Higher risk for meningioma in women with uterine myoma: a nationwide population-based retrospective cohort study

Clinical article

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Objective. Evidence suggests that hormones play a role in modifying both uterine myoma (UM) and meningioma. A number of studies have observed the positive association between these diseases. The aim of the current population-based study was to determine if women with UM are at a higher risk for meningioma.

Methods. The authors used data from the National Health Insurance system of Taiwan for the study. The UM cohort contained 281,244 women. Each woman was randomly frequency-matched with 4 women without UM, based on age, index year of diagnosis, occupation, urbanization (urbanization level was categorized by the population density of the residential area into 4 levels, with Level 1 as the most urbanized and Level 4 as the least urbanized), and comorbidity, to form the control cohort. Cox’s proportional hazard regression analysis was conducted to estimate the influence of UM on the meningioma risk.

Results. Among women with UM, the risk of developing meningioma was significantly higher (45%) than among women without UM (95% CI 1.23–1.70). The same phenomenon was observed among most age groups, but a significant difference was only seen in the middle-age range. For women with UM, further analysis did not show a significant change after myomectomy. The cumulative incidence of meningioma between groups with and without UM differed over time.

Conclusions. The nationwide population-based cohort study found that Taiwanese women with UM are at higher risk for developing meningioma.

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Key Words • uterine myoma • meningioma • population-based cohort study • oncology

Uterine myomas (UMs), which are also called leiomyomas or fibroids, are benign tumors originating from the myometrial compartment of the uterus. They are the most common benign tumor in females, occurring in more than 70% of those of reproductive age.11 They are the leading indication for hysterectomy in the United States.15 The majority of UMs are asymptomatic and are often detected incidentally in routine health examinations.5 The precise causes remain unclear, but advances have been made in understanding the hormonal factors, genetic factors, growth factors, and molecular biology of this benign tumor.10,27 Researchers have found that the development of UM is associated with the female hormone estrogen. Uterine myomas appear during the childbearing years when a woman’s estrogen levels are high.

Sex hormones have also been suggested to play a role in the development of brain tumors. Meningiomas originate in the meninges and are the most common type of primary brain tumor in adults. They accounted for 33.8% of all primary brain and CNS tumors reported in the United States between 2004 and 2006.3 Meningiomas occur approximately twice as often in women as in men, especially during a female’s reproductive period.2,3,23 The possible association between meningioma and breast can-
Information on clinical visits and admission for each insurant, as well as the existence of case reports of tumor progression during the luteal phase of the menstrual cycle or during pregnancy, supports a hypothesis of hormonal factors involved in the development of meningioma. Additional studies have suggested that meningioma patients are more likely to have a history of UM, but large-scale studies are needed to confirm these findings.

A much higher percentage of meningiomas was reported in Taiwanese individuals than in those from other countries. Therefore, we conducted a nationwide population-based retrospective cohort study to investigate a possible relationship between UM and meningioma risk in Taiwanese women. The original database was generated from the National Health Insurance (NHI) system in Taiwan.

**Methods**

**Data Sources**

The NHI, a universal health program, was established in Taiwan in 1995. The NHI program covers over 99% of the Taiwanese population and has contracts with 97% of the hospitals in Taiwan. For research purposes, the National Health Research Institute compiles all medical claims in the NHI program and releases the information annually to the public. Data for our cohort study were obtained from the National Health Insurance Research Database (NHIRD), which contains comprehensive information on clinical visits and admission for each insurant, such as demographic data, date of visits, diagnostic codes according to the ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification), and prescriptions. The details of the NHIRD have been described in previous studies. In addition, this study was also approved by the Ethics Review Board at China Medical University.

**Study Population**

We conducted a retrospective cohort study of women who were newly hospitalized for UM (ICD-9-CM 218) between January 1, 1998, and December 31, 2010. We excluded patients who had suffered from meningioma (ICD-9-CM 225.2), epilepsy (ICD-9-CM 345), stroke (ICD-9-CM 430–438), head injury (ICD-9-CM 850–854, 959.01), or brain cancer (ICD-9-CM 191, 192, 194.3, 194.4) before admission.

For the non-UM cohort, we randomly selected controls in a 4:1 ratio, frequency-matched by age, occupation, urbanization (urbanization level was categorized by the population density of the residential area into 4 levels, with Level 1 as the most urbanized and Level 4 as the least urbanized), comorbidity, and index year of diagnosis to the case group, using the same exclusion criteria.

**Outcome Measurement and Comorbidities**

All individuals were followed up for the period starting at the diagnosis date until the end of 2010, or until the meningioma developed. Patients were examined at the end of the follow-up period, or on the last recorded entry into or withdrawal from the database, whichever came first.

We also used inpatient diagnosis files to ascertain the existence of comorbidities, including hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), and hyperlipidemia (ICD-9-CM 272).

**Statistical Analysis**

We used the chi-square and Student t-test for the bivariate analysis. The incidence densities and incidence rate ratio (IRR), stratified with baseline characteristics, were determined under Poisson assumptions. The relative risk of meningioma development in patients with UM, compared with the control group, was analyzed using a multivariate Cox proportional hazard regression model. The model included age. For estimating the meningioma risk of the 2 groups, we performed a survival analysis, using the Kaplan-Meier method, with significance based on the log-rank test. A 2-tailed p value of < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software (version 9.2 for Windows; SAS Institute, Inc.).

**Results**

The baseline characteristics of the patients with and without UM are shown in Table 1. The mean ages of the UM cohort and non-UM cohort were 43.7 ± 7.82 and 43.1 ± 8.55 years, respectively. Distributions of age, occupation, urbanized area, and comorbidity were essentially the same in the 2 groups.

Table 2 shows the overall, age-, occupation-, and urbanization-specific incidence densities of meningioma for the 2 study cohorts. Overall, during the follow-up period, UM patients (11.1 per 100,000 person-years) had a higher incidence of meningiomas than non-UM patients (7.73 per 100,000 person-years; IRR 1.44, 95% CI 1.42–1.46). With regard to the age-specific incidence, the occurrence of UM tended to increase with age. For the UM patients, the highest incidence of meningioma was in patients over 65 years of age (39.0 per 100,000 person-years). Compared with the non-UM cohort, UM patients had a significantly increased hazard ratio of meningioma (HR 1.45, 95% CI 1.23–1.70), especially in individuals between 50 and 65 years of age (HR 1.64, 95% CI 1.19–2.26). The cumulative incidence of meningiomas was also significantly higher in patients with UMs than in those without UMs (log-rank p < 0.001) (Fig. 1).

In addition, the subjects living in areas with the highest, second-highest, and lowest levels of urbanization had a significantly increased hazard ratio (HR 1.46, 95% CI 1.10–1.95 for highest; HR 1.49, 95% CI 1.13–1.97 for second-highest; and HR 1.56, 95% CI 1.07–2.27 for lowest levels of urbanization), with a greater incidence rate ratio estimate for UM patients than for non-UM patients (Table 2).

The incidences of meningioma in UM patients who had undergone myomectomy versus those who had not
Meningioma in women with uterine myoma

undergone myomectomy were 11.3 (per 100,000 person-years) and 9.47 (per 100,000 person-years), respectively. Patients with UMs who underwent myomectomy had a higher risk of developing a meningioma than patients who did not undergo myomectomy (incidence rate ratio 1.19, 95% CI 1.12–1.27). However, the risk was not shown to be significant in the multivariate analysis (HR 1.23, 95% CI 0.68–2.21) (Table 3).

Discussion

This nationwide population-based cohort study found that women with UM had a significantly (45%) higher risk of developing meningioma than women without UM. Stratified analyses revealed that a higher risk of meningioma among women with UM was observed in most age groups, but a significant difference between the UM patients and the non-UM patients was only seen in the age range of 35 to 65 years. Both UM women having professional and nonprofessional occupations showed significantly higher risks of meningioma. Women living in areas of higher urbanization tended to have significant differences in risk. Further analysis revealed that having undergone a myomectomy did not influence the relationship between UM and meningioma. The cumulative incidence of meningioma between groups with and without UM differed over time.

The remarkable frequency of UM in women prompted an investigation into the role of environmental factors in tumor etiology. Having been implicated in the dramatic rise in hormone-related cancers in recent years, endocrine disruptors have been increasingly implicated in this pathogenesis. It has become clear that hormonal environment has a tremendous impact on the development and growth of UM. Both estrogen and progesterone have been linked to the development of UM. Englund et al. found that estrogen and progesterone receptors were overexpressed in fibroid tissue.14 Uterine myoma is most prevalent during a female's reproductive years, is rarely observed before puberty, and usually regresses after menopause. Factors that increase overall lifetime exposure to estrogen, such as early menarche and obesity, are considered to increase its incidence. It has been found that exercise decreased exposure to estrogen and the resulting hormonal balance was suggested to be protective.24 Paradoxically, UM rarely develops during pregnancy, despite extremely high steroid hormone levels, and, thus, pregnancy appears to exert a protective effect.26 Reproductive factors were also considered to be associated with the growth of meningioma, but published epidemiological studies have reported conflicting results. Cowpli-Bony et al. reviewed the epidemiological literature and concluded that female sex hormones protect against glioma and may increase the risk of meningioma. Jhawar et al. found that the risk of meningioma increased among women exposed to either endogenous or exogenous sex hormones but also noted an unexpected relationship with increasing age at menarche. However,
TABLE 2: Comparison of incidence rate ratio and adjusted hazard ratio of meningioma stratified by age, occupation, and urbanization between groups with and without UM

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<th>Person-Yrs</th>
<th>Rate*</th>
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<th>IRR (95% CI)</th>
<th>Age-adjusted HR (95% CI)</th>
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* Per 100,000 person-years. IRR = incidence rate ratio.
† Statistically significant at p < 0.001.
‡ Statistically significant at p < 0.01.
§ Statistically significant at p < 0.05.
other studies of age at menarche have demonstrated no significantly increased or decreased risk of meningioma development.\textsuperscript{12,17,21,22,25,31} No consistent results have been obtained regarding the role of menopause in epidemiological studies. Some studies have found significantly increased risks, with the odds ratios ranging from 2 to 2.8.\textsuperscript{12,22} On the contrary, Jhawar et al. found that postmenopausal women had a significantly lower risk of meningioma development than premenopausal women, whether they were being treated with postmenopausal hormones.\textsuperscript{20} No association between menopause and meningioma was found in others.\textsuperscript{17,25,31} Studies have not found a clear trend for age at menopause.\textsuperscript{17,21,31} The functional significance of hormone receptors in meningioma development remains controversial.\textsuperscript{30} The expression of hormonal receptors was investigated in 1 study.\textsuperscript{12} The authors of a pilot study of 31 meningioma samples reported that a specific gene expression pattern appeared to be more strongly associated with progesterone receptor status,\textsuperscript{8} and, therefore, only tumors expressing a progesterone receptor were analyzed. The results of several epidemiological studies regarding the effect of pregnancy were also controversial.\textsuperscript{10,17,20,22,31}

Although sex hormones are considered to have an etiological role in both UM and meningioma, as noted in the preceding discussion, not all hormone-related factors support the evidence of a link between UM and meningioma. Only 2 recent epidemiological studies have identified UM as a risk factor for meningioma. Johnson et al. used the Iowa Women's Health Study to conduct a population-based prospective study that evaluated the risk factors for meningioma in postmenopausal women. They found that a history of UM was positively associated with meningioma risk in a multivariate analysis (RR 1.72, 95% CI 1.19–2.50).\textsuperscript{21} Claus et al. investigated the family and personal history and risk of meningioma using a case-control study. Their data revealed that meningioma patients were more likely than control subjects to report UM (OR 1.2, 95% CI 1.0–1.5).\textsuperscript{7} Based on the nationwide population-
based source, with a larger-scale database, our findings are consistent with theirs.

Figure 1 shows a higher risk of meningioma in women with UM over time. However, the association is not likely to be causal. It is possible that these patients share a genetic predisposition or simply have overlapping risk factors.\textsuperscript{21} In addition, analysis of our data revealed that having undergone a myomectomy did not have a significant influence on the risk of meningioma, which implies that UM is not an independent predictor for meningioma. Our results also showed that only UM women ranging in age from 35 to 65 years had a significantly higher risk for meningioma, as indicated by the number of cases. The women in this age group had the most cases of UM, and statistically significant findings were expected to occur more frequently in this group than in other groups. Women with UM living in higher urbanization areas tended to have a significantly higher risk for meningioma, which may be partially explained by the higher availability of medical resources in urbanized areas.

The strengths of the present study lie in the population-based design with its large, nationally representative sample and data on UM and meningioma diagnoses, which were highly reliable. However, one main limitation needs to be addressed. The comparative analyses were not adjusted for potential confounders, including exogenous hormone use, circulating sex hormone levels, and other reproductive factors, body mass index, and family history of UM and/or meningioma. This limitation exists because of the inherent shortcomings of the NHIRD.

Conclusions

The results of this population-based retrospective cohort study indicated that women with UM had a higher risk of developing meningioma. Whether these conditions are related or simply share similar risk factors remains unclear. Further investigation is necessary to answer this question.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Kao, Yen, Sun. Acquisition of data: Yen, Sun, Lin. Analysis and interpretation of data: Kao, Yen, Sun, Lin. Drafting the article: Kao, Yen, Sun, Chang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kao. Statistical analysis: Lin, Chang, Sung. Administrative/technical/material support: Sung. Study supervision: Kao, Sung.

References

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