Original Article

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

Ai-Seon Kuan\textsuperscript{a,b}, Yung-Tai Chen\textsuperscript{b,c}, Chung-Jen Teng\textsuperscript{b,d,e}, Shuu-Jiun Wang\textsuperscript{a,b}, Ming-Teh Chen\textsuperscript{a,b,*}

\textsuperscript{a} Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
\textsuperscript{b} Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC
\textsuperscript{c} Division of Nephrology, Department of Medicine, Taipei City Hospital, Heping Fuyou Branch, Taipei, Taiwan, ROC
\textsuperscript{d} Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, ROC
\textsuperscript{e} Division of Oncology and Hematology, Department of Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan, ROC

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Abstract

\textbf{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.

\textbf{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.

\textbf{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\textsuperscript{5} person-years and 3.23/10\textsuperscript{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.

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

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

1. Introduction

Meningiomas are the most frequently diagnosed primary brain tumors.\textsuperscript{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.\textsuperscript{2}
Meningioma was first described to be associated with head trauma by Cushing and Eisenhardt in 1938. 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. A longer history of head trauma (10–19 years) and increased number of head traumas were reported to be related with higher risk. However, traumatic brain injury was shown not to be associated with primary brain tumors, including meningioma, in a cohort study in Sweden.

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. Several published papers have used the NHIRD as the basis for their studies. 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. 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-
year survival rate of 34%. 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 \( \chi^2 \) 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 \( \geq 4 \) 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 3.99/105 person-years in the head injury cohort and 3.23/105 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>
<thead>
<tr>
<th>Characteristic</th>
<th>Head injury cohort</th>
<th>Control cohort</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient numbers</td>
<td>75,292</td>
<td>75,292</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>44.7 (20.0)</td>
<td>44.7 (19.9)</td>
<td>0.745</td>
</tr>
<tr>
<td>Male (%)</td>
<td>39,370 (52.3)</td>
<td>39,370 (52.3)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Urbanization (%)</td>
<td></td>
<td></td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Level 1</td>
<td>41,073 (54.6)</td>
<td>41,073 (54.6)</td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>27,487 (36.5)</td>
<td>27,487 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>5754 (7.6)</td>
<td>5754 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Level 4</td>
<td>978 (1.3)</td>
<td>978 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index score (%)</td>
<td></td>
<td>0.003</td>
<td></td>
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<tr>
<td>0</td>
<td>35,026 (46.5)</td>
<td>34,326 (45.6)</td>
<td></td>
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<tr>
<td>1</td>
<td>17,092 (22.7)</td>
<td>17,304 (23.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9658 (12.8)</td>
<td>9691 (12.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5301 (7.0)</td>
<td>5429 (7.2)</td>
<td></td>
</tr>
<tr>
<td>( \geq 4 )</td>
<td>8215 (10.9)</td>
<td>8542 (11.3)</td>
<td></td>
</tr>
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</table>

SD = standard deviation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Head injury cohort</th>
<th>Control cohort</th>
<th>( p )</th>
</tr>
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<tbody>
<tr>
<td>No. of events</td>
<td>14</td>
<td>17</td>
<td></td>
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<tr>
<td>Person-years</td>
<td>433,250</td>
<td>426,104</td>
<td></td>
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<tr>
<td>Incidence rate(^b)</td>
<td>3.23</td>
<td>3.99</td>
<td></td>
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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control cohort</th>
<th>Head injury cohort</th>
<th>Hazard ratio (95% CI)</th>
<th>( p )</th>
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<tr>
<td>Crude</td>
<td></td>
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<td>As reference</td>
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<tr>
<td>Adjusted(^a)</td>
<td></td>
<td></td>
<td>1.24 (0.61–2.51)</td>
<td>0.555</td>
</tr>
</tbody>
</table>

CI = confidence interval.

\(^a\) Adjusted for Charlson Comorbidity Index score.

\(^b\) Per 10\(^5\) person-years.
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.

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 al19-21 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 al22 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 Eisenhardt3 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 ago20 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,17,18 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
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.

### References

9. Lindblad U, Råstam L, Ranstam J, Peterson M. Validity of register data on 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.

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