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ORIGINAL REPORT

Population-Based Risks of CNS Tumors in Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study

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ABSTRACT

Purpose
CNS tumors are the most common second primary neoplasm (SPN) observed after childhood cancer in Britain, but the relationship of risk to doses of previous radiotherapy and chemotherapy is uncertain.

Methods
The British Childhood Cancer Survivor Study is a national, population-based, cohort study of 17,980 individuals surviving at least 5 years after diagnosis of childhood cancer. Linkage to national, population-based cancer registries identified 247 SPNs of the CNS. Cohort and nested case-control studies were undertaken.

Results
There were 137 meningiomas, 73 gliomas, and 37 other CNS neoplasms included in the analysis. The risk of meningioma increased strongly, linearly, and independently with each of dose of radiation to meningeal tissue and dose of intrathecal methotrexate. Those whose meningeal tissue received 0.01 to 9.99, 10.00 to 19.99, 20.00 to 29.99, 30.00 to 39.99 and ≥ 40 Gy had risks that were two-fold, eight-fold, 52-fold, 568-fold, and 479-fold, respectively, the risks experienced by those whose meningeal tissue was unexposed. The risk of meningioma among individuals receiving 1 to 39,40 to 69, and at least 70 mg/m^2 of intrathecal methotrexate was 15-fold, 11-fold, and 36-fold, respectively, the risk experienced by those unexposed. The standardized incidence ratio for gliomas was 10.8 (95% CI, 8.5 to 13.6). The risk of glioma/primitive neuroectodermal tumors increased linearly with dose of radiation, and those who had CNS tissue exposed to at least 40 Gy experienced a risk four-fold that experienced by those who had CNS tissue unexposed.

Conclusion
The largest-ever study, to our knowledge, of CNS tumors in survivors of childhood cancer indicates that the risk of meningioma increases rapidly with increased dose of radiation to meningeal tissue and with increased dose of intrathecal methotrexate.

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INTRODUCTION

A serious consequence of treatment for childhood cancer is the development of second primary neoplasms (SPNs).[1] SPNs of the CNS are the most frequent types of SPNs observed in Britain.[2] An increased risk of such neoplasms after treatment with cranial irradiation has been reported.[3-6]

It is of particular interest to evaluate risks of brain tumor among individuals exposed during childhood, because the risk appears to be higher for that population than for those individuals exposed during adulthood.[7] Survival after CNS SPNs is generally poor, particularly after second primary gliomas, although survival is somewhat better after second primary meningiomas.[8]

CNS SPNs are mainly meningiomas and gliomas. Meningiomas may develop as a result of cranial irradiation,[3,5] including irradiation from atomic bombs.[9] The effect of cranial irradiation on the risk of subsequent gliomas has been investigated, but the dose response appears weaker than for meningiomas.[3,4] Possible effects of chemotherapy on the risk of CNS SPNs are poorly understood.[4,10]

Two published studies have investigated the dose-response relationship between radiation and risk of CNS SPNs in survivors of childhood cancer.[3,4] The larger study, carried out as part of the Childhood Cancer Survivor Study (CCSS), had less than half the number of CNS SPNs available to this study.[3]

We carried out the largest-ever population-based cohort and nested case-control study, to our knowledge, to investigate the risk of CNS SPNs in survivors of childhood cancer and to relate this risk to treatment and genetic susceptibility factors.

METHODS

Tumor localization and radiation dosimetry case-control study methods information is described in the Appendix (online only).

British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS)[11] is a population-based cohort study of late-treatment toxicities in 17,980 individuals in Britain diagnosed with cancer when they were less than 15 years of age, between 1940 and 1991, who survived at least 5 years from diagnosis. Survivors at least 16 years of age and contactable through their general practitioners were sent a questionnaire (N = 13,211). Ethical approval was obtained from a multicenter research ethics committee and from every local research ethics committee in Britain (n = 212).

The BCCSS cohort was linked to the National Health Service Central Registers (NHSCR). Such linkage of the entire population-based cohort with the national population-based cancer and death registration systems provides a means of informing the BCCSS when a survivor develops an SPN or dies.

Ascertainment, Definition, Confirmation, and Classification of CNS SPNs

Ascertainment of SPNs was first obtained from population-based record linkage through NHSCR. However, for survivors who had completed a questionnaire, SPN diagnosis also was crossed-checked with information provided by the survivor in a questionnaire. This resulted in the identification of a small number of additional meningiomas that were reported on the questionnaires but that were not ascertained by NHSCR. All cases, irrespective of the sources of ascertainment, were included in the case-control study. SPN status was confirmed principally from histopathology reports and occasionally from radiologic reports through writing to clinicians and pathologists. For survivors of a first primary CNS glioma who developed a potential CNS SPN that was also a glioma, all relevant diagnostic reports were considered by an international expert in pediatric neuropathology (D.E.) to determine whether they represented two separate primary neoplasms. A number of potential second primary gliomas were excluded in this way.

SPNs were coded to the International Classification of Diseases of Oncology (ICD-O-3) codes.[12] Cases were BCCSS cohort members who developed an SPN of any histology or behavior (ICD-O-3 fifth digit code 0-3) with a primary site in the CNS, meninges, or intracranial endocrine glands (ICD-O-3: C70.0 to 72.9, C75.1 to 75.3).

SPNs were grouped into five categories: meningioma (ICD-O-3 codes 9530 to 9539); glioma and other neuroepithelial neoplasms (ICD-O-3 codes 9380 to 9523, excluding codes 9470 to 9473); primitive neuroectodermal neoplasms (ICD-O-3 codes 9470 to 9473); schwannomas (ICD-O-3 codes 9560 to 9561); and other/unclassified CNS neoplasms.

Numbers Included in Cohort and Case-Control Study

All confirmed benign and malignant CNS SPNs occurring after 5-year survival and before December 31, 2002, were included in the cohort and nested case-control study (N = 247). Of the 247 SPNs in the cohort study, 243 were matched and included in the case-control study. The remaining four were never matched to a control because of lost or destroyed records for the case (n = 2) or registration after completion of data collection (n = 2).

Matching Criteria for Case-Control Study

A single control was randomly selected from the entire underlying population-based BCCSS cohort and was matched to each case on the following criteria: age at original cancer diagnosis in 3-year age bands (0 to 2, 3 to 5, 6 to 8, 9 to 11, and 12 to 14 years); sex (male or female); interval from first primary neoplasm (FPN) diagnosis (free of CNS SPN) for control that was at least as long as the interval between FPN and SPN in the case; and cases of bilateral or known family history (ie, heritable) retinoblastoma were matched to controls with the same original FPN diagnosis.

We did not match on other genetic conditions, but adjustment was made in the analysis. However, our measure of genetic susceptibility was crude and was related to associated genetic conditions without family history or biologic material (Appendix).

Quantifying Exposure to Chemotherapy: Case-Control Study

We subdivided treatment into cycles or courses; for each drug and each cycle, we recorded the dates of start and end of administration, the total dose (as milligrams per meter squared), and the route of administration. We summed across cycles the total cumulative dose received (as milligrams per meter squared) for each drug.

Because of the relatively small number of cases and the heterogeneity of multiple-agent therapy, we considered drugs in terms of exposure groups, as follows: alkylating agents; anthracyclines; intrathecal antimetabolites (without exception, methotrexate); nonintrathecal antimetabolites; epipodophyllotoxins; and vinca alkaloids. We used two methods of combining exposures to drugs within each exposure group.

Scores method. Tucker et al[13] proposed a scores method of combining exposures to drugs; for example, a cumulative alkylating agent score was obtained by assigning patients a score of 0, 1, 2, or 3 for each alkylating agent used, depending on whether they received none or the lower, middle, or upper third of the distribution of total doses per meter squared for that agent, respectively. The cumulative alkylating agent score was the sum of the scores for each alkylating agent. A similar process was undertaken for each of the other exposure groups.

Equivalent milligrams per meter squared method. We assumed all drugs within a particular exposure group are equally carcinogenic for a specified amount of drug given per meter squared. For this approach, the total cumulative exposure per patient was obtained by summing cumulative exposures to each individual drug within the exposure group; drugs for which individuals were unexposed received the value of 0 mg/m^2.

After analysis that used both methods, it became clear the results were similar; therefore, we only present results relating to the equivalent milligrams per meter squared analysis.

Statistical Analysis

Individuals entered risk at 5-year survival and exit date was December 31, 2002, if the survivor was still alive and had not developed an SPN. Otherwise, the exit date was the date of SPN, date of death, or date of loss to follow-up, whichever occurred first, provided it was not later than December 31, 2002. We report results that were statistically significant at the 5% level, by using two-tailed tests. All confidence intervals are 95%.

Cumulative risk: cohort study. We estimated cumulative incidence of SPN by treating death as a competing risk in terms of time from 5-year survival.[14] Log-rank tests were undertaken to determine statistical significance of the effect of treatment on cumulative risk.

Standardized incidence ratio and absolute excess risk: cohort study. Standardized incidence ratio (SIR) and absolute excess risk were calculated with Stata 9.0 (STATA, College Station, TX)[15] for gliomas. SIR is the ratio of observed (O) to expected (E) numbers of neoplasms. E was estimated from rates in the general population of England and Wales.

$$\text{Absolute excess risk was calculated as } [(O - E) \div \text{person years at risk}] \times 10{,}000. \quad (1)$$

Conditional logistic regression: case-control study. To investigate variation in the risk of meningioma or glioma/primitive neuroectodermal tumor (PNET) in relation to levels of cumulative exposure to radiation or cytotoxic drug dose (D), the following linear model was fitted:

$$\text{ERR} = \text{OR} - 1 = \beta D \quad (2)$$

in which excess relative risk (ERR), which is the odds ratio (OR) minus 1, is expressed as a linear function of dose. Consequently, β is a measure of the ERR per Gy or ERR per milligram per meter squared (Appendix).

RESULTS

Total person-years of follow-up was 310,816 years from 5-year survival; the mean follow-up was 17.3 years per survivor. We identified 247 SPNs (137 meningiomas, 73 gliomas, 16 schwannomas, nine PNETs and 12 other SPNs; Appendix Table A1, online only). The interval between FPN and SPN ranged from 5 to 52 years (Appendix Fig A1, online only). The mean interval was 20.5 years overall but varied by SPN type, as follows: meningiomas, 23.1 years; schwannomas, 20.0 years; gliomas, 17.4 years; and PNET, 9.2 years.

Cohort Analysis

SIR for gliomas overall was 10.8 (95% CI, 8.5 to 13.6; Table 1). It was highest after leukemia (SIR, 16.7; 95% CI, 10.1 to 26.1) and CNS FPN (SIR, 18.5; 95% CI, 12.7 to 26.2). The SIR was higher after radiotherapy treatment (14.3; 95% CI, 10.9 to 18.7) compared with after treatment without radiotherapy (SIR, 6.1; 95% CI, 3.1 to 11.0), $P = .008$. The SIR was 15.3 (95% CI, 10.3 to 21.9) after chemotherapy treatment compared with 10.2 (95% CI, 7.1 to 14.1) after treatment without chemotherapy ($P = .096$). The SIR increased among those treated more recently ($P < .001$). The SIR decreased with increasing follow-up ($P = .001$).

Cumulative incidence was 3.6% (95% CI, 2.9% to 4.3%) by 40 years of follow-up for all SPNs, comprising 2.3% (95% CI, 1.8% to 3.0%) for meningiomas and 0.8% (95% CI, 0.6% to 1.2%) for gliomas. Corresponding cumulative incidences were highest after CNS FPN 6.5% (95% CI, 5.0% to 8.2%) and leukemia FPN 3.4% (95% CI, 2.5% to 4.5%). Corresponding cumulative incidences after irradiated CNS FPN were 9.1% (95% CI, 7.9% to 11.7%), 6.3% (95% CI, 4.5% to 8.5%) for meningiomas, and 2.4% (95% CI, 1.3% to 4.1%) for gliomas, compared with 1.4% (95% CI, 0.6% to 2.8%) after nonirradiated CNS FPN (log-rank $P < .001$; Appendix Figs A2 and A3, online only).

Case-Control Study

Table 2 provides a summary of evidence of the influence of cumulative exposure to radiation and cytotoxic drugs on the risk of meningioma and glioma/PNET. The ERR of meningioma increased linearly both with increased cumulative exposure to radiation in Gy

Table 1. SIR for Glioma, *P* Value for Test of Heterogeneity and Trend in SIRs, and AERs

Category	No. of Survivors in Category	No. Observed	No. Expected	SIR	95% CI	*P*		AER	95% CI
						Heterogeneity	Linear Trend		
Overall	17,980	73	6.76	10.8	8.5 to 13.6			2.1	1.6 to 2.7
Sex						.09			
Male	9,886	37	4.09	9.0	6.4 to 12.5			1.9	1.2 to 2.7
Female	8,094	36	2.68	13.4	9.4 to 18.6			2.3	1.5 to 3.2
Age at original diagnosis, years						.31	.19		
0-4	8,248	34	2.82	12.0	8.3 to 16.8			2.1	1.3 to 2.9
5-9	4,812	21	1.70	12.3	7.6 to 18.9			2.4	1.3 to 3.5
10-14	4,920	18	2.24	8.0	4.8 to 12.7			1.9	0.9 to 2.9
Year of diagnosis of childhood cancer						< .0016	< .001		
1940-1959	1,118	5	1.29	3.9	1.3 to 9.1			1.0	0.0 to 2.2
1960-1969	2,628	12	1.79	6.7	3.5 to 11.8			1.5	0.5 to 2.4
1970-1979	5,379	32	2.00	16.0	11.0 to 22.7			2.8	1.8 to 3.9
1980-1991	8,855	24	1.70	14.1	9.1 to 20.9			2.3	1.3 to 3.2
Childhood cancer diagnosis						< .001			
Leukemia	4,851	19	1.13	16.7	10.1 to 26.1			2.8	1.4 to 4.1
CNS tumor	4,111	32	1.73	18.5	12.7 to 26.2			4.0	2.6 to 5.6
Genetic retinoblastoma	549	2	0.29	6.9	0.8 to 25.1			1.3	
Nongenetic retinoblastoma	651	1	0.35	2.9	0.1 to 16.1			0.4	
Lymphoma	2,206	7	0.97	7.2	2.9 to 14.9			1.6	0.2 to 2.9
Other types of childhood cancer	5,612	12	2.30	5.2	2.7 to 9.1			0.9	0.3 to 1.6
Period of follow-up, years						.0032	.0015		
0-4	17,980	27	1.31	20.6	13.6 to 30.1			3.0	1.8 to 4.2
5-9	16,450	9	1.20	7.5	3.4 to 14.3			1.0	0.3 to 1.8
10-14	13,129	11	1.00	11.0	5.5 to 19.7			1.8	0.6 to 3.0
15-19	9,362	11	0.88	12.5	6.2 to 22.3			2.6	0.9 to 4.2
20-29	6,424	10	1.38	7.2	3.5 to 13.3			2.1	0.6 to 3.6
≥ 30	2,370	5	0.99	5.0	1.6 to 11.7			2.6	0.0 to 5.5
Treatment for original childhood cancer									
Radiotherapy	9,223	57	4.00	14.3	10.9 to 18.7	.008		3.0	2.1 to 3.8
No radiotherapy	3,835	11	1.79	6.1	3.1 to 11.0			1.2	0.3 to 2.0
Chemotherapy	6,633	30	1.96	15.3	10.3 to 21.9	.096		2.6	1.6 to 3.6
No chemotherapy	6,038	36	3.54	10.2	7.1 to 14.1			2.3	1.5 to 3.2

Abbreviations: SIR, standardized incidence ratio; AER, absolute excess risk.

Table 2. Influence of Increased Cumulative Exposure to Radiation and Chemotherapeutic Drugs on the ERR of Meningioma and Glioma/PNET

Exposures Included in the Model	Meningioma			Glioma/PNET		
	Deviance	*df*	LRT *P*	Deviance	*df*	LRT *P*
Null model	127.54	92		81.79	59	
Radiation, Gy*	50.83	91	< .001†	69.58	58	< .001†
Radiation* + alkylating agents mg/m^2*	49.47	90	.245‡	69.55	57	.864‡
Radiation* + anthracyclines*	50.58	90	.621‡	68.89	57	.407‡
Radiation* + intrathecal methotrexate*	44.87	90	.015‡	68.81	57	.379‡
Radiation* + nonintrathecal antimetabolites*	49.22	90	.205‡	69.24	57	.561‡
Radiation* + epipodophyllotoxins*	49.69	90	.287‡	68.96	57	.429‡
Radiation* + vinca alkaloids*	48.12	90	.100‡	69.55	57	.854‡

NOTE. Radiation dosed in Gy; chemotherapeutic drugs dosed in milligrams per meter squared.
Abbreviations: ERR, excess relative risk; PNET, primitive neuroectodermal tumor; *df*, degrees of freedom; LRT, likelihood ratio test.
*Fitted as a linear trend in continuous dose (model 1).
†LRT *P* value relative to null model.
‡LRT *P* value relative to model with radiation fitted as a linear trend in continuous dose.

($P < .001$) and with increased cumulative exposure to intrathecal methotrexate in milligrams per meter squared ($P = .015$ adjusted for radiation exposure). In terms of model 1, specified in the Appendix, the estimates for β_1 and β_2 were 5.1 (95% CI, 0.7 to 107.7) per Gy and 2.2 (95% CI, 0.1 to 64.4) per mg/m^2, respectively. For no other group of cytotoxics investigated was there statistically significant variation in ERR of meningioma with increased cumulative exposure measured in milligrams per meter squared. The ERR of glioma/PNET increased linearly with increased cumulative exposure to radiation in Gy ($P < .001$). In terms of model 1, the estimate for β_1 was .079 (95% CI, 0.021 to .229) per Gy. For none of the groups of cytotoxics investigated was there statistically significant variation in the ERR of glioma/PNET, with increased cumulative exposure measured in mg/m^2.

Appendix Table A2 (online only) summarizes an investigation of evidence for nonlinearity in dose responses, interaction between exposures and potential effects of age at exposure, and time since exposure on the ERR of meningioma and glioma/PNET. The effect of cumulative exposure to radiation on the ERR of each of meningioma and glioma/PNET is well explained by a linear relationship. There was evidence of nonlinearity in the effect of cumulative exposure to intrathecal methotrexate on the ERR of meningioma ($P = .004$ for a cubic relationship), but such a complex dose-response relationship would need independent confirmation before being regarded as robust. There was no evidence of an interaction between cumulative exposure to radiation and intrathecal methotrexate on the ERR of meningioma. Neither age at exposure nor time since exposure revealed evidence of an effect on the ERR of meningioma. As indicated in Appendix Table A2, there is statistically significant decline in the ERR of glioma/PNET with increasing age at exposure ($P = .033$) but not with time since exposure. Appendix Table A2 also shows that, for meningioma, there is no statistically significant variation of ERR with genetic susceptibility. However, for PNET/glioma, there is statistically significant variation ($P = .016$), and risks appear markedly elevated in the susceptible group: the excess relative risk per Gy is higher by a factor of 5.69×10^5 (95% CI, 2.30 to $>10^6$; Appendix).

Tables 3 and 4 summarize variation in relative risks (RRs) of meningioma and glioma/PNET across increasing levels of cumulative exposure to radiation from radiotherapy. These tables provide RRs associated with each exposed level compared with the baseline level comprising those unexposed. For meningioma and glioma/PNET, the

Table 3. Variation in RR of Meningioma Across Different Levels of Radiation Exposure Resulting From Radiotherapy

Level of Exposure, Gy	Cases		Controls		RRs					
					Unadjusted*			Adjusted for Intrathecal Methotrexate Exposure*†		
	No.	Mean Dose (Gy)	No.	Mean Dose (Gy)	RR	95% CI	*P*	RR	95% CI	*P*
Incomplete information	25		25							
0	3		39		1			1		
0.01-9.99	6	2.66	33	0.88	1.1	0.1 to 7.5	.962	1.8	< 0.8 to 39.3	.632
10.00-19.99	12	16.58	10	15.17	35.1	2.9 to 419.1	.005	8.4	6.4 to < 10.7	.078
20.00-29.99	39	24.76	15	23.29	57.8	6.1 to 544.5	< .001	51.6	5.5 to < 69.5	< .001
30.00-39.99	21	34.73	8	34.66	69.6	6.6 to 736.4	< .001	567.9	29.3 to < 773.6	< .001
≥ 40.00	28	46.97	4	43.38	94.2	8.7 to 1,014.0	< .001	479.1	25.0 to < 657.2	< .001
Total	134		134							

Abbreviation: RR, relative risk.
*Likelihood ratio test for evidence of heterogeneity in RR across different levels of exposure to radiation: $P < .001$ for unadjusted analysis and for adjusted analysis.
†Adjusted for intrathecal methotrexate exposure fitted as a categoric exposure variable.

Table 4. Variation in RR of Glioma/PNET Across Different Levels of Radiation Exposure Resulting From Radiotherapy

Level of Exposure, Gy	Cases		Controls		Unadjusted Analysis		
	No.	Mean Dose (Gy)	No.	Mean Dose (Gy)	RR	95% CI	P
Incomplete information	13		13				
0	13		17		1		
0.01-9.99	11	0.78	27	0.79	0.5	0.2 to 1.5	.230
10.00-19.99	4	18.45	9	17.48	0.5	0.1 to 2.3	.406
20.00-29.99	18	23.57	8	23.84	2.6	0.9 to 8.0	.084
30.00-39.99	6	35.17	3	34.00	3.4	0.5 to 23.0	.215
≥ 40.00	16	45.04	4	46.43	4.4	1.2 to 16.4	.028
Total*	81		81				

Abbreviations: RR, relative risk; PNET, primitive neuroectodermal tumor.
*Likelihood ratio test for evidence of heterogeneity in RRs across different levels of exposure to radiation: *P* for unadjusted analysis = .0013.

RR associated with an exposure of at least 40 Gy was 479 times and four times, respectively, that experienced in unexposed tissue.

Table 5 summarizes the variation in RR of meningioma across different levels of cumulative exposure to intrathecal methotrexate, analogous to Tables 3 and 4. After adjustment for radiotherapy exposure, the RR of meningioma associated with a cumulative exposure of at least 70 mg/m^2 of intrathecal methotrexate was 36 times that experienced in those unexposed to intrathecal methotrexate.

DISCUSSION

The risk of meningioma after radiation was strongly and linearly related to dose. The risk of glioma also increased (linearly) with increasing radiation dose. There was modification of risk of glioma by age at childhood cancer diagnosis and genetic susceptibility. Increased exposure to intrathecal methotrexate significantly increases risk of meningioma, which is a novel finding. The risk among those exposed to at least 70 mg/m^2 of intrathecal methotrexate was 36-fold that among those unexposed.

The adjusted RR of meningioma among those irradiated with doses of at least 40 Gy was 479-fold that among those unexposed. The most comparable figure from the CCSS is 33-fold, which relates to those exposed to at least 45 Gy.[3] ERR of meningioma in this study was 5.1 (95% CI, 0.7 to 107.7) per Gy. In the CCSS study,[3] an ERR of 1.06 (95% CI, 0.21 to 8.15) per Gy for meningioma was reported. A study of atomic bomb survivors[9] reported an ERR of 0.64 (95% CI, −0.01 to 1.8) per Sievert. A Franco/British study of survivors of childhood cancer reported an ERR for benign/unspecified brain tumors of greater than 1,000 (95% CI, 0.25 to > 1,000) per Gy.[4] From studies of children treated for tinea capitis with cranial irradiation,[16] the ERR for benign meningiomas was 4.63 (95% CI, 2.43 to 9.12) per Gy, which is similar to our estimate.[16] We found no evidence of a significant association with known genetic susceptibility and risk of meningiomas, although there does appear to be evidence of such an association in other studies.[17] Recent data concerning cranially irradiated survivors of childhood acute lymphoblastic leukemia in Israel indicate that those undergoing regular scanning with magnetic resonance imaging or computed tomography had a cumulative risk of 15% of developing a meningioma within 20 years of irradiation.[5] Fifteen of 16 observed meningiomas were asymptomatic, and most were smaller than 4 cm in diameter.[5] These investigators commented that the chances of success of complete resection are higher for smaller lesions and that symptomatic patients usually have larger tumors that require riskier surgery. We found that 6% of survivors of irradiated CNS tumors developed a meningioma after 40 years. Practices in the United Kingdom are ad hoc, and there is no agreed-upon, standardized screening

Table 5. Variation in RR of Meningioma Across Different Levels of Intrathecal Methotrexate Exposure

Level of Exposure, mg/m^2	Cases		Controls		RRs					
					Unadjusted			Adjusted for Radiation Exposure*		
	No.	Mean Dose (mg/m^2)	No.	Mean Dose (mg/m^2)	RR	95% CI	*P*	RR	95% CI	*P*
Incomplete information	22		22							
0	79		97		1			1		
1-39	12	31	4	34	4.1	1.2 to 14.1	.024	15.4	2.2 to 179.6	.004
40-69	5	49	7	52	1.2	0.3 to 4.7	.817	10.8	1.3 to 143.0	.027
≥ 70	16	542	4	82	6.4	1.7 to 23.5	.006	35.6	4.8 to 599.4	< .001
Total†	134		134							

NOTE. Four and two of the 33 exposed patients and 15 exposed controls, respectively, received leucovorin after intrathecal methotrexate.
Abbreviation: RR, relative risk.
*Adjusted for radiation fitted as a linear trend in continuous cumulative radiation exposure (model 2).
†Likelihood ratio test for evidence of heterogeneity in RRs across different levels of exposure to intrathecal methotrexate: *P* for unadjusted analysis = .002; *P* for adjusted analysis = .001.

for CNS SPNs. Computed tomography or magnetic resonance imaging for symptoms is routine in survivors attending long-term follow-up clinics.

The overall SIR for glioma was 10.8 (95% CI, 8.5 to 13.6) and was highest after leukemia and CNS childhood neoplasms, which in this cohort were commonly treated with high doses of cranial irradiation. This compares with an SIR of 8.7 (95% CI, 6.2 to 11.6) in the CCSS study.[3] The RR of glioma/PNET was 4.4 (95% CI, 1.2 to 16.4) among those exposed to radiation doses of at least 40 Gy compared with those unexposed. The most comparable figure from the CCSS study was 17.5 (95% CI, 2.9 to 107.5), which related to those exposed to at least 45 Gy.[3] We found an ERR for glioma/PNET of 0.079 (95% CI, 0.021 to 0.229) per Gy, which compares with 0.33 (95% CI, 0.07 to 1.71) reported by the CCSS,[3] 0.6 (95% CI, −0.2 to 2.0) from a study of the atomic bomb survivors,[9] and 1.98 (95% CI, 0.73 to 4.69) per Gy from the tinea capitis cohort.[16] We found modification of ERR with age at exposure ($P = .033$) and genetic susceptibility ($P = .016$). The CCSS study found no statistically significant association between ERR and age at exposure for either gliomas or meningiomas, and they did not include genetic susceptibility as a factor in their analysis.[3] Preston et al[9] reported a weak association ($P = .06$) with age at exposure to atomic radiation and risk of CNS tumors (excluding schwannomas), in which ERR was higher in those exposed when younger than the age of 20 years (and this was also the case when meningiomas were examined separately). The study of children with tinea capitis also reports an association with age at exposure for malignant brain tumors (but not for meningiomas).[16]

We estimate ERR associated with intrathecal methotrexate was 2.2 (95% CI, 0.1 to 64.4) per mg/m^2. The CCSS did not investigate detailed dose response in relation to chemotherapy.[3] The Franco/British study looked solely at the effect of alkylating agents on risk of developing CNS SPNs and found a slightly increased risk relating to one subgroup.[4] The only previous paper reporting an association between intrathecal methotrexate and increased risk of brain tumors concerned an excess of gliomas after childhood acute lymphoblastic leukemia.[10] Two other studies have examined the role of intrathecal chemotherapy on risk of gliomas[18] and brain tumors[19] after childhood acute lymphoblastic leukemia but failed to find an association. There were insufficient survivors in our cohort treated with intrathecal methotrexate without cranial irradiation to assess their risk of meningioma. It is important that such populations are investigated, because intrathecal methotrexate is still widely used to treat leukemia and lymphoma.[20]

There are important advantages associated with this study, including that it has a large-scale, population-based design and has careful estimation of treatment exposures. The principal limitations relate to the interpretation of the finding that the risk of meningioma increased with increased cumulative exposure to intrathecal methotrexate. There are two reasons to be cautious about interpreting this association as causal. First, as reported in the previous paragraph, there were insufficient survivors exposed to intrathecal methotrexate without cranial irradiation to assess their risk of meningioma separately, and residual confounding is a possibility. Second, if this relationship were causal, then one might anticipate that systematic methotrexate (to which all except two of those who received nonintrathecal antimetabolites were exposed) might reveal evidence of a relationship, but it did not.

In conclusion, the largest-ever study, to our knowledge, of CNS tumors in survivors of childhood cancer indicates that the risk of meningioma increases strongly, linearly, and independently with dose of radiation to meningeal tissue and with dose of intrathecal methotrexate. The risk of glioma/PNET increased linearly with dose of radiation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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