The Role of Family History in Risk of Childhood Brain Tumors

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Background. **Although brain tumors are the second most frequent malignancy in children, relatively little is known about the role of family history in risk of these tumors.**

Methods. **Children under the age of 18 years (n = 361) in whom primary brain tumors were diagnosed were identified from eight United States population-based Surveillance, Epidemiology, and End Results registries and compared to matched controls (n = 1083) identified by random-digit dialing. Information regarding family history of birth defects or tumors was obtained, along with data on other potential risk factors, from interviews with the mothers and fathers of the index children.**

Results. **No significant differences were found in family history of epilepsy. However, moderate elevations in risk were observed for a history of birth defects in maternal relatives, particularly for female propositi. Significantly more mothers (odds ratio [OR] = 1.63, 95% confidence limits [CL] = 1.03, 2.57) and maternal female relatives (OR = 2.15, 95% CL = 1.14, 4.06) of cases than of controls were reported to have had birth defects. History of birth defects in maternal relatives was particularly associated with childhood brain tumors of "other" (not astrocytoma or medulloblastoma) histologic type (OR = 2.37, 95% CL = 1.25, 4.53) and infratentorial tumors (OR = 1.76, 95% CL = 1.06, 2.93). Slight excesses of tumors were observed in paternal relatives of children with astrocytomas (OR = 1.43, 95% CL 0.93, 2.20) or with infratentorial tumors (OR = 1.46, 95% CL 0.97, 2.20). Risk of childhood brain tumors did not increase with the number of relatives affected with brain tumors, breast cancer, leukemia or lymphoma, soft tissue sarcomas, or all of these tumor types combined (the Li-Fraumeni syndrome).**

Conclusions. **These findings suggest a modest increase in risk of childhood brain tumors associated with maternal family history of birth defects. Family history of tumors does not appear to contribute appreciably to an increased risk of brain tumors in children. *Cancer* 1994; 73:1302–11.**

Key words: brain tumors, children, epidemiology, familial, risk factors.

Brain tumors are the second most frequently occurring malignancy in children.[1] Although a small number of occupational and environmental factors have been suggested to play a role,[2–11] relatively little is known about risk factors for childhood brain tumors.

Although a few genetic conditions are known to be associated with an increased risk of brain tumors in children,[12–15] few studies have evaluated whether the risk of childhood brain tumors is associated with a family history of birth defects or with a family history of tumors not involving the brain.[2,16–19] If such an association were observed, it might suggest either a common underlying genetic abnormality or common exposure(s) resulting in variable expression. This information would be valuable in identifying populations at in-

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creased risk, if such a risk exists, or in providing reassurance to families if a risk is not found.

The current investigation was undertaken to examine this question using family history data collected in a large, multicenter, population-based, case–control study of childhood brain tumors.

Materials and Methods

Subject Selection

Cases were identified from eight population-based Surveillance, Epidemiology, and End Results tumor registries, representing a combined annual catchment population of 4.72 million children. Patients included were younger than 18 years at the time of diagnosis, had a histologically confirmed diagnosis of brain tumor between January 1, 1977 and December 31, 1981, and resided in the catchment areas of the registries at the time of diagnosis. Two neuropathologists simultaneously read histologic slides of each brain tumor and assigned diagnoses contained in the World Health Organization classification of tumors of the central nervous system.[20] Three control children were matched to each case by age, sex, and the mother's racial/ethnic classification. For 95% of the cases, controls were identified by random-digit dialing[21] and were matched to the case by area code and telephone prefix. For approximately half of the cases from Hawaii, alternative methods for selecting controls were used to obtain closer matching according to the five ethnic groups in Hawaii. The Hawaii State Department of Health is mandated to create lists of noninstitutionalized residents.[22] From these lists, children of the same ethnic group and similar age on the same island as the case were identified. In addition, controls for about 15% of the cases from Washington, those from Pierce County, were identified from a random sample of neighborhood households, a method that has been used previously there, whereas random-digit dialing was used in the other two counties in Washington.

The largest category of histologic types of tumors among cases were astrocytic tumors, including glioblastoma (46.8%) and medulloblastoma (16.9%). Tumors were most often located in the cerebellum, cerebellopontine angle, or other posterior fossa sites (39.6% of cases) or in the cerebrum (20.5%). These distributions are similar to those reported in previous studies[23,24] and, given the population-based nature and coverage of the eight registries, are believed to be fairly representative of childhood brain tumors.

Interviews

Information on demographic characteristics, occupational history, habits, and personal and family medical histories, including medication use, was obtained from each parent, after informed consent, for both cases and controls in a structured interview by trained interviewers in the home. Interviews were completed for 361 children with brain tumors and for 1083 control children within a year of the date of diagnosis of the case. The cases represent 85% of those identified by the registries. Reasons for exclusion included: physician refusal (14 cases), family refusal (24 cases), family not located (14 cases), child adopted (9 cases), and lack of histologic confirmation of brain tumor by study neuropathologists (5 cases). The rate of completion of interview with eligible control parents was 84.5%. The median number of telephone calls to enroll one control was 18, with a few controls requiring over 100 calls.

Information on pregnancy and delivery history and the child's medical history was obtained from the mother. Family history of birth defects and tumors was obtained for mothers, fathers, and maternal and paternal grandparents and great-grandparents of the index study children (propositi). Parents were asked, with reference to themselves, their parents, and their grandparents, whether they had birth defects; if the response was positive, they were asked to state the location and exact nature of the defect. The same questions were asked for relatives regarding tumors, cancers, cysts, or leukemia. For mothers and fathers of propositi, however, these conditions were ascertained by asking if the parents had "any other condition" and to specify it, after they responded to a list of questions that did not include tumors. Because cancer was unlikely to occur in siblings with sufficient frequency to make analyses statistically meaningful in a study group of this size, only information about birth defects, and not about tumors, was obtained for siblings of the propositi. For siblings, the information on birth defects was ascertained by asking if each child had a birth defect, and if the response was affirmative, by asking where the defect was located and exactly what the defect was.

Paternal information was supplied directly by the father in 71% of interviews, by the mother in 26%, and by other relatives in fewer than 1%. Information was missing for 2% of fathers. Maternal and child information was supplied directly by the mother in nearly 99% of interviews, by the father in 1%, and by other relatives in fewer than 1%. Information was missing for one mother (0.1%). Distributions of providers of information and numbers of subjects missing parental information were similar for cases and controls.

Data Analysis

Analyses were performed by considering all brain tumors together and then by considering tumor type and location. Analyses also were stratified by maternal or

Table 1. Demographic Characteristics of Parents

	Percent			
	Mother		*Father*	
Characteristic	*Cases (n = 361)**	*Controls (n = 1086)*	*Cases (n = 352)*	*Controls (n = 1063)*
Parental age at birth of propositus				
< 20 years	9.7	10.5	3.4	4.1
20–24	34.3	32.4	23.2	25.1
25–29	34.4	34.4	34.7	32.7
30–34	14.4	16.8	23.2	23.2
35+	7.2	5.9	15.5	14.9
Years of schooling				
< 12	16.7	14.9	17.5	14.1
12	41.8	39.6	27.5	29.7
> 12	41.5	45.5	55.0	56.2
Ethnicity				
White	77.3	77.9	77.3	79.2
Hispanic	5.0	5.0	5.2	4.5
Black	9.3	9.3	9.2	8.5
Filipino	2.8	3.3	2.9	3.0
Chinese	1.7	1.7	1.1	1.8
Japanese	1.4	0.8	0.9	0.9
Other Asian	2.5	2.0	3.4	2.1

* All variables for one mother of an additional case were unknown, but the data for the controls matched to this case are included in this table.

paternal relatives to allow for the possibility that the quality of information provided might have differed for fathers and mothers. In addition, for some analyses of familial birth defects, information about all great-grandparents of the index child was excluded to see if the risk estimates were altered, because errors of ascertainment might be greater for birth defects in this older group.

The odds ratio (OR) was used as an estimate of relative risk. Point estimates for the ORs and 95% confidence limits (CL) were calculated using conditional logistic regression for matched sets.[25] In the evaluation of risk of brain tumor associated with family history, if information was missing for 50% or more of the relatives of a case, the case and its set of three matched controls were excluded from the analysis. If information for 50% or more of the relatives of a control was missing, only that control was excluded, but the case and remaining controls in the set were included in the analysis.

Results

Parents of cases and controls were quite similar in the distribution of their ages at the time of birth of the index child, education, and ethnicity (Table 1). Other variables, such as parental smoking[26] and employment,[27] were examined but were not found to confound relationships with family history. In addition, neither mothers nor fathers of cases and controls differed in their reported frequencies of history of epilepsy (Table 2). Furthermore, cases and controls did not differ significantly in the reported frequency of epilepsy in maternal or paternal family members.

Birth Defects in Family Members

Cases and controls did not differ significantly in their distribution of birth defects, as reported by their parents (Table 3), although Von Recklinghausen's neurofibromatosis, defects of the vertebra or back, urogenital and skin defects, and club foot were reported for a greater proportion of cases than of controls. There also was no significant difference in the frequency of reported birth defects in siblings of cases (n = 726) and controls (n = 2143) (Table 4), although a greater proportion of siblings of cases than of controls were reported to have club foot or hydrocephalus.

Family history of birth defects was analyzed separately for male and female index children to permit detection of any excess risk that might indicate a sex-linked trait (Table 5). Overall, there was no significant excess risk associated with having any family history of a birth defect (OR = 1.37, 95% CL = 0.98, 1.91). However, the majority of ORs for specific relatives were in excess of 1, and all but one of the ORs for maternal

Table 2. Matched Odds Ratios and 95% Confidence Limits for Epilepsy in Parents and in Maternal and Paternal Relatives by Gender

	Mothers		Fathers		Total parents*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Affected	4	8	1	6	4	14
Unaffected	357	1078	347	1051	343	1041
	OR = 1.650 95% CL = 0.45, 4.98		OR = 0.50 95% CL = 0.06, 4.15		OR = 0.83 95% CL = 0.27, 2.57	
Maternal Relatives*						
	Female relatives		Male relatives		Total maternal relatives	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Any affected	8	25	7	20	15	46
None affected	314	956	296	892	312	953
	OR = 0.96 95% CL = 0.42, 2.17		OR = 0.84 95% CL = 0.31, 2.22		OR = 0.99 95% CL = 0.53, 1.85	
Paternal Relatives*						
	Female relatives		Male relatives		Total paternal relatives	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Any affected	2	11	3	12	6	23
None affected	283	807	246	743	285	826
	OR = 0.45 95% CL = 0.10, 2.12		OR = 0.83 95% CL = 0.22, 3.13		OR = 0.73 95% CL = 0.29, 1.85	

OR: odds ratio; CL: confidence limit.

* Excludes cases or controls in which information on epilepsy was missing or unknown for 50% or more of relatives. Crude frequencies indicate distribution before excluding sets with data missing for 50% or more of relatives of cases.

family history were in excess of 1. In addition, significantly more mothers of all cases than of all controls, and specifically of female cases than of female controls, reported birth defects (OR = 1.63, 95% CL = 1.03, 2.57 and OR = 2.00, 95% CL = 1.04, 3.84, respectively). A minimal excess was observed for mothers of male cases, and no excess was observed for fathers of cases of either sex.

Significantly more female maternal relatives (i.e., grandmothers and great-grandmothers of the propositi) of cases than of controls were reported to have birth defects (OR = 2.15, 95% CL = 1.14, 4.06). This was also true when great-grandparents were excluded from the analysis (to allow for the possibility that parents of cases and controls might not know or be able to recall information about birth defects in such older relatives). In addition, the differences tended to be more marked and were statistically significant for maternal relatives of female (OR = 2.70, 95% CL = 1.10, 10.4) than of male (OR = 1.71, 95% CL = 0.69, 4.24) propositi, although the CL were wide. However, no particular type of defect accounted for the excess, although eye defects occurred more frequently in maternal female relatives of cases than of controls (see Table A1 for specific defects in maternal relatives). Furthermore, moderate excesses were observed in the frequency of birth defects in maternal male relatives (grandfathers and great-grandfathers of the propositi), and no or modest excesses were observed for birth defects in paternal relatives. Only one OR exceeded 1.5 for birth defects among paternal relatives, that for history of birth defects in paternal grandfathers and great-grandfathers of female propositi, although the CL were quite wide (OR = 2.74, 95% CL = 0.60, 12.5).

When analyses of birth defects in relatives were stratified by type of brain tumor in the cases (astrocytoma, medulloblastoma, and others) or by location of tumor (supratentorial, infratentorial, or others), all ORs for maternal relatives were elevated to some degree. Notable excesses were observed for maternal relatives of cases with "other" tumor types (OR = 2.37, 95% CL = 1.25, 4.53) and with infratentorial tumors (OR = 1.76, 95% CL = 1.06, 2.93) and for all types and sites combined (OR = 1.56, 95% CL = 1.06, 2.30) (Table 6). The only notable elevation in ORs for birth defects in paternal relatives was for cases with "other" tumor locations, and the CL were very wide (OR = 2.09, 95% CL = 0.30, 14.7). There also was no pattern of increasing risk with increasing numbers of paternal or maternal relatives affected, and the findings were not substan-

Table 3. Types of Birth Defects in Propositi

Type of birth defect	Cases (n = 361)* No.	Cases %†	Controls (n = 1086) No.	Controls %†
Ears/congenital deafness	1	0.3	6	0.6
Vertebral/back/curvature of spine	3	0.8	3	0.3
Eye	3	0.8	6	0.6
Cleft lip or palate	0	—	1	0.1
Congenital heart disease	0	—	9	0.8
Polydactyly/other digit	0	—	7	0.6
Von Recklinghausen's neurofibromatosis	4	1.1	0	—
Absent/extra/deformed kidney	0	—	4	0.4
Spina bifida	0	—	1	0.1
Hydrocephalus	1	0.3	0	—
Club foot	5	1.4	3	0.3
Digestive system	1	0.3	10	0.9
Other urogenital system	2	0.6	2	0.2
Other/multiple‡	14	3.9	27	2.5
Total	34	9.4	79	7.3

* All variables for one additional case were unknown.
† % is the proportion of cases or of controls with defect.
‡ 1 case had more than one defect.

Table 4. Types of Birth Defects in Siblings* of Cases and Controls

Type of birth defect	Siblings of cases No.	Siblings of cases %†	Siblings of controls No.	Siblings of controls %†
Ears/congenital deafness	3	0.4	7	0.3
Vertebral/back/curvature of spine	4	0.5	6	0.3
Eye	3	0.4	13	0.6
Cleft lip or palate	0	—	5	0.2
Congenital heart disease	9	1.1	16	0.7
Polydacytly/other digit	2	0.2	15	0.6
Von Recklinghausen's neurofibromatosis	1	0.1	0	—
Absent/extra/deformed kidney	0	—	3	0.1
Anencephaly/spina bifida	1	0.1	2	0.1
Hydrocephalus	3	0.4	1	< 0.1
Club foot	4	0.5	4	0.2
Digestive system	0	0.0	14	0.6
Other urogenital system	4	0.5	8	0.4
Other/multiple‡	24	3.1	82	3.6

OR: odds ratio; CL: confidence limits.
* Overall OR = 0.99; 95% CL = 0.70, 1.40.
† % is the proportion of siblings of cases (n = 780) or of controls (n = 2291) affected.
‡ Siblings of two cases and ten controls had more than one defect.

tially changed when the data were analyzed without including great-grandparents.

Familial Tumors in Family Members

No difference was observed between cases and controls with respect to a history of a tumor in maternal or paternal relatives (Table 7). When analyses were stratified by type and location of the brain tumor in the propositi (Table 8), a slight excess was observed for maternal relatives of cases with "Other" types of brain tumors (OR = 1.62, 95% CL = 1.03, 2.56) and for paternal relatives of children with astrocytomas (OR = 1.43, 95% CL = 0.93, 2.20) or infratentorial tumors (OR = 1.46, 95% CL = 0.97, 2.20). There were no significant excesses of brain tumors, breast cancer, leukemia or lymphoma, soft tissue sarcomas, or all of these cancers combined (the Li-Fraumeni syndrome) in maternal or paternal relatives of cases, including parents of propositi (Table 9) (see Table A2 for specific tumors in relatives).

Discussion

The results of the current analyses of this large, case–control study indicate that a maternal family history of birth defects is associated with a modest increase in risk of childhood brain tumors, particularly in female cases. No association was found with family history of epilepsy, and largely no associations were found with family history of tumors. A previous examination of the data from only the cases in this study revealed a tendency for patients whose grandparents and great-grandparents had a history of any tumor to be younger at diagnosis than those without such a family history.[28]

Given the large number of comparisons made in this analysis, it is likely that some or all of the observed differences occurred by chance. A lack of difference would be consistent with a recent study in Texas of cancer in families of children with brain tumors.[29] However, a previous, smaller, population-based, case–control study of epilepsy in Baltimore,[2] as well as a study of familial cancer conducted in Connecticut showed significant excesses of central nervous system tumors and of leukemia and lymphoma and nonsignificant excesses of cancers of the breast and skin in families of cases, particularly those with medulloblastoma, compared to controls.[16]

In the last-mentioned study, 643 children were identified whose central nervous system tumor had been reported to the Connecticut Tumor Registry since 1935. Two age-matched controls were identified for each of 180 randomly selected cases. These served as controls for all 643 cases. Cancer in parents, siblings, and offspring were identified from the Connecticut Tumor Registry by matching names and birth dates for parents, names and ages for siblings, and names for offspring after allowing that offspring should be 15–60 years younger than the cases or controls. The authors

Table 5. Matched Odds Ratios and 95% Confidence Limits for Birth Defects in Maternal and Paternal Relatives, by Gender

Relatives	Boys		Girls		Total	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Mother*						
Any defect	14	32	16	25	30	57
No defect	188	573	143	455	331	1028
OR (95% CL)	1.34 (0.70, 2.56)		2.00 (1.04, 3.84)		1.63 (1.03, 2.57)	
Maternal grandmother and great grandmothers†						
Any defect	8	14	9	10	17	24
No defect	168	538	136	423	304	961
OR (95% CL)	1.71 (0.69, 4.24)		2.70 (1.10, 6.65)		2.15 (1.14, 4.06)	
Maternal grandfather and great grandfathers†						
Any defect	3	11	3	5	6	16
No defects	168	499	125	398	293	897
OR (95% CL)	0.93 (0.25, 3.51)		2.05 (0.40, 10.4)		1.26 (0.46, 3.43)	
Father*						
Any defect	9	39	12	37	21	76
No defect	186	550	143	428	329	978+
OR (95% CL)	0.67 (0.31, 1.42)		1.00 (0.51, 1.97)		0.83 (0.50, 1.37)	
Paternal grandmother and great grandmothers†						
Any defect	3	10	1	6	4	16
No defect	156	441	128	366	284	807
OR (95% CL)	0.73 (0.20, 2.73)		0.41 (0.05, 3.46)		0.61 (0.20, 1.85)	
Paternal grandfather and great grandfathers†						
Any defect	3	12	4	4	7	16
No defect	143	397	108	343	251	740
OR (95% CL)	0.67 (0.19, 2.37)		2.74 (0.60, 12.5)		1.14 (0.46, 2.81)	
Any relative						
OR (95% CL)	1.23 (0.77, 1.97)		1.52 (0.94, 2.45)		1.37 (0.98, 1.91)	

OR: odds ratio; CL: confidence limits.

* Any mother or father with unknown or missing information was excluded.

† Cases or controls were excluded for which information on birth defects was missing for 50% or more relatives. Crude frequencies indicate distribution prior to excluding sets for cases with such missing data for relatives.

state that these methods fail to identify cancer in relatives who lived or moved out of state or in sisters who marry and change their names, but that these factors were not likely to differ between cases and controls. However, another source of loss in identifying cancer in relatives might well be differential between cases and controls. Specifically, female cases and controls who marry and change their names might pose difficulties in matching by name to their offspring. Because cases may have been more likely to have disabilities resulting from their disease or not to survive until adulthood, they are less likely than controls to marry, change their names, and have children. Thus, the underascertainment of tumors in relatives would be greater in controls, which could result in an overestimation of the OR.

In addition, although a number of anecdotal reports and familial and case–control studies support the Connecticut findings, most of these studies refer to brain tumors in adults, whose clinical and epidemiologic characteristics are known to differ greatly from those occurring in childhood. Unfortunately, in the current study, data were not available on cancer occurrence in siblings of cases and controls or in siblings of parents of cases and controls. Therefore, an underascertainment of tumors in relatives was also likely in the current study but was not likely to have differed between case and control families.

Some studies have shown that children with brain tumors are more likely than controls to have congenital malformations[30] or to have a sibling who died with a brain tumor,[18,19] but these are associations we could not evaluate.

Even though this case–control study appears to be the largest one to date to examine the contribution of

Table 6. Matched Odds Ratios and 95% Confidence Limits for History of Birth Defects in Relatives, Stratified by Type and Site of Brain Tumor in Cases

	Maternal relatives*		Paternal relatives*	
	OR	*95% CL*	*OR*	*95% CL*
Type of brain tumor in case				
Astrocytoma (n = 169 cases)	1.20	0.67, 2.15	1.17	0.65, 2.10
Medulloblastoma (n = 61 cases)	1.29	0.49, 3.41	0.19	0.03, 1.51
Other (n = 132 cases)	2.37	1.25, 4.53	0.87	0.38, 2.03
Location of brain tumor in case				
Supratentorial (n = 151 cases)	1.17	0.59, 2.31	1.11	0.56, 2.20
Infratentorial (n = 193 cases)	1.76	1.06, 2.93	0.69	0.35, 1.34
Other (n = 18 cases)	2.18	0.53, 9.05	2.09	0.30, 14.7
Any type or site	1.56	1.06, 2.30	0.90	0.57, 1.43

OR: odds ratios; CL: confidence limits.

* Cases or controls were excluded in which information was unknown or missing for 4 or more maternal or paternal relatives.

family history of birth defects and tumors to the risk of childhood brain tumors, some CL were wide. The current study had 80% power to detect an OR of 2.5 for all types of birth defects in maternal or paternal relatives and an OR of 1.3 for all tumor types in relatives of cases and controls, although the statistical power was less for specific types of birth defects or tumors. Furthermore, the aggregation of all types of birth defects could result in misclassification and thus bias toward the null and resulting loss of power, if specific types of defects (that were too rare to analyze separately) are truly related to risk of brain tumors or possess a common underlying genetic defect. It also should be noted, however, that the etiology of approximately 65% of all birth defects is unknown,[31] so that identification of such specific defects is at best problematic.

Table 7. Matched Odds Ratios and 95% Confidence Limits for All Tumors in Maternal or Paternal Relatives

	Female relatives*		Male relatives†	
Maternal Relatives	*Cases*	*Controls*	*Cases*	*Controls*
Any affected	149	440	114	325
None affected	165	520	186	572
OR (95% CL)	1.02 (0.78, 1.33)		1.09 (0.83, 1.44)	
	Female relatives‡		**Male relatives§**	
Paternal Relatives	*Cases*	*Controls*	*Cases*	*Controls*
Any affected	106	336	110	259
None affected	176	484	149	485
OR (95% CL)	0.91 (0.68, 1.24)		1.34 (0.98, 1.84)	

OR: odds ratios; CL: confidence limits.

* 12% excluded due to information unknown or missing for > 50% of relatives. All crude frequencies indicate distributions before exclusion of sets in which information on > 50% of relatives was missing for cases.

† 18% excluded due to information unknown or missing for > 50% of relatives.

‡ 24% excluded due to information unknown or missing for > 50% of relatives.

§ 31% excluded due to information unknown or missing for > 50% of relatives.

Still another limitation of the current investigation was that validation of reported birth defects and tumors among family members was not available. This could have resulted in misclassification of family history of birth defects, which might thus lead to further bias toward the null and a resultant loss of statistical power. However, although respondents were not given advance notice of the information to be obtained in the interview (which might have improved the validity of responses), they were provided an opportunity after the interview to obtain and provide supplemental information about family history. If a family did not call the interviewer within 2 weeks after the interview, the interviewer called the family to obtain supplemental family history information, which should have helped to minimize misclassification. Of note is that the crude prevalence of reported birth defects among relatives of cases and controls is of similar magnitude and order of importance to that reported for the nationwide sample of births monitored in the Birth Defects Monitoring Program.[32] Among more distant relatives of both cases and controls, the prevalence of reported defects was less, however, suggesting that some underreporting did occur.

The potential for recall bias is always an important consideration in case–control studies,[33,34] particularly of such serious illnesses as childhood brain tumors, and is often difficult to document with certainty, as was the situation in the current study. Although interviewers were trained not to probe differently for cases than for controls, recall bias in a study such as this might lead to better recall on the part of case parents and result in artifactually raised ORs. However, the lack of such ele-

Table 8. Matched Odds Ratios and 95% Confidence Limits for History of All Tumors in Relatives, Stratified by Type and Site of Brain Tumor in Propositi*

	Maternal relatives		Paternal relatives	
	OR	*95% CL*	*OR*	*95% CL*
Type of brain tumor in propositi				
Astrocytoma (n = 169 cases)	0.80	0.55, 1.19	1.43	0.93, 2.20
Medulloblastoma (n = 61 cases)	1.37	0.64, 2.93	1.46	0.70, 3.04
Other (n = 132 cases)	1.62	1.03, 2.56	1.07	0.65, 1.77
Location of brain tumor in propositi				
Supratentorial (n = 151 cases)	1.05	0.70, 1.59	1.09	0.69, 1.73
Infratentorial (n = 193 cases)	1.18	0.80, 1.74	1.46	0.97, 2.20
Other (n = 18 cases)	1.21	0.35, 4.19	1.51	0.34, 6.73

OR: odds ratios; CL: confidence limits.

* Cases and controls were excluded if information was unknown for missing for 50% or more of maternal or paternal relatives (n = 133 cases or controls excluded from maternal relatives analysis; 278 cases or controls excluded from paternal relatives analysis).

vations for family history of epilepsy, for paternal family history of birth defects, and largely for any family history of tumors (particularly of the Li-Fraumeni syndrome tumors) argues against recall bias as a major factor in the results of this study.

Finally, it is also possible that the findings of no difference in the frequencies of all or specific types of tumors in the families of cases and controls could be due to differences in ages of the relatives in the two groups, resulting in different lengths of time for oppor-

Table 9. Matched Odds Ratios and 95% Confidence Limits for Leukemia, Lymphoma, Breast Cancer, or Brain Tumors in Parents and Maternal and Paternal Relatives of 361 Brain Tumor Cases and 1083 Matched Controls*

	Maternal relatives				Paternal relatives			
	Females		*Males*		*Females*		*Males*	
Type of tumor	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Brain								
Any affected	4	11	6	12	5	14	1	10
None affected	310	949	294	885	275	801	258	734
OR	1.06		1.30		1.02		0.21	
(95% CI)	(0.34, 3.33)		(0.46, 3.67)		(0.36, 2.88)		(0.03, 1.69)	
Breast								
Any affected	44	138	2	2	26	73	0	3
None affected	270	822	298	895	254	742	259	741
OR	0.98		2.71		1.07		0	
(95% CI)	(0.67, 1.42)		(0.38, 19.4)		(0.66, 1.72)		(—, —)	
Leukemia/lymphoma								
Any affected	8	15	5	11	5	20	7	11
None affected	306	945	295	886	275	795	252	733
OR	1.43		1.36		0.77		2.23	
(95% CI)	(0.61, 3.39)		(0.45, 4.11)		(0.28, 2.09)		(0.77, 6.47)	
Brain, breast, leukemia, lymphoma, Hodgkin's disease, or lymphosaroma								
Any affected	53	165	15	29	35	104	8	26
None affected	261	795	285	868	245	711	251	718
OR	0.96		1.40		1.00		0.87	
(95% CI)	(0.68, 1.36)		(0.72, 2.71)		(0.66, 1.51)		(0.38, 2.03)	

OR: odds ratios; CL: confidence limits.

* Cases and controls were excluded if information was unknown or missing for 50% or more of maternal or paternal relatives (n = 133 cases or controls excluded from maternal relatives analysis; 280 cases or controls excluded from paternal relatives analysis). When missing information was partitioned by gender, 173 maternal female and 250 maternal male relatives were excluded from the analysis; 320 female paternal and 412 male paternal relatives were excluded. Crude frequencies indicate distributions before exclusion of sets in which 50% or more of data for relatives of cases was missing.

tunity to develop tumors. Unfortunately, we did not have information on age at death of all relatives. However, that mothers and fathers of cases and controls were of very similar ages provides some reassurance in this regard.

In conclusion, the findings of the current study largely indicate that a family history of birth defects or tumors does not occur more frequently among families of children with brain tumors than among families of normal controls, with the possible exception of a modest increase of birth defects (of all types) among maternal relatives. These findings should, for the most part, provide some reassurance to families about the contribution of family history to the risk of childhood brain tumors.

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Appendix

Table A1. Types of Birth Defects in Maternal Relatives

	Numbers of affected relatives			
	*Female relatives**		*Male relatives**	
Type of birth defect	*Cases*	*Controls*	*Cases*	*Controls*
Ears/congenital deafness	3	2	1	1
Vertebral/back/curvature of spine	7	8	1	1
Eye (including blindness and reduced vision)	7	7	0	1
Cleft lip or palate	2	2	0	0
Congenital heart disease	1	7	1	6
Polydactyly/other digit	4	13	1	4
Von Recklinghausen's neurofibromatosis	2	0	0	0
Absent/extra/deformed kidney	3	7	0	2
Club foot	0	2	1	1
Digestive system	0	2	0	1
Other urogenital	3	0	0	0
Other	15	33	3	2

* Total maternal female relatives studied = 1289 for cases, 3890 for controls; total maternal male relatives studied = 880 for cases, 2644 for controls.

Table A2. Types of Tumors in Maternal and Paternal Relatives

	Numbers of affected relatives							
	Maternal relatives				*Paternal relatives*			
	Female relatives		*Male relatives*		*Female relatives*		*Male relatives*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Brain	3	11	6	14	5	16	1	12
Leukemia/lymphoma/lympho-sarcoma	8	21	6	17	7	21	8	14
Breast	40	132	1	1	27	78	0	3
Ovary, cervix, uterus	42	130	—	—	31	83	—	—
Male reproductive	—	—	20	43	—	—	19	44
Respiratory	6	20	21	65	2	15	20	38
Digestive	37	122	41	111	31	110	42	104
Urinary tract	5	6	4	5	2	8	7	7
Throat, larynx	0	13	6	20	0	6	4	18
Thyroid, other gland	2	8	1	4	2	4	0	0
Bone	2	6	1	9	1	8	3	5
Limbs	2	2	1	2	2	5	0	4
Skin	19	40	21	61	15	26	25	36
Back/spine	3	2	2	1	0	2	0	2
Other	8	10	6	12	5	11	3	13
Total relatives studied*	1180	3593	874	2589	1063	3214	764	2234

* All relatives with unknown information are excluded.