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Risk of second malignant neoplasms after childhood central nervous system malignant tumours: An international study

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ABSTRACT

Purpose: The aim of this study was to assess the risk of second malignant neoplasms (SMNs) other than central nervous system (CNS) neoplasms after childhood CNS cancer in an international multicentre study.
Methods: Individual data on cases of CNS cancer in children (0–14 years) and on subsequent SMNs were obtained from 13 population-based cancer registries contributing data for different time periods in 1943–2000. Standardised incidence ratios (SIRs) with 95% confidence intervals (CI), absolute excess risk and cumulative incidence of SMNs were computed.
Results: We observed 43 SMNs in 8431 CNS cancer survivors. The SIR was 10.6 (4.85–20.1) for thyroid cancer (nine cases), 2.75 (1.01–5.99) for leukaemia (six cases) and 2.47 (0.90–5.37) for lymphoma (six cases). The SIRs were highest in the first 10 years after CNS cancer diagnosis.

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The cumulative incidence of non-CNS SMNs was 3.30% (0.95–5.65%) within 45 years after a CNS cancer diagnosis. Within 15 years, the cumulative incidence was highest for cases diagnosed after 1980 (0.56%, 95% CI: 0.29–0.82%).
Conclusion: This population-based study indicates that about one every 180 survivors of a childhood CNS cancer will develop a non-CNS SMN within the following 15 years. The excess is higher after glioma and embryonal malignant tumour than after another CNS tumour.

1. Introduction

Brain cancers are the second most common malignancy in children after leukaemia, accounting for over 20% of all childhood tumours and representing the commonest cause of cancer-related death in children.[1] Recent European estimates report incidence rates of central nervous system (CNS) tumours of 30 per million child-years (standardised on the world standard population) in 1988–1997, with a statistically significant annual increase of 1.7% in the period 1978–1997.[2] In the United States (US), the CNS tumour incidence rate was 37 per million child-years (standardised on the 2000 US standard population) in 2001–2004, with a statistically significant annual increase of 1.1% in the period 1975–2004.[3]

In Europe, the 5-year survival rate has improved from about 40% in the 1970s to 64% in the 1990s,[2,4] and in the US it reached 71%, ranging from 84% for astrocytomas to 47% for gliomas (other than ependymomas and astrocytomas) in 1996–2003.[3] Such an improvement in survival rates is the result of considerable advances in neuroimaging, neurosurgery, radiotherapy and chemotherapy. However, childhood brain cancers are a very heterogeneous group composed of many histological subtypes arising in different regions of the CNS and with different prognoses, and a global quantification of therapeutic progress is difficult to define. For example, children with non-disseminated medulloblastoma have 5-year survival rates ranging from 85% to 65%, whereas survival rates for children with diffuse intrinsic brain stem glioma do not reach 10%.[5,6] Real improvements should be claimed only if concomitant improvement in the quality of life of survivors is achieved.[6] Delayed consequences of therapy, including neuropsychological impairment, endocrine dysfunction, growth retardation and risk of second cancer, may have a significant impact on the life of childhood CNS cancer survivors.

The occurrence of a second malignant neoplasm (SMN) is one of the most serious late effects of childhood CNS cancer treatment. Amongst SMNs affecting childhood CNS cancer survivors, malignant tumours of the CNS are the most frequent, and their incidence has been estimated with considerable precision in several studies.[7–11] On the other hand, information on the risk of SMNs in organs other than the CNS after a childhood CNS cancer is more limited.[8,12] To evaluate with adequate precision the relative and absolute risk of other SMNs, we took advantage of a unique source of data consisting in a large cohort of survivors of childhood CNS cancer built from 13 population-based registries located in Europe, America, Asia and Oceania.

2. Materials and methods

This study is part of an international multicentre study of SMNs that includes data from 13 population-based cancer registries (New South Wales (Australia), British Columbia, Manitoba and Saskatchewan (Canada), Denmark, Finland, Iceland, Norway, Singapore, Slovenia, Zaragoza (Spain), Sweden and Scotland (UK)) that have been in operation for at least 25 years and that were able to provide high quality data. There are no relevant differences in how individual registries collect their data: all the registries have contributed data to the series Cancer Incidence in Five Continents[13] and have similar and high proportion of completeness. The population covered by these cancer registries was approximately 47 million in the 1990s. The registries contributed data for different time periods in the years 1943–2000, with a median observation period of 32 years. This dataset partially overlaps with that used in a previous study[14] in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) that analysed SMNs after benign and malignant CNS tumours in childhood and adolescence diagnosed in the period 1943–1987.

Each cancer registry provided data on CNS primary cancers occurring in children aged 0–14 years, including age and sex of the subject, diagnosis and date of the first primary, follow-up for vital status, and date and diagnosis of the SMN, if any. Follow-up started at CNS cancer diagnosis and ended at the date of SMN diagnosis, date of migration out of the study area, date of loss to follow-up, death or general closing date (whatever was first). All children who survived at least 1 day after their CNS cancer diagnosis entered the survivors' cohort. Registries used different cancer codes that were systematically converted by the International Agency for Research on Cancer (IARC) to International Classification of Diseases, 9th Revision (ICD-9).[15] We analysed the occurrence of SMNs (other than SMNs of the central CNS) after CNS malignant tumours (ICD-9: 191–192), by specific histologic subtypes (gliomas (International Classification of Diseases for Oncology (ICD-O):[16] 9380–9384, 9391–9460, 9480, 9481), embryonal malignant tumours (ICD-O: 9470–9473, 9490, 9500–9504), and all other CNS malignant tumours). SMNs of the CNS have not been included in the analysis because exhaustive data on the occurrence of independent second primaries of the CNS were not available. The database included all SMNs (but those of the CNS), irrespective of the time elapsed from the first neoplasm. Coding of multiple primaries followed a common set of rules proposed by the International Associa-

tion of Cancer Registries and the IARC.[17] According to these rules, a new primary cancer is one that originates in a new primary site or tissue and is thus not an extension, a recurrence, or a metastasis. Subsequent cancers occurring after a SMN in the same patient were not analysed. In situ cancers were not considered to be second primaries.

All data were provided in an anonymous fashion with respect to patient identities. Approval for the study was obtained from the ethics committee of IARC. Informed consent was not required because the study was based on anonymised registry records.

Table 1 – Distribution of children with central nervous system malignant tumour according to their second malignant neoplasm status, by selected characteristics

Characteristics	First malignant neoplasm	Developed a second malignant neoplasm
Central nervous system malignant tumour (ICD 9th revision: 191–192)		
Sex		
Female	3859	25
Male	4572	18
Age at first neoplasm registration		
<1	403	1
1–4	2778	14
5–9	2888	11
10–14	2362	17
Calendar period at first neoplasm diagnosis		
Before 1970	1378	12
1970–1979	2002	12
1980–1989	2614	13
1990 or later	2437	6
Duration of follow-up (years)		
<1	2306	3
1–4	2107	9
5–9	1229	10
10–14	906	2
15–19	681	4
20–24	458	7
25–29	308	2
30–34	237	3
35–39	113	2
40+	86	1
Histologic type		
Glioma	4996	26
Embryonal malignant tumours	2346	11
Others	1089	6
Registry (observation period)		
Australia, New South Wales (1972–1997)	859	2
Canada, British Columbia (1970–1998)	517	3
Canada, Manitoba (1970–1998)	190	3
Canada, Saskatchewan (1967–1998)	174	0
Denmark (1943–1997)	771	8
Finland (1953–1998)	1568	11
Iceland (1955–2000)	79	1
Norway (1953–1999)	1295	8
Singapore (1968–1992)	181	0
Slovenia (1961–1998)	331	0
Spain, Zaragoza (1978–1998)	69	0
Sweden (1961–1998)	1823	7
UK, Scotland (1975–1996)	574	0
Total	8431	43

3. Statistical analysis

Standardised incidence ratios (SIRs) and corresponding 95% confidence intervals (CI) of SMNs were calculated as the ratio of the observed number of SMNs to the expected number, which was obtained by applying the age-, sex-, year- and registry-specific incidence rates of first primary cancers to the population of survivors of childhood CNS cancer.[18] SIRs were calculated for all types of SMNs by length of follow-up, age at

Table 2 – Standardised incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) and absolute excess risk per 100,000 person–years of selected second malignant neoplasms after childhood central nervous system malignant tumour, by second malignant neoplasm site

Neoplasm sites (ICD 9th revision)[a]	*n*	SIR	95% CI	AER[b]
Person-years at risk	72,514			
All malignant (other than central nervous system malignant neoplasm) (140–208)	43	2.3	(1.6–3.0)	33
Oral cavity, pharynx (140–149)	1	2.4	(0.1–13)	0.8
Salivary gland (142)	1	9.9	(0.3–55)	1.2
Colorectal (153,154)	3	3.6	(0.7–10)	3.0
Colon (153)	3	5.0	(1.0–15)	3.3
Liver, gallbladder, bile ducts (155–156) (excl. 155.2)	1	6.6	(0.2–37)	1.2
Liver (155) (excl. 155.2)	1	8.4	(0.2–47)	1.2
Soft tissue sarcoma (171)	4	7.7	(2.1–20)	4.8
Melanoma of skin (172)	2	1.0	(0.1–3.6)	0.0
Other neoplasm of skin (173)	2	2.7	(0.3–9.9)	1.8
Female breast (174)	3	1.3	(0.3-3.7)	0.9
Ovary (183)	1	1.4	(0.0–7.7)	0.4
Other male genital than testis (187)	1	36	(0.9-200)	1.3
Eye (190)	1	6.2	(0.2–35)	1.2
Thyroid gland (193)	9	11	(4.9–20)	11
Other endocrine gland (194, 164)	2	13	(1.6–48)	2.6
Lymphohaematopoietic (200–208)	12	2.6	(1.3–4.5)	10
Lymphomas (200–202)	6	2.5	(0.9–5.4)	4.9
Hodgkin lymphoma (201)	1	0.8	(0.0–4.4)	–0.4
Non-Hodgkin lymphoma (200, 202)	5	4.3	(1.4–10)	5.3
Leukaemias (204–208)	6	2.8	(1.0–6.0)	5.3
Lymphoid leukaemia (204)	2	2.2	(0.3–8.0)	1.5
Myeloid leukaemia (205)	1	2.2	(0.1–13)	0.8
Other leukaemia (206–208)	3	3.6	(0.7–11)	3.0
Other malignant than defined	1	3.5	(0.1–20)	1.0

a Second malignant neoplasms with at least 1 observed case.
b Per 100,000 person–years.

first cancer diagnosis and calendar period of first cancer registration. The incidence period of the first CNS neoplasm was divided into three intervals (before 1970, 1970–1979, and after 1980), chosen according to the time of occurrence of relevant changes in therapies, namely the introduction (in the period 1970–1979) of chemotherapy for the treatment of ependymomas (amongst gliomas) and medulloblastoma (amongst embryonal tumours) and its regular, widespread use from 1980 onwards.[6] A Poisson regression analysis[19] including periods of CNS cancer diagnosis and follow-up time as covariates was carried out to test how SIRs vary in subsequent calendar periods.

The absolute excess risk (AER) was calculated as the difference between observed SMNs and expected number of cases of each cancer type divided by the total number of person–years at risk.

Cumulative incidence of SMNs in the survivors' cohort was calculated taking into account death from any cause as a

Table 3 – Standardised incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) of selected second malignant neoplasms after childhood central nervous system malignant tumour subtypes (gliomas, embryonal tumours, others), by second malignant neoplasm site

Neoplasm sites (ICD 9th revision)[a]	*n*	SIR	95% CI	AER[b]
Gliomas (ICD-0: 9380–9384, 9391–9460, 9480, 9481)				
Person–years at risk: 47,056				
All malignant (other than central nervous system malignant neoplasm) (140–208)	26	2.2	(1.4–3.2)	30
Oral cavity, pharynx (140–149)	1	3.9	(0.1–22)	1.6
Salivary gland (142)	1	15	(0.4–83)	2.0
Colorectal (153,154)	3	5.8	(1.2–17)	5.3
Colon (153)	3	8.0	(1.7–24)	5.6
Soft tissue sarcoma (171)	4	12	(3.2–30)	7.8
Melanoma of skin (172)	1	0.8	(0.0–4.2)	–0.7
Female breast (174)	2	1.4	(0.2–5.2)	1.3
Ovary (183)	1	2.2	(0.1–12)	1.1
Eye (190)	1	11	(0.3–62)	1.9
Thyroid gland (193)	4	6.8	(1.9–18)	7.2
Other endocrine gland (194, 164)	1	10	(0.3–57)	1.9
Lymphohematopoietic (200–208)	8	2.7	(1.2–5.3)	11
Lymphomas (200–202)	6	3.8	(1.4–8.2)	9.4
Hodgkin lymphoma (201)	1	1.2	(0.0–6.5)	0.3
Non-Hodgkin lymphoma (200, 202)	5	6.7	(2.2–16)	9.1
Leukaemias (204–208)	2	1.5	(0.2–5.4)	1.4
Myeloid leukaemia (205)	1	3.5	(0.1–20)	1.5
Other leukaemia (206–208)	1	2.0	(0.1–11)	1.1
Embryonal tumors (ICD-0: 9470-9473, 9490, 9500-9504)				
Person–years at risk: 15,600				
All malignant (other than central nervous system malignant neoplasm) (140–208)	11	3.9	(1.9–7.0)	52
Melanoma of skin (172)	1	3.8	(0.1–21)	4.7
Other neoplasm of skin (173)	1	20	(0.5–111)	6.1
Thyroid gland (193)	4	30	(8.2–77)	25
Other endocrine gland (194, 164)	1	30	(0.8–169)	6.2
Lymphohaematopoietic (200–208)	3	3.0	(0.6–8.9)	13
Leukaemias (204–208)	3	5.5	(1.1–16)	16
Lymphoid leukaemia (204)	1	4.3	(0.1–24)	4.9
Other leukaemia (206–208)	2	8.4	(1.0–30)	11
Other malignant than defined	1	28	(0.7–154)	6.2
Others				
Person–years at risk: 9858				
All malignant (other than central nervous system malignant neoplasm) (140–208)	6	1.4	(0.5–2.9)	16
Liver, gallbladder, bile ducts (155–156) (excl. 155.2)	1	29	(0.7–161)	9.8
Liver (155) (excl. 155.2)	1	40	(1.0–222)	9.8
Other neoplasm of skin (173)	1	2.8	(0.1–16)	6.5
Female breast (174)	1	1.3	(0.0–7.4)	2.5
Other male genital than testis (187)	1	153	(3.8–854)	10
Thyroid gland (193)	1	7.7	(0.2–43)	8.8
Lymphohaematopoietic (200–208)	1	1.4	(0.0–7.9)	2.9
Leukaemias (204–208)	1	3.5	(0.1–19)	7.2
Lymphoid leukaemia (204)	1	9.7	(0.2–54)	9.1

a Second malignant neoplasms with at least 1 observed case.
b Per 100,000 person–years.

competing risk event.[20] Expected cumulative incidence was calculated using the life-table method[21] without considering competing risks: in the general population, mortality was negligible in the age range included in our analysis: 0–14 years at diagnosis plus an average follow-up time of 8.6 years. The standardised death rate for all causes reported in the European mortality database of the World Health Organization for people aged 1–19 in 2004 was 21.6 per 100,000.[22] All statistical tests were two-sided. The Breslow–Day test was used to assess SIRs heterogeneity between registries and time trends.[19]

4. Results

A total of 8431 survivors of CNS cancer contributing 72,514 person–years of observation were identified. During follow-up, 43 non-CNS SMNs were registered. The median age at the occurrence of a SMN was 20 years, and the median interval between CNS cancer and SMN was 8.8 years. The distribution of first primary CNS cancers according to selected characteristics and the corresponding number of SMNs is shown in Table 1.

Table 2 reports the number of observed SMNs, and the corresponding SIRs and AERs (per 100,000 person–years) for neoplasms with at least one observed case. The overall SIR for having a non-CNS SMN was 2.25 (95% CI: 1.63–3.04). Increased SIRs were found for thyroid, other endocrine glands and colon cancer, soft tissue sarcoma, leukaemia and non-Hodgkin lymphoma. Table 3 shows SMNs and corresponding SIRs and AERs (per 100,000 person–years) by subtype of CNS cancer. The most frequent SMNs observed were non-Hodgkin lymphoma, soft tissue sarcoma and thyroid cancer after a glioma, and thyroid cancer and leukaemia after embryonal cancer.

Significant increasing time trends for non-CNS SMNs after all CNS cancers together ($p = 0.018$) and after 'other CNS cancers' ($p = 0.007$) were found using the Poisson multivariate analysis. There was no effect of calendar period of diagnosis in the relative risks of lymphohaematopoietic malignancies after all CNS cancers ($p = 0.190$) and of non-CNS SMNs after glioma ($p = 0.275$) and embryonal tumours ($p = 0.458$). After adjusting for the length of follow-up, the relative risks for non-CNS SMNs were 2.37 (95% CI: 0.94–6.01) for CNS cancer cases diagnosed in 1970–1979 with respect to those diagnosed before 1970, and 3.85 (95% CI: 1.20–12.3) for those diagnosed after 1980.

Children diagnosed with CNS cancers in all age groups were at increased risk of SMNs (age less than one year: one case, SIR = 1.37 (95% CI: 0.03–7.64); age 1–4: 14 cases, SIR = 3.73 (95% CI: 2.04–6.25); age 5–9: 11 cases, SIR = 2.00 (95% CI: 1.00–3.59); age 10–14: 17 cases, SIR = 1.87 (95% CI: 1.09–2.99)).

Table 4 shows the SIRs of SMNs with at least four observed cases by the time elapsed since CNS cancer diagnosis. The SIR for non-CNS SMNs was highest in the first 10 years after the CNS cancer diagnosis. Most thyroid cancers (66.7%) occurred between 5 and 24 years, all leukaemias and non-Hodgkin lymphomas within 9 years from CNS cancer.

Cumulative incidence of non-CNS SMNs after childhood CNS cancer by calendar periods of diagnosis are shown in Fig. 1. The overall cancer risk in the survivors' cohort was

Table 4 – Standardised incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) of the most frequent (at least four observed cases) second malignant neoplasms after childhood central nervous system malignant tumour, by length of follow-up after the first cancer diagnosis

	Years since central nervous system malignant tumor diagnosis																	
	Less than 1 year			1–4 years			5–9 years			10–14 years			15–19 years			20+ years		
Person–years at risk:	7108			19,128			16,811			11,551			7735			10,181		
Neoplasm sites (ICD 9th revision):	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI
All malignant (other than central nervous system malignant neoplasm) (140–208)	3	4.0	(0.8–12)	9	4.8	(2.2–9.1)	10	5.1	(2.4–9.3)	2	0.9	(0.1–3.2)	4	1.6	(0.4–4.1)	15	1.6	(0.9–2.6)
Soft tissue sarcoma (171)	0	0.0	(0.0–90)	0	0.0	(0.0–37)	2	20	(2.4–73)	0	0.0	(0.0–43)	0	0.0	(0.0–54)	2	17	(2.0–60)
Thyroid gland (193)	1	141	(3.5–785)	1	24	(0.6–136)	2	21	(2.6–77)	0	0.0	(0.0–25)	2	12	(1.4–43)	3	7.6	(1.6–22)
Lymphohaematopoietic (200–208)	1	2.3	(0.1–13)	7	6.3	(2.5–13)	3	3.4	(0.7–10)	1	1.4	(0.0–7.9)	0	0.0	(0.0–7.0)	0	0.0	(0.0–3.6)
Lymphomas (200–202)	1	10	(0.3–57)	2	5.8	(0.7–21)	2	4.4	(0.5–16)	1[a]	2.2	(0.1–12)	0	0.0	(0.0–9.8)	0	0.0	(0.0–5.3)
Non-Hodgkin lymphoma (200, 202)	1	15	(0.4–82)	2	10	(1.2–36)	2	11	(1.3–39)	0	0.0	(0.0–24)	0	0.0	(0.0–28)	0	0.0	(0.0–8.7)
Leukaemias (204–208)	0	0.0	(0.0–11)	5[b]	6.6	(2.1–15)	1[c]	2.4	(0.1–13)	0	0.0	(0.0–15)	0	0.0	(0.0–25)	0	0.0	(0.0–14)

a Hodgkin lymphoma.
b Two lymphoid leukaemias and 3 other leukaemias.
c Myeloid leukaemia.

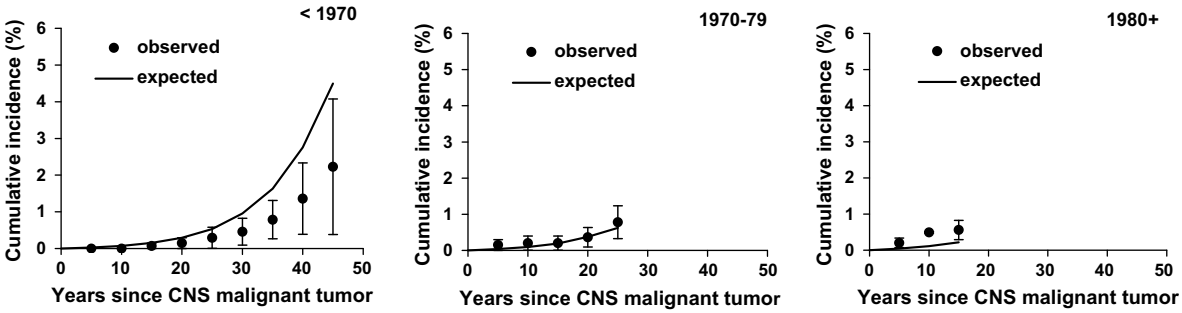

Fig. 1 – Cumulative incidence (%) of second malignant neoplasms (other than central nervous system tumours) after childhood central nervous system malignant tumour stratified by calendar periods of first cancer diagnosis (before 1970, 1970–1979, after 1980). Expected cumulative incidence is based on that of the general population. Bars represent 95% confidence intervals.

3.30% (95% CI: 0.95–5.65%) within 45 years after the CNS cancer diagnosis, not significantly different from the expected risk in the general population. The relative difference between the cumulative incidence of non-CNS SMNs amongst CNS cancer survivors and the normal population in the first 15 years of follow-up increased with calendar period of CNS cancer diagnosis. The risk was lower than that expected for CNS cancer cases diagnosed before 1970, similar to that expected for those diagnosed in 1970–1979, and higher than that expected for those diagnosed after 1980. Within 15 years after CNS cancer, the cumulative incidence was 0.56% (95% CI: 0.29–0.82%) for cases diagnosed after 1980, 2.5 times higher than expected.

5. Discussion

Our study focussed on non-CNS SMNs after a childhood CNS cancer. We found that survivors of childhood CNS cancer had an elevated risk of developing a non-CNS SMN, which increased with the calendar period of CNS cancer diagnosis. The relative risk was significantly higher after both glioma and embryonal malignant tumours. The cumulative incidence within 15 years after CNS cancer for survivors' diagnosed after 1980 was more than twice the one expected in the general population.

Radiotherapy, chemotherapy, genetic/host predisposition to developing multiple cancers, and their interactions have been shown to increase the risk of SMNs after CNS cancer.[23,24]

Individual treatment information was not available from the registries contributing data to our study and hence no causal inference on the effects of therapies can be drawn. Nevertheless, knowledge of temporal changes in treatment practice in paediatric oncology may help the interpretation of our results, if it is assumed that inter-country variations in treatment procedures were small amongst the high-income countries of the 13 cancer registries included in our analysis. Similar trends in survival after childhood cancer in European countries and the United States confirm a general uniformity of procedures and treatments.[25,26] A short revision of the risk associated to treatments is given below.

Surgery is the main therapeutic option for children with brain tumours. Radical resection is possible in only about 50% of cases with superficial CNS tumours and 8% of those with deeper tumours.[27] Surgery is not related to the risk of SMNs.

Radiotherapy is effective in the treatment of several paediatric CNS tumours, although it has been associated with late consequences affecting the quality of life: neurocognitive dysfunction, hormonal deficiencies and SMNs. Hawkins and colleagues[28] found that SMN risk after childhood CNS tumour was not different from that expected in the absence of radiotherapy, but observed almost 9-fold the number of the expected SMNs amongst cases who received radiotherapy. Similar differences were observed by Inskip and Curtis[12] and by Devarahally and colleagues.[7] In the last few years, several refinements in the radiotherapy techniques allowed for the delivery of high and uniform doses of radiation to a small volume of tissue, thus minimising the doses received by the normal brain tissue.[1] Radiotherapy is commonly used to treat medulloblastoma, with increasing attention being directed to reducing both the dose and the irradiation volume, and ependymomas, where it has proved to be very effective.[6] Radiotherapy is known to induce solid tumours at various sites including brain and thyroid.[23,29] In our study, we observed nine thyroid SMNs, seven of which occurred at least five years after the first diagnosis of childhood brain cancer. Eight thyroid SMNs occurred in patients who were diagnosed with childhood CNS cancer before 1989, when radiation doses were higher and the techniques used did not allow uniform delivery to precisely defined tissue volumes, most likely affecting the thyroid gland also.[30] Four occurred after a glioma, four after embryonal tumours and one after other CNS cancers. They are, therefore, compatible with a delayed effect of radiotherapy.[31] In a recent study, Neglia and colleagues[11] found a SIR of 14.2 (95% CI: 6.51–26.5) for secondary glioma based on eight cases of CNS childhood cancer. Inskip and Curtis[12] estimated a SIR of 12.6 (95% CI: 5.4–25) for CNS SMNs after astrocytoma (eight cases), and of 44.6 (95% CI:19–88) for CNS SMNs after primitive neuroectodermal tumour (eight cases). Other relevant findings on CNS SMNs are summarised in Table 5. In our study, the risk of CNS SMNs could not be estimated because complete data on their occurrence were not available.

Chemotherapy has been successfully introduced into the therapeutic strategy after primary surgery, often in combination with radiotherapy, and has proven to reduce tumour size

Table 5 – Summary of results of studies on second malignant neoplasms (SMNs) after central nervous system (CNS) malignant tumour (SIR: standardised incidence ratio, n: observed number of cases, PNET: primitive neuroectodermal tumour)

Reference	Area	Period of first diagnosis	Age at first diagnosis (years)	Minimum survival after first diagnosis	Cohort size	Number of first malignant CNS tumours	All malignant SMNs after CNS tumours	CNS SMNs after all malignant tumours	CNS SMNs after CNS tumours
Inskip and Curtis[12]	US (SEER)	1973–2002	0–17	2 months	25,965	4806	*n* = 69, SIR = 6.3 (4.9–8.0)	*n* = 51, SIR = 7.9 (5.9–10)	After astrocytoma: *n* = 8, SIR = 13 (5.4–25) After PNET: *n* = 8, SIR = 45 (19–88)
MacArthur et al.[36]	Canada (BC)	1970–1995	0–19	5 years	2322	438	*n* = 9, SIR = 5.1 (2.7–9.6)	–	*n* = 3
Cardous-Ubbink[37]	The Netherlands	1966–1996	0–18	5 years	1368	109	*n* = 7, SIR = 17 (7.0–36)[a]	*n* = 13, SIR = 40 (21–69)[b]	–
Peterson et al.[31]	US (SEER)	1973–1998	0–19	5 years	2056	2056	*n* = 39	–	After astrocytoma: *n* = 3 After PNET: *n* = 2 After other glioma: *n* = 5 After other CNS tumour: *n* = 2
Neglia et al.[11]	US-Canada (CCSS cohort)	1970–1986	0–20	5 years	14,361	–	–	Glioma: *n* = 40, SIR = 8.7 (6.2–12)	Glioma: *n* = 8, SIR = 14 (6.5–27)
Bassal et al.[38]	US-Canada (CCSS cohort)	1970–1986	0–20	5 years	13,136	1876	*n* = 4, SIR = 2.1 (0.8–5.7)[c]	–	–
Hammal et al.[39]	North of England	1968–1999	0–24	6 months	4072	745	*n* = 14, SIR = 6.1 (3.3–10)	*n* = 9	*n* = 6
Jazbec et al.[40]	Slovenia	1961–2000	0–15	None	1577	336	*n* = 11	*n* = 16, SIR = 9.7 (2–28)	*n* = 8
Jenkinson et al.[41]	Great Britain	1962–1987	0–14	3 years	16,541	4009	*n* = 55, SIR = 4.7 (3.6–6.2)	*n* = 44, SIR = 12 (9.0–17)	–
Klein et al.[42]	Germany, Switzerland, Austria, The Netherlands	1980–1998	0–24	None	24,203	–	*n* = 29	*n* = 53	*n* = 10
Inskip[9]	US (SEER)	1973–1998	All ages	2 months	28,558	28,558	*n* = 419, SIR = 1.1 (1.0–1.2) *n* = 46, SIR = 7.2 (5.3–9.6)[d]	*n* = 1391, SIR = 1.0 (0.9–1.0)	*n* = 36, SIR = 5.9 (4.1–8.2) *n* = 16, SIR = 22 (13–36)[d]

Devarahally et al.[7]	US (SEER)	1973–1998	0–19	–	4553	4553	$n = 46$, SIR = 5.1 (3.7–6.8)	–	$n = 17$
Neglia et al.[43]	US-Canada (CCSS cohort)	1970–1986	0–20	5 years	13,581	1779	$n = 24$, SIR = 4.4 (2.9–6.6)	$n = 36$, SIR = 9.9 (6.9–14)	$n = 6$, RR = 0.9 (0.3–2.4)[e]
Garwicz et al.[44]	Nordic countries	1960–1987	0–19	None	25,120	–	$n = 47$	$n = 48$	$n = 26$
Westermeier et al.[45]	Germany	1980–1995	0–14	None	20,338	12,046	$n = 26$, SIR = 18 (12–27)	$n = 35$, SIR = 18 (13–26)	$n = 12$
Goldstein et al.[8]	US (SEER), Sweden	1935–1992	All ages	None	1262	1262[e]	$n = 20$, SIR = 5.4 (3.3–8.4)[f]	–	$n = 5$, SIR = 22 (7.0–51)[f]
Olsen et al.[14]	Nordic countries	1943–1987	0–19	None	30,880	6580	$n = 50$, SIR = 3.0 (2.2–3.9)	$n = 56$, SIR = 6.7 (5.0–8.7)	$n = 27$, SIR = 13 (8.7–19)
Hawkins et al.[28]	Great Britain	1940–1979	0–14	3 years	10,106	2343	$n = 17$, SIR = 5.0 (2.9–8.1)	$n = 12$, SIR = 7.0 (3.6–12)	$n = 1$, SIR = 2.4 (0.1–14)

a Includes 3 second benign meningiomas.
b Includes 12 second benign meningiomas.
c Only second carcinomas.
d Age <17 years.
e RR: relative risk, estimated through a Poisson multiple regression model, reference category: leukaemia.
f Only first diagnosis of medulloblastomas.

and vascularity. Medulloblastoma protocols generally include chemotherapy (e.g. cisplatinum, cyclophosphamide) together with or after radiotherapy. The role of chemotherapy for ependymomas is still uncertain, but there is evidence that, in combination with radiotherapy, it might improve survival for infants and for children with subtotal resections.[6] Treatment for childhood CNS cancers was mainly based on surgery or surgery with adjuvant radiotherapy until 1970. Chemotherapy was first trialled with at the beginning of the 1970s, introduced in the following decade, and became an established procedure for the treatment of ependymomas and medulloblastomas from 1980 onwards. We therefore divided the observation time into three calendar periods of CNS malignant tumour diagnosis (<1970, 1970–1979, 1980+), expecting to observe radiation-related cancers throughout the whole observation period but chemotherapy-induced cancers only in the most recent one. The multivariate analysis evidenced an increasing trend in the risk for non-CNS SMNs after all CNS cancers ($p = 0.018$), with a relative risk nearly four times higher for children diagnosed after 1980 with respect to those diagnosed before 1970. This result is consistent with the recent findings from the surveillance, epidemiology and end results program.[31] Peterson and colleagues[31] show that, compared to patients treated before 1979, those treated in the periods 1979–1984 and 1985–1998 had statistically significant 4.7-fold and 6.7-fold increased risks of developing any SMN, respectively. Results, however, were not shown separately for CNS and non-CNS SMNs.

Secondary acute myeloid leukaemia is the most frequent SMN after chemotherapy.[23] In our study, there was no increasing trend in the risk for lymphohaematopoietic diseases after all CNS cancers ($p = 0.190$). We observed one myeloid leukaemia 5–9 years after glioma, and three other leukaemias 1–4 years after CNS cancers diagnosed after 1980, when the treatment plans for ependymoma and medulloblastoma commonly included alkylating agents. However, the observed behaviour of leukaemia relative risk, with a peak after 1–4 years since the first neoplasm diagnosis and no observed cases after 9 years, is also compatible with the effects of radiation.[32]

Late effects of therapy may have been more evident if a finer breakdown of brain cancer subtypes were available for separate analysis. For example, in the treatment of gliomas, radiotherapy and chemotherapy are not routinely used to treat low grade astrocytomas, which are usually surgically removed and have more benign behaviour, but are largely employed for ependymomas, astrocytomas located in non-surgical sites, and other glioma subtypes.[27]

A small fraction of the SMNs arising after a childhood CNS cancer may be attributed to genetic predisposition syndromes. It has been estimated that in Britain the hereditary fractions for childhood brain and spinal cord is 2.0%,[33] and the proportion of childhood CNS cancer cases with congenital anomalies is 3.1%.[34] Neurofibromatosis type 1 (NF1) is associated with optic gliomas, malignant peripheral nerve sheath tumours, sarcomas and acute non-lymphoid leukaemia,[35] in particular myeloid leukaemia; Turcot syndrome[27] is characterised by the association between brain tumours with colon cancer; and Gorlin and Goltz (nevus basal cell carcinoma) syndrome[27] is found in approximately 10% of children diag-

nosed with medulloblastoma at age 2 years or younger. Such genetic predisposition syndromes could have played a role in the development of the observed soft tissue sarcomas, acute myeloid leukaemia, colon cancers and skin neoplasms. However, since in our study individual information on these conditions was not available, this could not be investigated.

This study allowed an up-to-date estimation of cumulative incidence of non-CNS SMNs after CNS cancers in children. The cumulative risk within 15 years from the diagnosis was higher than the expected only for patients diagnosed with CNS cancer after 1980. This result is compatible with recent findings showing that the largest risk factor for SMN development was the treatment era of the primary CNS cancer.[31] The observed cumulative incidence, calculated taking into account death as a competing risk, may appear surprisingly low, especially for subjects who received their first cancer diagnosis in the older calendar periods. This is due to the high mortality associated to CNS cancer, especially for patients diagnosed before 1970.

The major strengths of this population-based study are the size of this cohort, formed by pooling together 13 well-established cancer registries with uniform criteria for the definition of SMNs, and the length of follow-up, which have provided a valuable opportunity to evaluate both the relative and the absolute risk of SMNs for long-term CNS cancer survivors.

Childhood brain tumours still represent a therapeutic challenge. The survival rates of some of the malignant varieties are still very poor, whilst those of others have improved dramatically over the last decades. The investigation of large and population-based databases contributes to the accurate evaluation of the risk associated to different therapies. It is therefore an essential complement to studies focussing on the molecular genetics and biology of brain tumours and the development of more effective therapeutic modalities, free from late consequences affecting the quality of life of survivors.

Conflict of interest statement

None declared.

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