

Incidence of intracranial tumors following hospitalization for head injuries (Denmark)

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The incidence of brain and other intracranial tumors following head trauma was evaluated in a cohort of 228,055 Danish residents hospitalized because of concussion, fractured skull, or other head injury between 1977 and 1992 and followed for an average of eight years (maximum, 17 years). Traffic accidents, falls, and sports-related incidents were the usual causes of the injury. Malignant and benign neoplasms were identified by linking the study roster with records of the Danish Cancer Registry for the years 1977 to 1993. This approach precludes differential reporting of injuries by study participants as an explanation for any associations seen. Intracranial tumors of the nervous system occurred more often than expected based on incidence rates for the Danish population; however, most of the excess occurred during the first year after the injury and likely was due to the detection of tumors that were present before the injury occurred. Excluding the first year of follow-up, the standardized incidence ratio (SIR) was 1.15 (95 percent confidence interval [CI] = 0.99-1.32). The same general temporal pattern was seen for the major subtypes of brain tumor as for all types combined. SIRs after the first year were 1.0 for glioma (CI = 0.8-1.2), 1.2 for meningioma (CI = 0.8-1.7), and 0.8 for neurilemmoma (CI = 0.4-1.7). However, hemangioblastoma and hemangioma were more frequent than expected, based on 15 cases (SIR = 2.6, CI = 1.4-4.2). Results indicate that head trauma causes, at most, a small increase in the overall risk of brain tumors during the ensuing 15 years; however, a possible association with intracranial vascular tumors warrants further evaluation. *Cancer Causes and Control* 1998, 9, 109-116

Key words: Brain neoplasms, Denmark, glioma, head trauma, hemangioblastoma, meningioma.

Introduction

The possibility that traumatic injury to the head might play a role in the pathogenesis of brain tumors has been considered for many years, but the issue remains unresolved.¹⁻³ Positive associations between brain tumor incidence and self- or proxy-reported history of head injuries have been observed in case-control studies of

malignant and benign brain tumors in children and adults,^{4,11} and the association did not appear to be attributable to diagnostic X-rays given because of the injury.⁴ Proposed causal mechanisms include injury-induced proliferation of postmitotic cells, increased formation of oxygen-free radicals, and breakdown of the blood-brain

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barrier, resulting in exposure of brain tissue to blood-borne carcinogens.^{7,12-16} However, interpretation of findings from these case-control studies is uncertain because of the possibility, even likelihood, that cases give a fuller accounting than controls of past injuries to the head. In one of the above-mentioned studies,⁸ the positive association disappeared when analysis was restricted to injuries serious enough to warrant hospitalization, possibly because more serious injuries are less prone to differential recall. Evidence of an association with head trauma was not seen in studies that relied on information about head injuries recorded in medical records before brain tumors were diagnosed, but sample sizes were small.^{17,18}

The existence of nationwide registries of hospital discharges and incident cancers in Denmark provided a rare opportunity to assemble a large cohort of persons who had been hospitalized because of head trauma and follow them over time to identify incident tumors of the brain and nervous system. This approach precludes differential reporting as a possible explanation for any associations seen.

Materials and methods

The Hospital Discharge Register, a nationwide registry of hospital discharges for Denmark covering the years 1977-92, was used to identify persons hospitalized because of injuries to the head. In 1979, 99.4 percent of all non-psychiatric admissions in Denmark were included.¹⁹ During the study period, only ward admissions were included. Injuries treated on an outpatient basis were not included until 1994.

Each record in the Register includes the population identification number (a unique identifier assigned to every Danish citizen and to non-citizens holding a residence permit), dates of admission and discharge for the hospitalization, codes for surgical procedures performed, and up to 20 discharge diagnoses. Serious preexisting conditions (e.g., epilepsy) may be listed among discharge diagnoses even if not diagnosed or treated during that particular admission. Discharge diagnoses were coded according to a modified version of ICD-8.²⁰ A total of 232,608 such persons having one or more discharges for a fractured skull (ICD-8 code 800-803), concussion (ICD-8 code 850), or cerebral laceration or contusion (ICD-8 code 851) were identified. Before 1987, modified ICD-8 codes (E-codes) were used for classifying the type of accident resulting in the head injury (e.g., traffic, home, work place, sports, other, nonaccident). From 1987 on, the type of accident was coded according to a Nordic classification of accidents,²¹ which includes information about how and where the injury occurred.

The population identification number was used to link

the roster of individuals ascertained from the Discharge Register with the National Death Certificate file to obtain information about vital status. A total of 4,552 subjects died during the admission for head injury, and one person with a listed age of 110 years was excluded because of suspicion of data error. The remaining 228,055 individuals comprised the study cohort. Person-years (PY) of follow-up were accumulated beginning with the first day of the month following the first hospital discharge for head injury after 1976, and continuing until the earlier of date of death or end of study (31 December 1993). Information about emigration of cohort members from Denmark was not available.

The roster was linked with records of the Danish Cancer Registry for the years 1977-93 to identify incident cases of cancer. The Cancer Registry was established in 1942, and reporting of cancers to the Registry is mandated by law.²² Benign tumors of the nervous system also are reportable and were included in the present study. Since 1978, all tumors in the Cancer Registry have been coded according to both ICD-7²² and ICD-O.²³ Expected numbers of cancers were calculated based on Danish population incidence rates and the observed distribution of PYs, with adjustment for gender, age, and calendar year (five-year intervals). The standardized incidence ratio (SIR) was estimated as the number of cancers observed (Obs) divided by the number expected (Exp). Ninety-five percent confidence intervals (CI) for SIRs were calculated based on the assumption that Obs was distributed as a Poisson random variable.²⁴

Results

The study population was predominantly male (Table 1). Most of the head injuries occurred at a young age, with a median age at the time of injury (or discharge) of 22.5 years. Concussion and fractured skull were, by far, the most common types of injury, together accounting for 97 percent of the total. Traffic accidents, falls, and sports-related incidents were the most common known causes. Epilepsy was listed among the discharge diagnoses for the injury hospitalization for 1,499 persons. There was a total of 1,845,427 PYs of observation, an average of 8.1 years per person (maximum, 17 years).

Linkage with the Danish Cancer Registry identified 7,117 incident cancers of all types combined, which was very close to the number expected based on general population rates (SIR = 1.03, CI = 1.01-1.05) (Table 2). There were 299 tumors of the brain and nervous system, of which 20 involved peripheral nerves outside of the head, 15 were in the spine, and three were pituitary or pineal gland tumors. Of the remaining 261 intracranial tumors, there were 113 gliomas (50 glioblastomas, 44 other astrocytic tumors, six oligodendrogliomas, one ependymoma,

Table 1. Distribution of the cohort of 228,055 former head injury patients by selected characteristics, Denmark

Characteristic	Number	%
Gender		
Male	143,769	63
Female	84,286	37
Age at time of injury or discharge (yrs)		
< 10	36,551	16
10-19	60,228	26
20-29	43,747	19
30-39	26,495	12
40-49	18,328	8
50-59	13,069	6
60-69	11,630	5
70-79	11,078	5
80+	6,929	3
Year of injury or discharge ^a		
1977-86	158,832	70
1987-92	69,223	30
Type of head injury (ICD-8 code ²⁰)		
Fractured skull (800-803) ^b	59,371	26
Concussion (850) ^c	162,117	71
Cerebral laceration and contusion (851) ^d	6,567	3
Type of accident or location of injury ^a		
Traffic	76,459	33
Home	29,563	13
Workplace	6,126	3
Sports	11,060	5
Other or unknown	104,847	46
Epilepsy ^e		
Yes	1,499	1
No	226,556	99

^a Coding scheme for injuries changed in 1987. Prior to 1987, type of accident was coded. After 1986, the classification included location where the injury occurred.

^b With or without a concussion or other head injury.

^c Without fractured skull.

^d Without fractured skull or concussion.

^e Listed as one of the discharge diagnoses for the injury hospitalization.

and 12 of other or unspecified type), 36 meningiomas, 12 neurilemmomas (of which 11 were acoustic neuromas), eight medulloblastomas, and 16 vascular tumors (eight hemangioblastomas, three cavernous hemangiomas, and five hemangiomas, not otherwise specified). The observed number of intracranial tumors of the nervous system was 36 percent greater than expected (SIR = 1.36, CI = 1.20-1.53). Much of the excess occurred during the first year following the injury (SIR = 3.38, CI = 2.59-4.34); the SIR for subsequent years dropped to 1.15 (CI = 0.99-1.32). Of the 62 intracranial tumors diagnosed in the first year of follow-up, 43 were diagnosed during the first six months.

This same general pattern was seen for the major subtypes of brain tumor; that is, an elevated rate during the first year of follow-up and little or no excess in later years (Table 2). This applies both for high-grade, and typically more rapidly growing tumors (such as glioblastoma multiforme and anaplastic astrocytoma), as well as for less aggressive tumors (such as lower-grade astrocytomas, meningiomas, and neurilemmomas). Only the vascular tumors are notably at odds with this pattern; the SIR after the first five years of follow-up was 3.70 (CI = 2.02-6.21). The mean age at diagnosis of the vascular tumors was 34 years, and the average interval from injury hospitalization to vascular tumor diagnosis was 7.7 years. Seven of the eight hemangioblastomas were located in the cerebellum, whereas five of the eight hemangiomas were in the cerebellum, two in the cerebellum, and one in the brain stem.

There was a male predominance of glioma and a female predominance of meningioma, but these patterns were apparent only after the first year of follow-up (Table 3). Variation in the SIR with time since injury was qualitatively similar for males and females. The SIR during the first year after the injury was higher for people who were older at the time of the injury, but a similar gradient was not seen after the first year. There was little difference in results for persons with fractured skulls compared with those with concussions, the two predominant types of injury. Unlike traffic, household, or workplace accidents, sports injuries were not associated with an early excess of intracranial tumors, but the sample size was small; the risk of glioma was especially high among head injury patients who also had been diagnosed with epilepsy. The SIR was 17.2 for the first five years following the head injury (CI = 6.3-37.5) and 2.6 thereafter (CI = 0.0-14.4).

Eleven persons diagnosed with a tumor of the brain or nervous system also had one or more primary cancers of another site, and three of these individuals had two additional primary cancers. Of the 14 other cancers, eight were diagnosed prior to the nervous system tumor, and three concurrently. These included three kidney cancers, two lung cancers, two skin cancers, and one each of several other sites. All three kidney cancers (two hypernephromas, one cancer of renal pelvis) occurred in people who also were diagnosed with meningioma. Information about cancer treatments prior to the occurrence of the brain tumor is not available.

Discussion

Cancers of the brain and nervous system occurred decidedly more often than expected among persons who suffered head injuries serious enough to lead to hospitalization, but the excess was confined largely to the first year after the injury. It is unlikely that head trauma caused tumors that grew rapidly enough to come to diagnosis

Table 2. Observed number of cancers (Obs), standardized incidence ratio (SIR), and 95% confidence intervals (CI), by type of tumor and time since discharge from the hospital following head injury, Denmark

Type of tumor	Years since injury or discharge																	
	< 1.0				1.0-4.9				5.0-9.9				≥ 10.0		Total ^a (≥ 1)			
	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)
No. persons	228,055			224,421			173,171			102,081			224,421			224,421		
No. person-years	216,169			795,960			690,322			359,146			1,845,427			1,845,427		
All cancers	767	1.1	(1.0-1.2)	2,619	1.0	(1.0-1.0)	2,382	1.0	(1.0-1.1)	1,349	1.1	(1.0-1.1)	6,350	1.0	(1.0-1.1)	6,350	1.0	(1.0-1.1)
Brain and nervous system	63	3.0	(2.3-3.8)	91	1.1	(0.9-1.4)	106	1.4	(1.1-1.7)	39	0.9	(0.6-1.2)	236	1.2	(1.0-1.3)	236	1.2	(1.0-1.3)
Intracranial tumors ^{b,c}	62	3.4	(2.6-4.3)	77	1.1	(0.9-1.4)	87	1.3	(1.1-1.6)	35	0.9	(0.6-1.3)	199	1.1	(1.0-1.3)	199	1.1	(1.0-1.3)
Glioma	34	3.9	(2.7-5.5)	36	1.1	(0.8-1.5)	30	1.0	(0.7-1.4)	13	0.8	(0.4-1.3)	79	1.0	(0.8-1.2)	79	1.0	(0.8-1.2)
Glioblastoma	11	2.9	(1.4-5.1)	20	1.4	(0.9-2.2)	11	0.9	(0.4-1.5)	8	1.1	(0.5-2.2)	39	1.1	(0.8-1.6)	39	1.1	(0.8-1.6)
Anaplastic astrocytoma	2	6.9	(0.8-24.8)	1	0.8	(0.0-4.5)	3	2.1	(0.4-6.1)	0	0.0	(0.0-4.3)	4	1.1	(0.3-2.9)	4	1.1	(0.3-2.9)
Other astrocytoma	14	4.8	(2.6-8.0)	6	0.5	(0.2-1.2)	14	1.3	(0.7-2.1)	4	0.6	(0.2-1.6)	24	0.8	(0.5-1.2)	24	0.8	(0.5-1.2)
Oligodendroglioma	3	4.2	(0.8-12.3)	3	1.1	(0.2-3.2)	0	0.0	(0.0-1.5)	0	0.0	(0.0-2.7)	3	0.5	(0.1-1.3)	3	0.5	(0.1-1.3)
Other glioma	4	4.7	(1.2-11.9)	6	1.9	(0.7-4.2)	2	0.8	(0.1-2.8)	1	0.8	(0.0-4.5)	9	1.3	(0.6-2.5)	9	1.3	(0.6-2.5)
Meningioma	6	2.2	(0.8-4.8)	12	1.2	(0.6-2.1)	13	1.4	(0.8-2.4)	5	0.9	(0.3-2.1)	30	1.2	(0.8-1.7)	30	1.2	(0.8-1.7)
Embryonal tumors	2	3.0	(0.3-10.8)	2	0.9	(0.1-3.2)	4	2.6	(0.7-6.6)	0	0.0	(0.0-5.0)	6	1.3	(0.5-2.9)	6	1.3	(0.5-2.9)
Neurilemmoma	3	3.1	(0.6-9.1)	2	0.5	(0.1-1.8)	5	1.2	(0.4-2.8)	2	0.8	(0.1-2.9)	9	0.8	(0.4-1.6)	9	0.8	(0.4-1.6)
Vascular tumors	1	2.0	(0.0-11.1)	1	0.5	(0.0-2.7)	10	4.3	(2.0-7.8)	4	2.8	(0.8-7.2)	15	2.6	(1.4-4.2)	15	2.6	(1.4-4.2)
Other and unspecified types	16	3.3	(1.9-5.4)	24	1.3	(0.8-1.9)	25	1.4	(0.9-2.0)	11	1.0	(0.5-1.9)	60	1.3	(1.0-1.6)	60	1.3	(1.0-1.6)

^a 'Total' column excludes the first year of follow-up.

^b Follows taxonomy of Kleihues *et al.*²⁵ for ICD-O topography codes 191.0-192.1.²³ ICD-O morphology codes for subtypes of brain tumors are as follows: glioma (93800-94603, except 93923); meningioma (95300-95393); embryonal tumors (93923, 94703, 94713, 94723, 94733, 94903, 95003, 95013); neurilemmoma (95400-95700); blood vessel tumors (91200-91611); other and unspecified tumors (all other morphology codes not specified above).

^c Does not include pituitary gland tumors (of which there were two craniopharyngiomas) or pineal gland tumors, of which there was one.

Table 3. Observed numbers of cases (Obs) of glioma, meningioma, and intracranial tumors of the nervous system of all types, with standardized incidence ratios (SIR) and 95% confidence intervals (CI), by time since injury, gender, age at injury, type of injury, cause of injury, and presence of epilepsy as a discharge diagnosis at the time of hospitalization; the maximum follow-up was 17 years, Denmark

Characteristic	Glioma						Meningioma						All intracranial tumors					
	Years since injury or discharge			Years since injury or discharge			Years since injury or discharge			Years since injury or discharge			Years since injury or discharge			Years since injury or discharge		
	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)	Obs	SIR	(CI)
Total	34	3.9	(2.7-5.5)	79	1.0	(0.8-1.2)	6	2.2	(0.8-4.8)	30	1.2	(0.8-1.7)	62	3.4	(2.6-4.3)	199	1.1	(1.0-1.3)
Gender																		
Male	17	3.0	(1.7-4.8)	48	0.9	(0.6-1.2)	3	2.7	(0.5-7.7)	10	0.9	(0.4-1.7)	31	2.8	(1.9-4.0)	111	1.0	(0.8-1.2)
Female	17	5.8	(3.4-9.3)	31	1.3	(0.9-1.8)	3	1.9	(0.4-5.4)	20	1.4	(0.9-2.2)	31	4.2	(2.8-5.9)	88	1.3	(1.1-1.7)
Age at injury (yrs)																		
<10	0	0.0	(0.0-7.0)	4	0.8	(0.2-2.0)	0	0.0	(0.0-1.98)	0	0.0	(0.0-0.98)	2	1.6	(0.2-6.0)	13	1.1	(0.6-1.9)
10-19	2	2.5	(0.3-9.1)	10	1.0	(0.5-1.8)	0	0.0	(0.0-41.2)	2	1.4	(0.2-4.9)	3	1.8	(0.4-5.1)	27	1.3	(0.8-1.9)
20-29	2	2.4	(0.3-8.6)	7	0.6	(0.2-1.2)	0	0.0	(0.0-38.8)	1	0.4	(0.0-2.3)	4	2.6	(0.7-6.8)	17	0.8	(0.4-1.2)
30+	30	4.6	(3.1-6.6)	58	1.1	(0.8-1.4)	6	2.4	(0.9-5.1)	27	1.3	(0.9-1.9)	53	3.8	(2.9-5.0)	142	1.2	(1.0-1.4)
Type of injury (yrs)																		
Fractured skull	7	2.1	(1.3-6.7)	14	0.7	(0.4-1.1)	1	1.6	(0.0-9.1)	9	1.5	(0.7-2.9)	15	3.4	(1.9-5.7)	43	1.0	(0.7-1.3)
Concussion	27	4.4	(2.9-6.3)	61	1.1	(0.8-1.4)	4	2.0	(0.5-5.0)	21	1.2	(0.7-1.8)	45	3.4	(2.5-4.5)	150	1.2	(1.0-1.4)
Laceration or contusion	0	0.0	(0.0-12.3)	4	1.6	(0.4-4.2)	1	11.1	(0.1-61.6)	0	0.0	(0.0-5.0)	2	3.2	(0.4-11.7)	6	1.2	(0.4-2.5)
Type or location of accident																		
Traffic	8	2.9	(1.2-5.5)	19	0.7	(0.4-1.1)	1	1.1	(0.0-6.2)	11	1.3	(0.6-2.3)	14	2.3	(1.3-3.9)	59	1.0	(0.8-1.3)
Home	9	6.8	(3.1-12.9)	14	1.7	(0.9-2.8)	2	3.5	(0.4-12.7)	7	2.0	(0.8-4.0)	17	5.3	(3.1-8.5)	29	1.4	(0.9-2.0)
Workplace	2	5.7	(0.6-20.7)	4	1.0	(0.3-2.6)	0	0.0	(0.0-47.6)	0	0.0	(0.0-4.0)	3	4.8	(1.0-14.0)	8	1.1	(0.5-2.1)
Sports	0	0.0	(0.0-15.8)	4	1.6	(0.4-4.1)	0	0.0	(0.0-93.5)	0	0.0	(0.0-7.2)	0	0.0	(0.0-8.1)	6	1.2	(0.4-2.6)
Other or unknown	15	3.9	(2.2-6.4)	38	1.0	(0.7-1.4)	3	2.6	(0.5-7.6)	12	1.0	(0.5-1.8)	28	3.5	(2.3-5.1)	97	1.2	(1.0-1.4)
Epilepsy ^a																		
Yes	2	26.3	(3.0-94.9)	5	7.6	(2.4-17.7)	0	0.0	(0.0-152)	0	0.0	(0.0-16.8)	3	19.7	(4.0-57.6)	9	6.5	(3.0-12.3)
No	32	3.7	(2.6-5.3)	74	0.9	(0.7-1.2)	6	2.2	(0.8-4.8)	30	1.2	(0.8-1.7)	59	3.2	(2.5-4.2)	190	1.1	(1.0-1.3)

^a Listed as one of the discharge diagnoses for the injury hospitalization.

within one year after the injury. It is far more likely that these early tumors were already present at the time the injury occurred. Indeed, associated seizures, ataxia, or aphasia may have contributed to the fall or accident that resulted in the head injury. Brain tumor risk was particularly high among persons who also had a discharge diagnosis of epilepsy listed for the hospitalization for head injury. Some of the seizure disorders diagnosed as epilepsy may have been early manifestations of a yet-to-be-diagnosed brain tumor.²⁶ Although only a small minority of the study population had a notation of epilepsy, symptoms related to an undiagnosed brain tumor may have contributed to other accidents as well.¹ Among people who suffered head injuries in the course of participating in sports, brain tumors occurred at close to the expected rate. Sports injuries might be expected to be due more often to purely external factors and unrelated to preclinical tumors.

Pre-existing, asymptomatic tumors also may have been detected incidentally in the course of the diagnostic evaluation following the head injury. Imaging scans conducted because of the trauma may have led to the detection of indolent tumors, particularly for meningioma.^{27, 28} The positive association between the SIR and age at injury for the first year of follow-up likely reflects the increasing prevalence of such tumors with age. Because follow-up began the first day of the month following the date of hospital discharge, tumors diagnosed *during* the hospitalization for head trauma were not counted in the observed numbers reported here. (There were 32 such tumors.) However, other patients' tumors may have been discovered shortly after discharge in the course of ongoing care for their injury. It also is possible that trauma accelerates growth of existing tumors.

If head injuries advanced the diagnosis of preclinical brain tumors in members of the study cohort, this could obscure a real increase in the risk of brain tumors in later years, because similar baseline screening was not done for the general (comparison) population. Under the null hypothesis of no effect of head trauma, an initial excess incidence of tumors due to screening would be expected to be followed by a deficit in later years, during which time some of the tumors detected by screening otherwise would have come to clinical attention. However, a deficit of intracranial tumors during years one to five was not seen in these data, either overall or for glioma or meningioma, the two most common subtypes. While one might conjecture that a deficit attributable to baseline screening was offset by a trauma-induced increase, a more comprehensive examination of the data does not support this view. If that explanation were correct, one would expect an increase in the rate ratio over time, which is not apparent. The SIR for the interval 10 to 17 years following the injury was 0.8 for glioma and 0.9 for meningioma.

These slight, nonsignificant deficits during later follow-up periods, while possibly due to chance, also might indicate that the effect of detection bias at the beginning of follow-up is delayed and becomes manifest only years later, possibly extending for many years. Some of the tumors detected during the evaluation for head injury might not otherwise have come to diagnosis within the time period covered by our study. This is perhaps more plausible for typically slow-growing tumors such as meningioma²⁸ than for aggressive astrocytic tumors. Because of the relatively short follow-up in this study (maximum, 17 years), we cannot address possible long-term risks.^{6,15}

We did not have information about persons who emigrated from Denmark during the study period. The assumption that all persons not known to have died were still alive and living in Denmark could lead to overestimates of PYs of observation and expected numbers of tumors, and a downward bias in the estimated SIR. Published emigration rates for 1985 were up to 1.3 percent, ranging from a low of 52 per 100,000 for persons over age 60 to a high of 1,315 per 100,000 for 20 to 29 year olds; rates were 584 and 674 per 100,000 for persons age 10 to 19 and 30 to 39, respectively.²⁹ The SIR for all cancers combined, exclusive of tumors of the brain and nervous system, was very close to 1.00; that is, there was no sign of a nonspecific lowering of SIRs. This suggests that PYs have not been seriously overestimated and that adjustment for emigration would not influence interpretation of results.

Results of previous case-control studies have been inconsistent about the specificity of association between recalled history of head injury and the occurrence of particular histologic subtypes of intracranial tumors. Positive findings were reported for meningioma, but not glioma, among men and women from the Los Angeles area (California, United States).^{4,6} Early reports of case series also more often noted meningiomas as arising at the site of head injuries.² However, other investigators have described positive associations for astrocytic tumors and embryonal tumors.^{7, 9-11} Neither glioma nor meningioma were associated with self-reported history of head injury in two other studies.^{30,31} In the present study, glioma, meningioma, neurilemmoma, and embryonal tumors all occurred at close to the expected rate after the first year. Only vascular tumors showed a clear excess in later years.

The literature concerning the etiology of vascular tumors is sparse, apart from hemangioblastoma associated with von Hippel-Lindau (VHL) disease, a heritable tumor syndrome linked to a tumor suppressor gene on the short arm of chromosome 3.^{32,33} In reviews of case series, authors have commented on an apparent association between intracranial vascular tumors and history of head injury,^{34,35}

but analytic epidemiologic studies have not previously addressed the question. If Sargent and Greenfield³⁴ are correct in their hypothesis that head trauma initiates the formation of hemangiomas in patients with pre-existing cerebellar vascular tumors, an effect of head trauma could be on the clinical appearance of the tumors, rather than their onset.²

The VHL gene is mutated in sporadically occurring hemangioblastoma as well as in familial forms of the disease.³⁶ In the present study, we did not have information that would enable us to address whether the risk associated with head injury differs for sporadic and familial cases or, phrased differently, whether persons from VHL families are at particularly high risk of injury-induced (or associated) tumors. Clear-cell renal carcinoma is part of the VHL syndrome,³⁷ but, for the three persons in the present study who were diagnosed with cancer of the kidney and a tumor of nervous system, the nervous system tumor was meningioma rather than hemangioblastoma in each instance.

In conclusion, results of this large cohort study of persons with head injuries serious enough to lead to hospitalization indicate that if traumatic injury to the head increases the risk of brain tumors, the increase is very small, restricted to uncommon subtypes, or delayed until decades later. The excess risk during the first year following injury almost certainly is attributable to pre-existing tumors. The observed 10 to 20 percent elevation in incidence for later years is compatible with the recent report of a 40 percent increase,¹¹ but also with zero or negligible effect. The strong positive associations between head trauma and incidence of brain tumors that have been observed in case-control studies well may have been due largely to differential recall of past injuries by cases and controls. It is the type of exposure-disease association that would appear to be particularly prone to this type of error.

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