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Original Article

Risk of meningioma in patients with head injury: A nationwide population-based study

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Abstract

Background: Head injury has been suggested to correlate with meningioma. However, results of studies investigating the relationship between head injury and meningioma were inconsistent. Therefore, we conducted this study to assess the association between head injury and meningioma, and to determine the possible risk factors.

Methods: Head injury patients aged 18 years and older, without antecedent diagnosis of brain tumor, and who were followed up for more than 30 days between January 1, 2001, and December 31, 2010, were recruited from the Taiwan National Health Insurance Research Database. Hazard ratios (HRs) of meningioma risk for head injury patients compared with an age- and sex-matched cohort were calculated by Cox proportional regression analysis. The difference in cumulative incidence between head injury patients and the matched cohort was analyzed using the Kaplan–Meier method and tested with the log-rank test.

Results: Each cohort (i.e., the head injury cohort and the matched cohort) consisted of 75,292 individuals with a mean age of 44.7 years, and 52.3% of these patients were male. The incidence rates of meningioma were $3.99/10^5$ person-years and $3.23/10^5$ person-years in the head injury cohort and the comparison cohort, respectively, with a Charlson Comorbidity Index score-adjusted HR of 1.27 ($p = 0.514$). There were no associations between head injury and risk of meningioma, neither overall nor in stratified analyses according to severity of head injury, age, and sex of patients.

Conclusion: Head injury, regardless of severity, patient sex, or age, is unlikely to be a cause of meningioma.

Keywords: head injury; meningioma; population-based study; Taiwan National Health Insurance Research Database

1. Introduction

Meningiomas are the most frequently diagnosed primary brain tumors.[1] Although most meningiomas are typically benign, a small number of such tumors could potentially cause a fatal outcome due to their close proximity to vital intracranial structures. The main risk factors for meningioma are genetic factors and high-dose radiation exposure while hormone and head trauma were also reported to be associated with elevated risk.[2]

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Meningioma was first described to be associated with head trauma by Cushing and Eisenhardt in 1938.[3] An increased risk of meningioma in patients with a history of head trauma as well as in men whose head was ever boxed during sports activities was demonstrated in case–control studies.[4–6] A longer history of head trauma (10–19 years) and increased number of head traumas were reported to be related with higher risk.[7] However, traumatic brain injury was shown not to be associated with primary brain tumors, including meningioma, in a cohort study in Sweden.[8]

Because the result of these studies were inconsistent, it remains unclear whether brain injury patients exhibit an elevated risk of developing meningioma compared with the general population. Therefore, a population-based matched cohort study using the Taiwan National Health Insurance Research Database (NHIRD) was conducted to examine this issue.

2. Methods

2.1. Data source

In this current study, we used data from the Longitudinal Health Insurance Database (LHID) from 1995 to 2010 obtained from the NHIRD. The National Health Insurance (NHI) Program was launched in Taiwan in 1995, which now covers 99% of Taiwan's population of 23 million. The LHID information used consisted of 1 million beneficiaries randomly sampled from the original NHI beneficiaries. The LHID consists of deidentified secondary data released for research purposes. The database includes the entire registry and claims data from this health insurance system, ranging from demographic data to detailed orders from ambulatory and inpatient care. The accuracy of diagnoses in the NHIRD has been previously validated for several diseases.[9–12] Several published papers have used the NHIRD as the basis for their studies.[13–15] The diseases were coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes, 2001 edition. Because the Taiwan NHIRD contains encrypted computerized data for research purposes, the Ethics Committee of Taipei Veterans General Hospital, Taipei, Taiwan informed us that this study was exempted from full review and that each patient's informed consent was not required.

2.2. Study design

This is a nationwide, population-based, observational retrospective cohort study in Taiwan to determine the association between the risks of meningioma in patients with head injury. Two cohorts, namely, the head injury cohort and the matched control cohort without head injury, were enrolled in our study (Fig. 1). The head injury cohort consisted of patients with new diagnosis of head injury with ambulatory visit or hospitalization coding ICD-9-CM 800-804 or 850-854 between January 1, 2000, and December 31, 2010. Patients with the following characteristics were excluded: age <18 years, history of meningioma, and follow-up period of <30 days. We extracted the baseline demographic data, which included age, sex, and urbanization level. Urbanization levels in Taiwan are divided into four strata with Level 1 for the highest urbanization according to the Taiwan National Health Research Institute publications. For each patient, the Charlson Comorbidity Index (CCI) score was used to determine overall systemic health.[16] With each increased level of CCI score, there were stepwise increases in the cumulative mortality: a score of 0 had a 10-year survival rate of 99%, and a score of 5 had a 10-

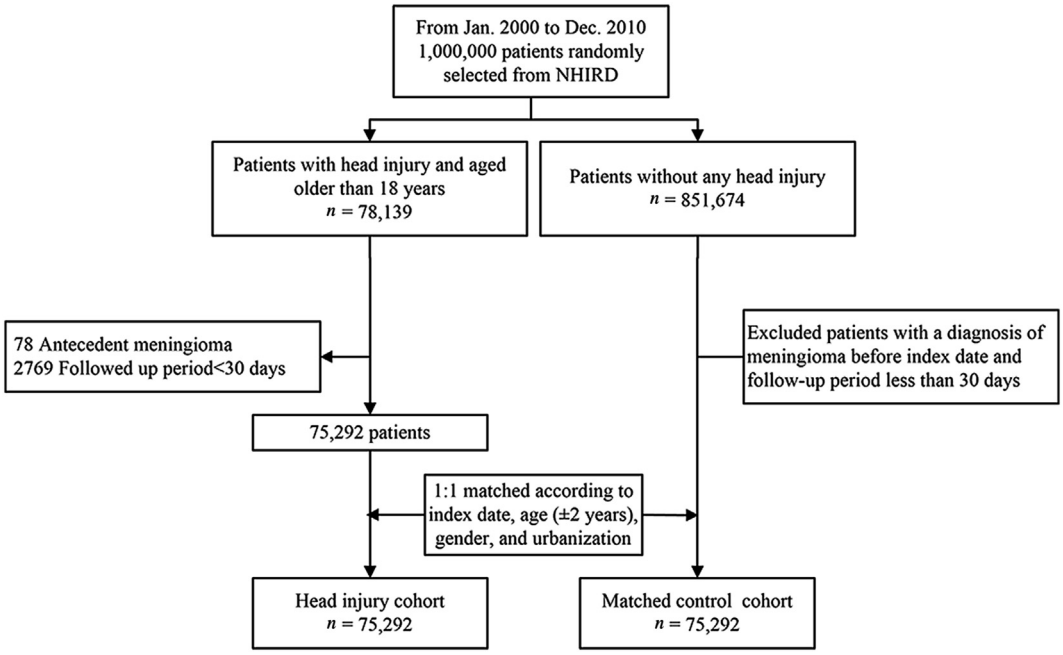

Fig. 1. Patient selection flowchart. NHIRD = National Health Insurance Research Database.

Table 1
Demographic and clinical characteristics of patients.

Characteristic	Head injury cohort	Control cohort	p
Patient numbers	75,292	75,292	
Mean age (SD), y	44.7 (20.0)	44.7 (19.9)	0.745
Male (%)	39,370 (52.3)	39,370 (52.3)	> 0.99
Urbanization (%)			> 0.99
Level 1	41,073 (54.6)	41,073 (54.6)	
Level 2	27,487 (36.5)	27,487 (36.5)	
Level 3	5754 (7.6)	5754 (7.6)	
Level 4	978 (1.3)	978 (1.3)	
Charlson			0.003
Comorbidity			
Index score (%)			
0	35,026 (46.5)	34,326 (45.6)	
1	17,092 (22.7)	17,304 (23.0)	
2	9658 (12.8)	9691 (12.9)	
3	5301 (7.0)	5429 (7.2)	
≥4	8215 (10.9)	8542 (11.3)	

SD = standard deviation.

year survival rate of 34%.[16] The control cohort was selected from the remaining patients in the LHID and consisted of patients who were never diagnosed with a head injury. Using the same exclusion criteria of the head injury cohort, we identified one control patient for each patient in the head injury cohort, who was matched according to index date, age, sex, and urbanization level.

2.3. Outcomes

The outcome was the occurrence of meningioma during the follow-up period. Meningioma was defined as ambulatory visit or hospitalization with primary diagnosis coding ICD-9-CM 225.2 and receiving brain image examination, including computer tomography or magnetic resonance imaging. Both cohorts were followed until December 31, 2010, death, or the occurrence of outcome.

2.4. Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of our cohort. Baseline characteristics of the two groups were compared using Pearson χ^2 tests for categorical variables; the independent *t* test and the Mann–Whitney *U* test were used for parametric and nonparametric continuous variables, respectively. The incidence rate of meningioma between the two groups was calculated by Poisson distribution. The relative risk of meningioma between groups was calculated with the hazard ratio (HR) from Cox regression models.

Microsoft SQL Server 2008 R2 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing, and sampling. All other statistical analyses were conducted using Stata statistical software (version 12.0; StataCorp., College Station, TX, USA).

3. Results

3.1. Characteristics of the study population

During the follow-up period, we identified 75,292 patients with a diagnosis of head injury who met the inclusion criteria between January 1, 2000, and December 31, 2010. A matched control cohort of 75,292 patients without head injury was also identified. The demographic characteristics of the study group and the matched cohort (1:1 ratio of patient number) are shown in Table 1. All patients in both groups were similar in age, sex, and urbanization level, and the mean age of both cohorts was 44.7 years. Compared with the matched control cohort, more patients in the head injury cohort had a CCI score of 0, whereas the number of patients with a CCI score ranging from 1 to ≥4 was similar in both groups.

3.2. Risk of meningioma

During the follow-up period, there were 31 newly diagnosed cases of meningioma: 17 among 426,104 person-years in the head injury cohort and 14 among 433,250 person-years in the control cohort, respectively. The incidence rate of meningioma was $3.99/10^5$ person-years in the head injury cohort and $3.23/10^5$ person-years in the control cohort. Compared with the control cohort, the head injury cohort did not have a significantly higher risk of meningioma. The adjusted HR (aHR) was 1.27 [95% confidence interval (CI), 0.62–2.57; $p = 0.514$; Table 2]. The log-rank test showed a higher cumulative incidence of meningioma in the head injury group than in the matched cohort but the difference was not statistically significant ($p = 0.554$; Fig. 2).

When the study patients were stratified into different subgroups, the risk of meningioma seemed to be higher in patients

Table 2
Crude and adjusted hazard ratios of meningioma among patients with head injury and matched control cohort.

	All patients			Propensity score matched			
				Crude		Adjusted[a]	
	No. of events	Person-years	Incidence rate[b]	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Control cohort	14	433,250	3.23	As reference		As reference	
Head injury cohort	17	426,104	3.99	1.24 (0.61–2.51)	0.555	1.27 (0.62–2.57)	0.514

CI = confidence interval.
[a] Adjusted for Charlson Comorbidity Index score.
[b] Per 10^5 person-years.

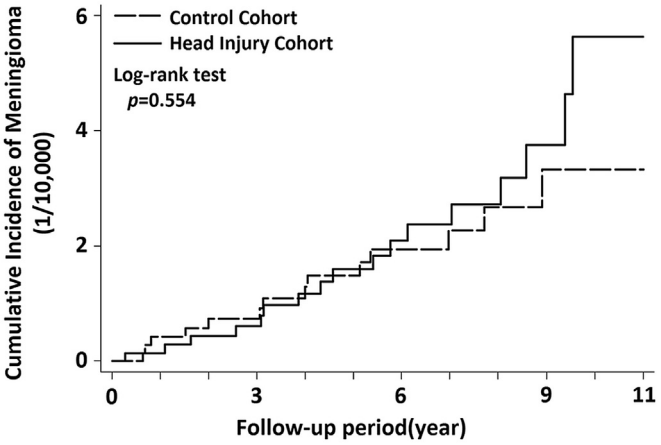

Fig. 2. Cumulative incidence of meningioma among patients with head injury and matched control cohort.

who were <45 years (aHR, 2.55; 95% CI, 0.50–13.16; $p = 0.263$) compared with those ≥ 45 years (aHR, 1.05; 95% CI, 0.47–2.34; $p = 0.904$); however, the difference was not statistically significant. The effects of sex and severity of head injuries were similar to the effects of age where women were likely to be at a higher risk (aHR, 1.94; 95% CI, 0.82–4.58; $p = 0.130$), whereas men with head injury were less likely to suffer from meningioma (aHR, 0.36; 95% CI, 0.10–1.76; $p = 0.205$). Severe head injury (aHR, 1.58; 95% CI, 0.65–3.87; $p = 0.315$) appeared to impose higher risk of meningioma compared with mild head injury (aHR, 0.85; 95% CI, 0.26–2.81; $p = 0.796$; Table 3).

4. Discussion

Our population-based cohort study revealed that brain injury patients had no increased risk of developing meningioma. Although severity of head injury, female sex, and age <45 years demonstrated a tendency toward higher risk of meningioma, the risks were not statistically significant.

Table 3
Subgroup analysis for risk of meningioma among patients with head injury and matched control cohort.

Characteristic	Head injury	Matched control	Adjusted[a]	
	No. of events/ no. of patients	No. of events/ No. of patients	Hazard ratio (95% CI)	*p*
By age				
<45 y	5/40,608	2/40,628	2.55 (0.50–13.16)	0.263
≥45 y	12/34,684	12/346,64	1.05 (0.47–2.34)	0.904
By sex				
Male	2/39,370	6/39,370	0.36 (0.1–1.76)	0.205
Female	15/35,922	8/35,922	1.94 (0.82–4.58)	0.130
By severity of head injury[b]				
Mild	5/36,366	6/36,366	0.85 (0.26–2.81)	0.796
Severe	12/38,926	8/38,926	1.58 (0.65–3.87)	0.315

CI = confidence interval.
[a] Adjusted for age, sex, urbanization level, and Charlson Comorbidity Index score.
[b] In this subgroup analysis, the risk of meningioma was calculated by patients with head injury and their matched control cohort.

Likewise, cumulative incidences of meningioma of both cohorts were similar in the follow-up period.

There have been multiple studies that have investigated the risk of meningioma in patients with head injury. Table 4 provides a summary of these studies.[4–8,17,18] The results in the present study resemble that of a population-based cohort study,[8] where no overall increased risk of meningioma [standardized incidence ratio (SIR), 1.1; 95% CI, 0.8–1.4] was found. Similarly, after excluding tumors found in the first follow-up year to avoid detection bias, a Danish study found a higher tendency for meningioma (SIR, 1.2; 95% CI, 0.9–1.7), but it was statistically insignificant.[17] Our study demonstrated a similar tendency (Table S1 in the supplementary material online). On the contrary, Preston-Martin et al[4–6] conducted a series of case–control studies, demonstrating elevated risk [Odds ratio (OR), 1.9–2.3] with statistical significance. A multicenter international case–control study also suggested an association between head injuries and meningioma in men (OR, 1.5; 95% CI, 0.9–2.60), especially in those who had a latency period between 15 years and 24 years (OR, 5.4; 95% CI, 1.7–16.6).[18] Phillips et al[7] revealed an increased meningioma risk (OR, 1.83; 95% CI, 1.28–2.62) in a population-based case–control study. The association between head injury and meningioma reported in the case–control series may be an example of recall bias. In the international case–control study, significant risk was found only in a male subgroup whose mild injuries were sustained 15–24 years earlier, but not in women with mild injury or in patients with serious injuries in either sex.[18] Our study revealed that the risk of meningioma is not increased in head injury patients of both sexes, and latency period does not impose a significant risk. Meningioma patients might have differential recall ability, which could link their tumors to any head injury in the past. Moreover, men were two times as likely as women to report having head injuries.[18] Together, these factors might explain the higher risk of meningioma in men with head injuries observed in case–control studies but not in our population-based cohort studies.

Since Cushing and Eisenhardt[3] raised the possibility of a relationship between head injury and meningioma by presenting 65 cases in the 1930s, researchers have attributed greater weight to this potential connection. Case reports such as the occurrence of meningioma surrounding a foreign wire that was introduced into the brain of a man 20 years earlier in an accident,[19] and development of meningioma from a head lump sustained in a bomb explosion 20 years ago[20] reinforced this idea over the years. Case–control studies have demonstrated the association of meningioma with a history of head injury ranging from 10 years to 24 years,[4,7,18] which may suggest a slow-growing nature of such benign tumors. Transplantation of meningeal fragments within brain tissues after head injury that eventually led to the formation of meningioma had been suggested.[21] Some studies have shown that severe injury imposed a higher risk,[4,6] whereas others showed that a mild injury induced more meningiomas.[7,18] Our study revealed that neither severe nor mild head injury created a higher risk of meningioma. The incongruity among the

Table 4
Summary of studies exploring the risk of meningioma in head injury patients.

Author (y)	Country	Study design	Patient number	Major finding in meningioma risk
Preston-Martin et al[5] (1980)	USA	CC	188 pairs	Head injury in women is a risk factor (OR, 2.0; $p = 0.01$)
Preston-Martin et al[6] (1983)	USA	CC	105 pairs	Head ever boxed as a sport (OR, 2.0; $p = 0.03$) or serious head injury (OR, 1.9; $p = 0.01$) in men
Preston-Martin et al[4] (1989)	USA	CC	70 pairs	Serious head injuries >20 y (OR, 2.3; 95% CI = 1.1–5.4) or number of head injuries ≥3 (OR, 6.2; 95% CI, 1.2–31.7)
Inskip et al[17](1998)	Denmark	Co	228,055	SIR excluding 1st year after head injury, 1.2 (95% CI, 0.8–1.2)
Preston-Martin et al[18] (1998)	Six countries[a]	Int. CC	330 cases	Head injury in men (OR, 1.5; 95% CI, 0.9–2.60); latency period between 15 and 24 y (OR, 5.4; 95% CI, 1.7–16.6); no risk found for female patients
Nygren et al[8] (2001)	Sweden	Co	311,006	Hospitalized traumatic brain injury patient (SIR, 1.1; 95% CI, 0.8–1.4); no increased risk imposed by latency period, sex, and severity of head injury
Phillips et al[7] (2002)	USA	CC	200 cases	Head injury (OR, 1.83; 95% CI, 1.28–2.62); latency period of 10–19 y (OR, 4.33; 95% CI, 2.06–9.10); no increased risk imposed by severity
This study (2014)	Taiwan	Co	75,292	Head injury (aHR, 1.27; 95% CI, 0.62–2.57); no increased risk imposed by longer latency period, sex, and severity of head injury

aHR = adjusted hazard ratio; CC = case–control study; CI = confidence interval; Co = cohort study; Int. = international; OR = odds ratio; SIR = standardized incidence ratio.
[a] Australia, France, Germany, Canada, Sweden, and USA.

severity of head injury and occurrence of meningioma had weakened this causal relationship. Furthermore, if head injuries could cause formation of tumor through meningeal irritation during healing and inflammatory process, it could be postulated that meningioma would develop close to the injury site. A prospective follow-up study of head trauma patients disclosed that occurrence of subsequent brain tumor was not associated with location of head injury.[22] Moreover, to the best of our knowledge, no study had shown a correspondence between previous injury site and location of subsequent meningioma, suggesting the spontaneous growth of meningioma in head trauma patients.

This study has several limitations. Lifestyle variables and data on behavioral factors such as cell phone usage and diet (cured meat), which were postulated to be one of the risk factors for meningioma,[5,23] were not available in the NHI database. Second, types of meningioma and histology were not available in this database, and thus their association with head injury could not be identified. Third, information on causes of death of the patient was not available; meningiomas that caused death were not included in our study resulting in a possible underestimation of the association. Finally, our follow-up duration is relatively insufficient compared with the latency period suggested by previous studies. Despite these limitations, our study was based on a nationwide, population-based database that could identify all cases of head injury and meningioma during the study period, contributing to its substantial statistical power.

In conclusion, this nationwide population-based study demonstrated that head injury, regardless of its severity, patient sex, and age, is unlikely to be a cause of meningioma. Therefore, the positive associations demonstrated in previous studies may well be caused by study limitations as well as bias.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcma.2014.06.005.

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