex, year of diagnosis, chemotherapy, or growth hormone exposures. We found a higher EOR/Gy among the oldest patients at the time of first cancer diagnosis for glioma and, on the other hand, a higher risk for meningioma among the youngest patients. Individuals who were aged 10 years or more at first cancer diagnosis in the glioma dataset (nine cases; 56% being diagnosed within the 15 first years of follow-up) were followed for a shorter time period (median = 18.1 years) than younger individuals (median = 27.0 years). This pattern was not observed in the meningioma dataset (median follow-up time: 31.9 and 30.3 years, after a first cancer diagnosis at age <10 years and age ≥10 years, respectively). The effect of age on glioma risk may thus, have been confounded by the effect of follow-up time. The observed variation in the EOR/Gy for meningioma with age at first cancer diagnosis/exposure was not reported in previous childhood or adolescent cancer (4, 5, 8, 14) or atomic bombing (15) survivorship studies.

For meningioma, we found a nonsignificantly higher EOR/Gy in patients treated for a first non-CNS tumor than in those treated for a first CNS tumor, and in patients with genetic syndrome (who were mainly CNS cancer survivors; Supplementary Table S7) compared with those without reported predisposition (**Table 3**). This finding was consistent with the apparent downward curvature in the radiation dose risk estimate at doses ≥30 Gy (**Fig. 1**). The suggestion of an increased excess risk per dose unit at lower doses was also consistent with findings of previous studies among individuals irradiated at lower doses for treatment of tinea capitis (median dose, 1.5 Gy; range, 1–6 Gy; excess relative risk per Gy, 4.63; 95% CI, 2.43–9.12; ref. 16), or for diagnostic purposes (17, 18), which reported higher excess risks per Gy than childhood or adolescent cancer survivorship studies. The apparently, but nonsignificantly, increased EOR/Gy for glioma with genetic syndrome was consistent with a decreasing radiation-related risk with longer follow-up time, while median time to diagnosis of subsequent glioma after cranial irradiation was 25.3 (n = 11) and 16.6 years (n = 15) in patients with and without reported genetic syndrome, respectively.

One previous study reported an increased risk of meningioma (33 exposed cases) with higher cumulative doses of intrathecal methotrexate (but not with nonintrathecal methotrexate exposures), after adjustment for reported genetic conditions and cumulative radiation doses (4). This finding was not confirmed in another large cohort (8) or in this study. In our study, if there was any increased risk with methotrexate, it would be rather driven by nonintrathecal exposures (Supplementary Table S4). These inconsistent findings cannot be explained by higher intrathecal doses in the United Kingdom study (ref. 4; doses ≥70 mg/m^2, 42% of exposed patients) than in this study (doses ≥70 mg/m^2, 72% of exposed patients). The timing of methotrexate administration versus radiotherapy may, however, be a key factor (19).

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Table 3. EOR/Gy for meningioma and glioma by host characteristics and time since exposure.

	Meningioma						Glioma					
	Cases, *n*	Mean radiation dose, in Gy	EOR/Gy	95% CI	*P* (1)	*P* (2)	Cases, *n*	Mean radiation dose, in Gy	EOR/Gy	95% CI	*P* (1)	*P* (2)
Overall	86	8.2	1.377	0.416–5.058	na	na	47	6.5	0.049	−0.003–0.301	na	na
Gender												
Male	38	9.9	0.678	0.125–6.038	ns	na	23	5.9	0.229	<−0.059–5.006	ns	na
Female	48	7.5	1.943	0.477–9.017			24	7.1	0.012	<−0.025–0.176		
Age at 1st cancer diagnosis, in years[a]												
0–<5	38	6.5	4.789	0.839–52.29	<0.05	<0.05	24	4.4	0.050	<−0.015–0.616	<0.05	<0.05
5–<10	33	11.3	1.256	0.268–7.537			14	7.1	−0.012	−0.018–0.058		
10+	15	6.9	0.218	0.008–1.770			9	11.7	0.721	<−0.386–22.52		
Year of 1st cancer diagnosis												
<1980	45	6.8	1.788	0.482–7.066	ns	ns	17	5.5	0.052	<−0.025–0.537	ns	ns
1980–2000	41	9.9	0.942	0.242–4.206			30	7.2	0.048	<−0.040–0.404		
Genetic syndrome reported												
No	71	7.6	1.546	0.451–5.947	ns	na	26	6.1	0.082	<−0.003–0.556	ns	na
Yes	15	17.4	0.409	<−0.164–9.161			21	9.6	0.004	<−0.032–63.59		
Type of 1st cancer												
Non-CNS	29	3.1	1.988	0.563–9.105	0.08	na	13	2.2	0.032	##−0.505	ns	na
CNS	57	25.7	0.241	<−0.044–2.401			34	19.5	0.056	##−0.430		
Type of 1st cancer (detailed)												
Medulloblastoma	37	29.5	0.307	<−0.052–3.337	0.07	na	5	25.6	−0.007	##−0.165	ns	na
Other CNS tumors	20	21.1	0.228	<−0.081–2.575			29	17.6	0.128	##−1.192		
Lymphoma	15	6.3	6.146	1.117–45.15			1	4.4	0.080	##−1.210		
Other non-CNS tumors	14	2.4	1.308	0.269–7.261			12	1.7	0.013	##−0.477		
Time since 1st cancer diagnosis, in years												
5–<15	3	17.5	0.350	<−0.053–4.141	ns	ns	18	9.5	0.453	<−0.506–8.977	ns	0.05
15–<25	13	8.3	1.100	<−0.042–7.751			12	7.8	0.015	<−0.020–0.206		
25+	70	7.9	1.808	0.503–7.604			17	4.9	0.124	<−0.072–2.909		
Attained age, in years												
0–<30	34	8.9	1.901	0.400–10.94	ns	ns	36	6.1	0.035	−0.010–0.308	ns	ns
30+	52	7.8	1.172	0.290–4.943			11	7.7	0.086	<−0.088–3.523		

Abbreviations: ##, not estimable; na, not applicable; ns, not significant ($P > 0.10$); *P* (1), $P_{heterogeneity}$; *P* (2), $P_{linear\ trend}$.
[a]This variable is considered as a proxy for first radiation exposure.

Two other studies found an increased risk of meningioma with receipt of platinum agents on the basis of few exposed cases, with no dose–response relationship (8, 10). We did not confirm this finding, but we found a modest increase of risk with higher cumulative doses of alkylating agents overall. Given the small number of cases exposed to specific chemotherapy agents in this study (and the previous ones), we cannot exclude that this finding was due to chance, confounding factors, or a lack of statistical power. The same limitation can also be conveyed regarding the significant association between epipodophyllotoxins and glioma risk, all the more as there was no dose–response relationship. The latter association, which has also been noted in the U.S. study (5), is nevertheless worth to be further explored in larger datasets.

Experimental data and follow-up of individuals with genetic growth disorders or acromegaly showed an association between growth factors and carcinogenesis, and thus, raised concerns about a possible increased SPN risk among brain cancer survivors treated with growth hormone (20). Investigating this question requires accumulation of data from large populations, with a high rate of completeness, a long duration of follow-up, and detailed information on cranial radiation exposure, which can induce growth hormone deficiency and thus, be an important confounding factor (21). Very few studies have evaluated the effect of growth hormone therapy while accounting for radiation doses (21). Our study is the largest published one so far, and does not find any increased risk of meningioma on the basis of 35 exposed cases. This finding is consistent with the results of a recent large study on CNS tumors among individuals treated with growth hormone during childhood for cancer or other reasons without radiotherapy (22, 23), but follow-up of these populations should be continued.

This multicenter study benefited from detailed therapeutic data and a long duration of follow-up, and is one of the very few large studies considering radiation doses to the SPN/matched location. There were, nevertheless, several limitations. First, there was no data on radiation dose fractionation and volume, which may explain why the risk of meningioma was highest at doses of 20–40 Gy, because this dose range corresponds to craniospinal or whole-brain irradiation for medulloblastoma or non-Hodgkin lymphoma (64% and 12% of cases in this dose range, respectively). Nonetheless, we found similar EORs per Gy among individuals with medulloblastoma (craniospinal irradiation) or other CNS tumor (mostly focal irradiation) as first cancer (**Table 3**). At the lowest dose ranges, there were also too few cases to detect low increased risks. Second, we acknowledge the presence of uncertainties in the retrospective dosimetry of past treatment plans, especially due to anatomic approximations by mathematical phantoms (24). Third,

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because genetic predispositions for CNS cancers were routinely tested only when they were suspected because of a specific clinical presentation and/or family cancer history, this information was probably incomplete, which may have led to residual confounding in the reported associations. Fourth, we cannot exclude differential detection rates of SPN between asymptomatic individuals with a first CNS or non-CNS tumor, and those with or without cranial irradiation. However, the impact of such a possible surveillance bias was mitigated by the use of multiple sources of information and adjustment for first tumor type. Finally, the reported associations with chemotherapy agents were based on few exposed cases, and even though we did not find obvious underlying clinical or therapeutic factors, they should be interpreted with much caution.

In conclusion, this study shows that a prolonged surveillance beyond 30 years after treatment should involve all patients with cranial irradiation. The possibility of a role of some chemotherapy agents in the long-term risk of CNS SPN should be further investigated in very large datasets, probably through international collaborations because all studies conducted so far have involved too few cases for providing robust analyses. Such collaborative studies could also provide insights in the risk factors of specific tumor subtypes.

Disclosure of Potential Conflicts of Interest

C. Thomas-Teinturier reports personal fees from Novo Nordisk (expertise, advisory board), Merck Serono (advisory board), and Ipsen (lectures) and grants from Novo Nordisk (for attending meetings) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

N.M.Y. Journy: Conceptualization, formal analysis, investigation, methodology, writing–original draft. **W.S. Zrafi:** Formal analysis, investigation, methodology, writing–review and editing. **S. Bolle:** Resources, investigation, writing–review and editing. **B. Fresneau:** Resources, investigation, writing–review and editing. **C. Alapetite:** Resources, investigation, writing–review and editing. **R.S. Allodji:** Investigation, methodology, writing–review and editing. **D. Berchery:** Resources, investigation, writing–review and editing. **N. Haddy:** Investigation, methodology, writing–review and editing. **I. Kobayashi:** Resources, writing–review and editing. **M. Labbé:** Resources, writing–review and editing. **H. Pacquement:** Resources, investigation, writing–review and editing. **C. Pluchart:** Resources, investigation, writing–review and editing. **B. Schwartz:** Investigation, methodology, writing–review and editing. **V. Souchard:** Resources, methodology, writing–review and editing. **C. Thomas-Teinturier:** Investigation, methodology, writing–review and editing. **C. Veres:** Resources, investigation, writing–review and editing. **G. Vu-Bezin:** Resources, investigation, writing–review and editing. **I. Diallo:** Resources, methodology, writing–review and editing. **F. de Vathaire:** Supervision, funding acquisition, investigation, methodology, writing–review and editing.

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Risk Factors of Subsequent Central Nervous System Tumors after Childhood and Adolescent Cancers: Findings from the French Childhood Cancer Survivor Study

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