© International Epidemiological Association 1998 Printed in Great Britain International Journal of Epidemiology 1998;27:579–586

An international case-control study of adult glioma and meningioma: the role of head trauma

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Background Increased brain tumour risk after head trauma suggested by case reports and clinical series has been previously studied epidemiologically with mixed results. An international multicentre case-control study investigated the role of head trauma from injury or sports participation in adult brain tumour risk.

Methods In all, 1178 glioma and 330 meningioma cases were individually or frequency matched to 2236 controls. Only exposures that occurred at least 5 years before diagnosis and head injuries that received medical attention were considered.

Results Risk for ever having experienced a head injury was highest for male meningiomas (odds ratio [OR] = 1.5, 95% confidence interval [CI] : 0.9–2.6) but was lower for 'serious' injuries, i.e. those causing loss of consciousness, loss of memory or hospitalization (OR = 1.2, 95% CI : 0.6–2.3). Among male meningiomas, latency of 15 to 24 years significantly increased risk (OR = 5.4, 95% CI : 1.7–16.6), and risk was elevated among those who participated in sports most correlated with head injury (OR = 1.9, 95% CI : 0.7–5.3). Odds ratios were lower for male gliomas (OR = 1.2, 95% CI : 0.9–1.5 for any injury; OR = 1.1, 95% CI : 0.7–1.6 for serious injuries) and in females in general.

Conclusions Evidence for elevated brain tumour risk after head trauma was strongest for meningiomas in men. Findings related to sports should be interpreted cautiously due to cultural variability in our data and our lack of complete data on physical exercise in general which appeared to be protective.

Keywords Head injuries, brain injuries, brain neoplasms, sports medicine

Accepted 2 December 1997

Head trauma as a risk factor for adult brain tumour has been a controversial topic in medicine for over a century. Although early case reports and clinical series are often vague and difficult to evaluate,[1] some are quite striking, such as the case reported in which a piece of wire was extracted from the centre of a meningioma, presumably driven in 20 years earlier by an explosion in which the patient had been involved.[2] In their classic study, Cushing and Eisenhard reported a history of head trauma in one-third of their brain tumour patients which led them to postulate a relationship between head trauma and subsequent brain tumour development.[3]

Few epidemiological studies have analysed head trauma and brain tumour risk. Case-control studies have found meningiomas to be associated with serious head injuries or head injuries requiring medical attention,[4–6] and, in men, with increasing number of such injuries.[6] In the only study that included data related to contact sports, increased risk of meningioma was observed among boxers.[5] Other case-control studies have found no relationship between serious head injury and meningioma but included very few cases.[7,8] One case-control study of glioblastoma reported a relative risk of 10.6 for severe head injury over age 15 but had several methodological limitations, including the fact that it was not population-based.[9] Several other studies of gliomas in adults have not observed a head

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trauma association,[6,7,10–12] and studies of head trauma and childhood brain tumours, which are primarily gliomas, have produced conflicting results.[13–17] Two additional adult brain tumour studies that investigated head trauma are part of the international collaborative study and are thus not detailed here.[18,19]

We analysed data from a multicentre international case-control study of adult brain tumour involving 1509 cases from eight study centres. Specifically, we tested the hypotheses that adult glioma and meningioma risk is related to a history of (1) medically-treated head injuries, and (2) participation in sports that may result in a serious head blow or repetitive head trauma (such as boxing).

Methods

Study design

Data originated from a multicentre international case-control study conducted to investigate risk factors for primary adult brain tumour, specifically glioma and meningioma. Investigators from eight centres in six countries (Adelaide and Melbourne, Australia; Grenoble, France; Heidelberg, Germany; Toronto and Winnipeg, Canada; Stockholm, Sweden; and Los Angeles, California, USA) collaborated to develop the international protocol, design a standardized questionnaire, and make decisions regarding study design, field work, and analysis. The study was coordinated by the International Agency for Research on Cancer (Lyon, France), where data from all centres were compiled and merged into combined data sets. In all, 729 male cases from seven centres and 779 female cases from eight centres were included. Inclusion periods varied slightly by study centre, with an average selection period of 2 years. The range of diagnosis ages was 20–79 years; most cases were diagnosed in the late 1980s, however diagnosis years ranged from 1984 to 1992. Both individual (Grenoble, Los Angeles, Melbourne, Stockholm, Winnipeg) and frequency (Adelaide, Heidelberg, Toronto) matching by age and gender was used. Some centres also matched on race or geographical region. At seven centres (all but Stockholm), proxy respondents were used for index subjects unavailable for interview (325 cases, 65 controls).

Exposure variables

Information was sought only on medically treated head injuries. A subgroup, 'serious injuries,' was defined as medically-treated injuries causing loss of consciousness, loss of memory or requiring hospitalization. Indicator variables representing three exposure periods (5–14, 15–24, and ≥25 years before diagnosis) were created for the analysis of latency; subjects who had experienced more than one injury could be exposed in more than one period. Although questionnaires were similar for all centres, questions about sports participation varied substantially by centre. Each centre compiled a list of sports common to the geographical region (therefore each centre's list of sports was different), and these sports were explicitly asked about; however some centres also recorded responses on additional sports participation. For analysis purposes, subjects were considered to have sports participation exposure if, at least 5 years before diagnosis, they participated in any sport on that centre's list or if they participated in another sport that was then added to the centre's list. Correlation with head injuries (not necessarily caused by the sport) was computed for each sport among those subjects (both cases and controls) with exposure data available for that sport; sports were then trichotomized by degree of correlation with head injuries (high = $r \geq 0.10$, moderate = $0.01 < r < 0.10$, low = $r \leq 0.01$). Education level was used as a measure of socioeconomic status (SES) according to a seven-point scale: 7 = college degree; 6 = some college; 5 = technical training, apprenticeship, or adult classes; 4 = high school graduate; 3 = some high school; 2 = 7–9 years of schooling; 1 = <7 years of schooling. Subjects who first had a head or neck x-ray at least 5 years before diagnosis were considered to be exposed to head x-rays.

Statistical analysis

Maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (CI) were computed using both conditional and, to minimize the problem of missing data within strata, unconditional logistic regression. For individually matched studies, strata for conditional analyses were defined by matched sets; for frequency matched studies, strata were defined by centre, gender and 5-year age groups. Unconditional analyses were stratified by centre, gender, and 5-year age groups, and all controls were used for tumour-specific analyses. Since estimates were similar using both methods, only results from conditional analyses are reported. Risk estimates and CI from random effects models[20] (with centre as the random effect) are reported for exposure effects that signicantly differed by centre, based on the likelihood ratio tests;[21] otherwise, results from fixed effects models are reported. Correlations between participation in individual sports and history of head injury were calculated using a modification of the Cramér coefficient,[22] denoted Φ_2[23] in this paper. The three head injury latency indicators were used in a multiple logistic regression to assess their independent effects on risk. Similarly, multiple logistic regression was used to test for independent effects of participation in each of three categories of sports grouped by correlation with head injuries. In this paper, multiple logistic regression (involving a single outcome) is referred to as 'multivariate analysis.' Hypothesis testing was two-sided.

For analyses involving head injuries occurring ≥25 years before diagnosis, subjects <25 years old at reference date were excluded. Also, subjects with no opportunity to respond that they had participated in a particular sport because the sport was not on their centre's list were excluded from analyses involving that sport. All analyses excluded exposures occurring within the 5-year period before diagnosis. Subjects with missing data (mostly cases) were excluded from analyses involving those data. Other methods of handling missing data were considered (defining as unexposed, treating as a separate exposure group) but had no effect on results. Analyses were performed both including and excluding proxy data.

Results

Distributions of tumour morphology and topography by major tumour type are shown in Table 1. Distributions by centre, gender, age group, and education for each of the two major types are shown in Table 2. Cases were less educated than controls; this was a significant trend for male gliomas ($P = 0.007$), which contrasts with a clear trend of increasing incidence of male

Table 1 Distribution of tumour classifications, multicentre international case-control study of adult brain tumours, 1984–1991

Morphology	No. cases	(%)	Topography	No. cases	(%)
Gliomas			**Gliomas**		
Glioma, NOS	58	(5)	Cerebrum	59	(5)
Gliomatosis cerebri	1	(0.1)	Frontal lobe	324	(28)
Mixed glioma	50	(4)	Temporal lobe	263	(22)
Subependymal giant cell astrocytoma	2	(0.2)	Parietal lobe	208	(18)
Choroid plexus papilloma	1	(0.1)	Occipital lobe	35	(3)
Ependymoma, NOS	15	(1)	Ventricle, NOS	24	(2)
Ependymoma, anaplastic type	1	(0.1)	Cerebellum, NOS	22	(2)
Colloid cyst	1	(0.1)	Brainstem	18	(2)
Astrocytoma, NOS	297	(25)	Other parts of the brain	75	(6)
Astrocytoma, anaplastic type	79	(7)	Brain, NOS	149	(13)
Protoplasmic astrocytoma	4	(0.3)	Cranial nerve	1	(0.1)
Gemistocytic astrocytoma	15	(1)			
Fibrillary astrocytoma	12	(1)			
Pilocytic astrocytoma	12	(1)			
Spongioblastoma polare	1	(0.1)			
Xanthoastrocytoma	3	(0.3)			
Astroblastoma	12	(1)			
Glioblastoma, NOS	541	(46)			
Giant cell glioblastoma	2	(0.2)			
Glioblastoma with sarcomatous component	3	(0.3)			
Oligodendroglioma, NOS	58	(5)			
Oligodendroglioma, analplastic type	4	(0.3)			
Medulloblastoma, NOS	5	(0.4)			
Meningiomas			**Meningiomas**		
Meningioma, NOS	199	(60)	Cerebral meninges	330	(100)
Meningotheliomatous meningioma	48	(15)			
Fibrous meningioma	36	(11)			
Psammomatous meningioma	4	(1)			
Angiomatous meningioma	1	(0.3)			
Hemangiopericytic meningioma	5	(2)			
Transitional meningioma	38	(12)			

glioma (as well as all histologies combined) with increasing SES observed in Los Angeles County.[6] Since education, as a measure of SES, is likely to be related to medically-treated head injuries as well as sports participation, it was considered a potential confounder in all analyses.

Univariate results of medically-treated head injury analyses are presented in Table 3. Although male meningioma cases were 1.5 times more likely than controls to have sustained a medically-treated injury, this difference was not statistically significant and risk decreased to 1.15 when restricted to serious head injuries. For gliomas, OR for any injury and for serious injuries were not significantly different from 1.0. For female gliomas, OR significantly varied by study centre ($P = 0.02$). In general, cases were more likely than controls to have experienced more than one injury (OR = 1.4, 95% CI : 1.0–2.0 for gliomas and meningiomas, males and females combined). Considering all subjects, men were twice as likely as women to have ever had any head injury (31% versus 16%) or a serious injury (19% versus 9%), and among women with head injuries, brain tumour risk was not significantly elevated. Age at first injury (child versus adult) had no effect on risk (data not shown). In a multivariate analysis of latency (i.e. length of period from injury to tumour diagnosis), the only significant increase in risk was among male meningioma cases, who were five times more likely than controls to have sustained a head injury 15–24 years before diagnosis ($P = 0.004$; Table 4). There were no significant increases in risk for any latency period for gliomas or for female meningiomas.

Adjusting for education did not appreciably affect risk estimates. Head x-ray exposure was also considered for confounding effects; however, in these data, controls were more likely to have been exposed to head x-rays, even after controlling for education. Thus, head x-ray exposure was not a positive confounder. Excluding proxy data had little effect on risk estimates.

Weak inverse associations between risk of brain tumour and sports participation ≥5 years before diagnosis were observed (Table 5); this association was statistically significant for gliomas in men. Level of involvement, measured by total hours of participation, had no effect on risk (not shown). In a multivariate analysis of participation in sports 'groups' defined by

Table 2 Demographics by tumour type, multicentre international case-control study of adult brain tumours, 1984–1991

	Gliomas				Meningiomas			
	No. cases	(%)	No. controls[a]	(%)	No. cases	(%)	No. controls[a]	(%)
Study centre								
Adelaide	110	(9)	417	(21)	61	(18)	371	(33)
Grenoble	61	(5)	122	(6)	53	(16)	108	(10)
Heidelberg	115	(10)	417	(21)	81	(25)	389	(35)
Los Angeles	93	(8)	93	(5)	0	(0)	0	(0)
Melbourne	412	(35)	412	(21)	0	(0)	0	(0)
Stockholm	153	(13)	153	(8)	80	(24)	80	(7)
Toronto	158	(13)	221	(11)	25	(8)	115	(10)
Winnipeg	76	(7)	152	(8)	30	(9)	60	(5)
Gender								
Male	638	(54)	1038	(52)	91	(28)	481	(43)
Female	540	(46)	949	(48)	239	(72)	642	(57)
Age								
20–24	22	(2)	20	(1)	1	(0.3)	2	(0.2)
25–34	176	(15)	223	(11)	13	(4)	39	(3)
35–44	232	(20)	329	(17)	50	(15)	178	(16)
45–54	231	(20)	438	(22)	82	(25)	274	(24)
55–64	298	(25)	506	(25)	96	(29)	326	(29)
65 +	219	(19)	471	(24)	88	(27)	304	(27)
Education								
College degree	165	(14)	295	(15)	20	(6)	130	(12)
Some college	138	(12)	199	(10)	20	(6)	80	(7)
Adult classes[b]	371	(32)	698	(35)	119	(36)	414	(37)
High school graduate	81	(7)	107	(5)	17	(5)	43	(4)
Some high school	149	(13)	198	(10)	43	(13)	115	(10)
7–9 years schooling	214	(18)	427	(22)	92	(28)	303	(27)
<7 years schooling	46	(4)	53	(3)	16	(5)	35	(3)

[a] Number of controls available for tumour-specific analyses (all controls from centres with frequency-matched design, individudally-matched controls from centres with individually-matched designs).

[b] Includes technical training and apprenticeships.

Table 3 Medically treated head injuries at least 5 years before diagnosis, conditional univariate analysis, multicentre international case-control study of adult brain tumours, 1984–1991

	Gliomas						Meningiomas					
	No. cases	(%)	No. controls	(%)	OR	(95% CI)	No. cases	(%)	No. controls	(%)	OR	(95% CI)
Ever any injury												
Males	210	(33)	309	(30)	1.18	(0.94–1.48)	26	(29)	125	(26)	1.49	(0.86–2.57)
Females	87	(16)	165	(17)	1.03	(0.42–2.55)[a]	33	(14)	114	(18)	0.83	(0.54–1.28)
Ever serious[b]												
Males	127	(20)	197	(19)	1.13	(0.87–1.48)	12	(13)	77	(16)	1.15	(0.57–2.34)
Females	52	(10)	89	(9)	1.07	(0.74–1.56)	17	(7)	59	(9)	0.79	(0.45–1.39)
No. of injuries												
Males												
1	156	(25)	249	(24)	1.09	(0.85–1.39)	21	(23)	104	(21)	1.45	(0.80–2.62)
>1	52	(8)	60	(6)	1.52	(1.00–2.32)	5	(5)	23	(5)	1.67	(0.56–4.98)
Females												
1	70	(13)	146	(15)	0.89	(0.64–1.23)	29	(12)	99	(15)	0.87	(0.55–1.36)
>1	17	(3)	19	(2)	1.70	(0.84–3.45)	4	(2)	15	(2)	0.64	(0.20–2.05)

[a] Based on random effects model; $P = 0.02$ for the test of exposure/centre interaction using the likelihood ratio test; centre-specific OR (95% CI) were as follows: Adelaide = 0.99 (0.44–2.22), Grenoble = 2.00 (0 50–8.00), Heidelberg = 0.37 (0.14–0.99), Los Angeles = 0 46 (0 22–0.96), Melbourne = 1.88 (1.02–3.44), Stockholm = 1.60 (0.52–4.89), Toronto = 1.77 (0.52–6.05), Winnipeg = 0.82 (0.28–2.41).

[b] Loss of consciousness, loss of memory, or hospitalization required.

Table 4 Medically treated head injuries at least 5 years before diagnosis, multivariate conditional analysis of latency periods, multicentre international study of adult brain tumours, 1984–1991

	Gliomas						Meningiomas					
Years since injury[a]	No. cases	(%)	No. controls	(%)	OR	(95% CI)	No. cases	(%)	No. controls	(%)	OR	(95% CI)
Males												
5–14	41	(6)	65	(6)	0.97	(0.62–1.52)	6	(7)	20	(4)	1.71	(0.60–4.87)
15–24	64	(10)	95	(9)	0.97	(0.67–1.39)	7	(8)	18	(4)	5.35	(1.72–16.62)
≥25	130	(21)	181	(18)	1.28	(0.98–1.67)	16	(18)	95	(20)	1.17	(0.62–2.21)
Females												
5–14	34	(6)	51	(5)	1.17	(0.72–1.90)	10	(4)	34	(5)	0.73	(0.34–1.55)
15–24	29	(5)	43	(5)	1.06	(0.63–1.78)	8	(3)	22	(3)	0.99	(0.42–2.33)
≥25	37	(7)	82	(9)	0.91	(0.60–1.40)	18	(8)	66	(10)	0.79	(0.45–1.40)

[a] Groups are not mutually exclusive; subjects <25 years old at reference are excluded; reference group is subjects who did not sustain a head injury requiring medical treatment ≥5 years prior to diagnosis.

Table 5 Sports participation at least 5 years before diagnosis, conditional analysis, multicentre international case-control study of adult brain tumours, 1984–1991

	Gliomas						Meningiomas					
	No. cases	(%)	No. controls	(%)	OR	(95% CI)	No. cases	(%)	No. controls	(%)	OR	(95% CI)
All sports[a]												
Males	349	(56)	649	(63)	0.75	(0.60–0.93)	56	(62)	304	(63)	0.90	(0.53–1 52)
Females	70	(13)	160	(17)	0.78	(0.55–1.11)	39	(16)	127	(20)	0.69	(0.45–1.07)
Boxing												
Males	31	(5)	72	(7)	0.80	(0.51–1.27)	2	(2)	40	(8)	0.40	(0.09–1.81)
Females	1	(0.2)	0	(0)		–	0	(0)	0	(0)		–
Rugby or football[b]												
Males	168	(27)	298	(29)	0.77	(0.59–1.01)	12	(14)	110	(23)	0.77	(0.33–1.81)
Females	10	(2)	17	(2)	0.71	(0.32–1.56)	3	(1)	3	(0.5)	3.57	(0.70–18.27)

[a] A subject is exposed if he reported participation in any sport on that centre's list or if he participated in another sport that was then added to the centre's list.
[b] American, Australian rules or Gaelic football

degree of correlation with head injuries (Table 6), no significant risk relationships were observed; however, risk was elevated for male meningioma cases who participated in sports most highly correlated with head injuries (Table 7). A much lower elevated risk was evident for female glioma cases who participated in sports highly correlated with head injuries. Education was not a confounder. Unconditional analyses and the exclusion of proxies produced similar results, although the multivariate sports group analysis was difficult to evaluate due to sparse data.

Discussion

The evidence that head injuries are a risk factor for brain tumour is strongest for meningiomas. Furthermore, almost all anecdotal cases have involved meningiomas.[24] In the present study, risk of ever having had a head injury was highest for meningiomas in males, particularly when injuries were sustained 15–24 years before diagnosis. No such increased risk was observed for female meningiomas or for either gender when analyses were restricted to serious injuries (the subset of medically-treated injuries causing loss of consciousness, loss of memory or requiring hospitalization), suggesting recall bias as a possible explanation for the findings relating to any injury. Yet if recall bias occurred, we might expect elevated risks regardless of tumour type since it is not likely that lay people are aware of the meningioma association. In our data, the only potential risk factor that resulted in elevated risk for all tumour types was number of injuries among males. In studies of differential recall of exposures related to birth outcome, it has been shown that spurious inferences occur only under extreme conditions and that concerns about recall bias are overrated.[25,26] Another possible reason for a lack of an association for serious injuries is that we excluded (by the way respondents were queried) all injuries that were not treated medically. In an earlier study of meningiomas in men in Los Angeles County, a sizeable proportion of injuries that had caused loss of consciousness or a permanent scar had not been treated medically.[5]

The interval between head injury and tumour diagnosis noted in published case reports has varied widely and ranges from 1 to 67 years. Our finding of a strong association of meningioma with trauma 15–24 years before diagnosis is consistent with a previous study of male meningioma cases in Los Angeles County, in which risk was significantly associated with head injuries experienced ≥20 years before diagnosis.[6] Latency periods of this length are feasible for meningiomas, which are usually benign, slow-growing tumours.[27]

Table 6 Correlations between reported head injuries and individual sports, multicentre international case-control study of adult brain tumours, 1984–1991[a]

Individual sport	Centres[b]	No. subjects[c]	Φ_2[d]
Weight lifting	G	316	0.16
Canoeing/kayaking	G	318	0.15
Mountain climbing	G	320	0.15
Horseback riding	G	318	0.13
Snow skiing	G	325	0.12
Australian rules football	A,M	1389	0.12
Boxing	all	3657	0.12
Auto racing	G	316	0.11
Gymnastics	G	317	0.11
Scuba diving	G	318	0.10
Volleyball	W,T,L	904	0.10
Parachuting/paragliding/hang gliding	G	317	0.10
American football	W,T,L	904	0.09
Soccer	all	3670	0.09
Swimming	G	319	0.06
Caving	G	318	0.06
Martial arts	G,S,W,T,A,M,L	3063	0.06
Rugby	G,H,W,T,A,M	3467	0.06
Handball/squash	G,H,S,W,T	2084	0.04
Figure skating	W,T	718	0.04
Biking	G	317	0.04
Wrestling	H,S,W,T,A,M,L	3337	0.03
Motocross	G	316	0.03
Ice hockey	G,H,S,W,T,A,L	2854	0.02
Field hockey	H,S,W,T,L	1232	0.02
Basketball	S,W,T,L	1358	0.02
Running	G	316	0.01
Lacrosse	W,T	718	0.006
Baseball/softball	W,T,L	904	0.006
Board diving	M	803	−0.006
High jumping	W,T	718	−0.02
Water skiing	M	803	−0.03
Discus throwing	G	317	−0.03
Acrobatics	G	316	−0.03
Flying	G	316	−0.03
Water polo	W,T	718	−0.04
Skating	G	316	−0.05

[a] Solid lines represent cutpoints for categorical analysis.

[b] G = Grenoble, H = Heidelberg, S = Stockholm, W = Winnipeg, T = Toronto, A = Adelaide, M = Melbourne, L = Los Angeles.

[c] Not all subjects within centres were asked about sports on the centres' lists (some sports were added to lists in the course of interviewing).

[d] Measure of correlation between two dichotomous variables.

Problems inherent in analysing risk factors for male meningioma include the rarity of the disease, the low incidence in males, and the fact that many registries still do not include benign brain tumours. Despite data from six studies conducted in five different countries (Melbourne and Los Angeles did not include meningiomas), exposure prevalence was not high enough to enable certain analyses or to achieve statistical significance for the relative risks observed. For example, risk of sustaining more than one injury was highest among male meningiomas (OR = 1.7) but was based on only five cases (95% CI : 0.6–5.0).

Assessing the effect of head trauma that may result from sports participation proved difficult, mainly because of cultural differences in popularity and definitions of different sports. Not only did each centre use a different sports list, depending on the area's most popular sports, but different activities may share a common sports name among regions. For example, 'football' can be synonomous with 'soccer,' depending on geographical region. Furthermore, some centres asked about sports in general while others restricted the questioning to 'contact' sports, which assumes that contact sports are most likely to result in

Table 7 Participation in sports at least 5 years before diagnosis grouped by degree of correlation with reported head injuries, conditional multivariate analysis, multicentre international case-control study of adult brain tumours, 1984–1991

	Gliomas						Meningiomas					
Group[a]	No. cases	(%)	No. controls	(%)	OR	(95% CI)	No. cases	(%)	No. controls	(%)	OR	(95% CI)
Males												
High	156	(25)	283	(28)	0.85	(0.61–1.19)	21	(24)	116	(24)	1.91	(0.69–5.29)
Medium	211	(34)	407	(40)	0.76	(0.56–1.02)	41	(45)	185	(39)	0.99	(0.43–2.28)
Low	10	(2)	22	(4)	0.50	(0.21–1.22)	3	(8)	12	(9)	1.08	(0.27–4.35)
Females												
High	16	(3)	25	(3)	1.19	(0.54–2.62)	11	(5)	31	(5)	0.78	(0.29–2.09)
Medium	43	(8)	77	(8)	0.70	(0.41–1.19)	20	(8)	41	(7)	0.90	(0.33–2.45)
Low	10	(3)	19	(4)	0.80	(0.35–1.80)	2	(3)	7	(5)	0.83	(0.14–4.99)

[a] Not mutually exclusive; based on correlation (high = $\Phi_2 \geq 0.1$, medium = $0.01 < \Phi_2 < 0.10$, low = $\Phi_2 \leq 0.01$) with head injuries. Number of centres with sports in high, medium, and low groups are 8, 7, and 5, respectively. Reference group is subjects that did not participate in any sport on the centre's list and did not report participation in any other sport that was then added to the centre's list.

head injuries. This premise is probably false, the most notable exception being horseback riding. We were therefore forced to use data from the case-control study itself to correlate head injuries with specific sports, and our data did not link the head injuries reported with sports participation. Also, because some centres asked only about contact sports, we were unable to control for the potential confounding effect of general physical activity. Finally, the only method available for evaluating level of participation was total hours of participation rather than a skill level, such as professional or amateur, which may more accurately reflect intensity of participation. Given these weaknesses, a notable observation was that, among male meningiomas only, risk was elevated (although not significant) for participation in sports most correlated with head injuries.

The fact that epidemiological studies, including this one, have not shown a convincing causal relationship between head trauma and brain tumour development may reflect the deficiencies of studies investigating this association and the fact that the association, if one exists, is not a direct one. Experimental data have shown that trauma can act as a cocarcinogen in the presence of an initiating carcinogen.[28–33] For example, among offspring of pregnant rats injected with ethylnitrosourea, a significant increase in gliomas in the region of a brain injury induced at one month of age was observed compared to a non-injured control group;[33] it was hypothesized that cells damaged by the initiating carcinogen proliferated as a natural result of the trauma, leading to tumour formation. Future studies of head trauma and brain tumour risk should consider potential initiators of carcinogenesis, such as nitrite from cured meats, as modifiers of the trauma effect on risk of brain tumour.

Our findings suggest that an association between head trauma and brain tumour risk cannot be ruled out and should therefore be further studied. Study designs that consider possible effect modifiers, that minimize recall bias and, for analyses of sports-related head injuries, that effectively control protective effects of exercise are essential. Large study populations are also imperative because of the relatively low prevalence of head injuries and the low incidence of brain tumours, particularly meningiomas for which increased risk was observed in our data.

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