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Association Between Melanoma And Glioma: An Observaitonal Study In A Random Sample Of The Taiwanese Populaiton

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**ASSOCIATION BETWEEN MELANOMA AND GLIOMA: AN
OBSERVATIONAL STUDY IN A RANDOM SAMPLE OF THE
TAIWANESE POPULATION**

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ABSTRACT

Background: In a previous study, it was shown that melanoma patients have a greater incidence of glioma as compared to the general population in United States. Because glioma and melanoma do not have common environmental risk factors, this observation suggests a common genetic predisposition shared by glioma and melanoma that maybe used to lead future research of the specific genes and drug targets for both malignancies. However, this observation has to be confirmed in other populations. The aim of this study was to investigate the association between melanoma and glioma in Taiwanese population.

Methods: We used claim data of Taiwan's National Health Insurance Research Database (NHIRD) from year 1998 to 2010. The study population included 1,000,000 randomly selected men and women ages 20 and older from the NHIRD database. Glioma was defined by ICD-9-CM codes 191, 192.0-192.3, 192.8, 192.9, 225 and 237.5. Melanoma was defined by ICD-9-CM codes 172, 173, 190.0, 190.9, 192.1, 216.X (X=0, 3-7, 9), 224, 223.2, 235.1, 235.2, 237.6, 238.2, 238.3, 238.8. We excluded participants under ages 20 at 1998 and unknown gender (n=324,879). Cox's proportional hazard regression analysis was conducted to estimate the association between the history of melanoma on glioma risk.

Main results: The hazard ratio of developing glioma was significantly higher in patients with melanoma than in those without melanoma (hazard ratio (HR) = 6.18; 95% confidence interval (CI) = 5.57-6.85). The hazard ratio for developing glioma was lower in male patients than in female patients, with the hazard ratio of 0.77 (95% CI = 0.71-0.84), adjusted for melanoma and age. The hazard ratio increased with age peaking at age group age from 60 to 69 and decrease after 70 years and older.

Conclusion: The present study showed that Taiwanese patients with melanoma are at a higher risk of developing glioma. The exact underlying etiologies require further investigation.

Keywords: Epidemiology, Melanoma, Glioma

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ABBREVIATIONS

CNS	central nervous system
SEER	Surveillance Epidemiology and End Results
NHI	National Health Insurance
NHRI	National Health Research Institute
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
HRs	hazard ratios
CI s	confidence intervals

CHAPTER I

INTRODUCTION

1.1 Background and Purpose of the Study

Gliomas are the tumors that arise from the glial cells of the brain, and constitute a large portion of all malignant central nervous system (CNS) tumors in the United States (77%), and approximately 91% of CNS tumors in Taiwan 2013 (Chien et al., 2016; Scarbrough, Akushevich, Wrensch, & Il'yasova, 2014; Schwartzbaum, Fisher, Aldape, & Wrensch, 2006; Health Promotion Administration, 2016). The glioma incidence rate is approximately 6 cases per 100,000 in the United States and 3 cases per 100,000 in Taiwan (Chien et al., 2016; Health Promotion Administration, 2016; Scarbrough, Akushevich, Wrensch, & Il'yasova, 2014). Although glioma is a rare malignancy, it is a highly fatal tumor, with the five year survival rate of 30% in the United States and 34.3% in Taiwan (Chien et al., 2016; Schwartzbaum et al., 2006).

The etiology of glioma is largely unknown. Understanding glioma etiology can help develop prevention measures as well as to identify drug targets to improve treatment (Bondy et al., 2008). One way to explore a window of glioma susceptibility maybe via examining the associations between glioma and other diseases. Finding a connection between different diseases could help discovering the common etiological components. A suspected association between melanoma and glioma may help discover a common etiological component for the two malignancies and provide a new information guiding the development of new therapy.

Several published reports support the familial association between glioma and melanoma, known as the melanoma-astrocytoma syndrome (Azizi et al., 1995; Kaufman,

Kimmel, Parisi, & Michels, 1993; Paunu et al., 2002; Scarbrough et al., 2014). At the population level, the association between melanoma and glioma was suggested by the analysis of the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database in the United States (Scarbrough et al., 2014). This finding requires confirmation in other populations. Our hypothesis is that in Taiwan, melanoma patients have higher risk of glioma. To test this hypothesis, we used Taiwan National Health Insurance (NHI) research database.

1.2 Research question and hypothesis

Our research question is whether in the Taiwan Population ages 20 and over patients with melanoma have a greater risk of developing glioma as opposed to individuals without a melanoma history.

Our hypothesis is that individuals with history of melanoma have a greater risk of developing glioma compared to those who do not have a history of melanoma.

CHAPTER II

LITERATURE REVIEW

2.1 Epidemiology of glioma

Gliomas account for almost 80% of primary malignant brain tumors (Scarborough et al., 2014; Schwartzbaum, Fisher, Aldape, & Wrensch, 2006). The world age-adjusted incidence rate was 3.7 cases per 100,000 for men and 2.6 cases per 100,000 for women (Bondy et al., 2008). In the United States, the age-adjusted incidence rates were 6 cases per 100,000 and 3 cases per 100,000 in Taiwan (Bondy et al., 2008; Chien et al., 2016). Approximately 18,000 new diagnose cases and 13,000 deaths in the US (Schwartzbaum et al., 2006). The five year survival rate of 30% in the United States and 34.3% in Taiwan (Chien et al., 2016; Schwartzbaum et al., 2006). The incident rate changes in the different country. The glioma incident was higher in Europe, America, and Australia than in Asia and pacific area (Bondy et al., 2008; Schwartzbaum et al., 2006). Most malignant brain tumors have a greater incidence among males than in females (Bondy et al., 2008; Chien et al., 2016; Scarborough et al., 2014). The incidence rate for glioma were 14.07 cases per 100,000 person-years in adults and 0.18 cases per 100,000 person-years in children using data from United States, Belgium, and England (de Robles et al., 2015). The diagnosis tools and the level of medication might be the reason cause area difference between United States and Taiwan (Chien et al., 2016). The culture and the racism also need to take in to consider (Chien et al., 2016).

The etiology of glioma remains mostly unknown. Several studies investigate the factors that might have the association with the glioma. Genetic predisposition to glioma is suggested by several syndromes, familial aggregation, linkage studies, and mutagen

sensitivity studies (Bondy et al., 2008). The only environmental factor linked to glioma risk is ionizing radiation (Bondy et al., 2008; Thompson et al., 1994). Specifically, therapeutic radiation has also been reported to be associated with glioma risk (Furst, Lundell, Holm, & Silfversward, 1988; Griem et al., 1994). The correlation between glioma and non-ionizing radiation cell phone use were also investigated but the results are mostly inconsistent (Bondy et al., 2008; Morgan, Miller, Sasco, & Davis, 2015). The atopic conditions, including allergies, and systemic infections have been reported to have inverse association with the glioma (Linos, Raine, Alonso, & Michaud, 2007). Other factors like viruses, neuro-carcinogens and metals are suspected to be associated with glioma (Bondy et al., 2008).

2.2. Epidemiology of melanoma.

Melanoma is the skin cancer that starts from the melanocytes cells. Although the occurrence of melanoma is less than non-melanoma, this malignancy presents the major cause of skin cancer mortality (WHO, 2016). Every year about 132,000 melanoma cases occur globally each year (WHO, 2016). The rates of melanoma have been increasing during the last 30 years. The rates of new melanoma cases is 22 per 100,000 person-years in United States (WHO, 2016). In Taiwan, the age standardized incidence rate is 9.72 per 100,000 in males and 7.69 per 100,000 in females. The melanoma incidence rate are ranked as being the 8th most common malignancy among both males and females in 2013 in Taiwan and melanoma rates increase with age (Health Promotion Administration, 2016; NHIA, 2010).

The risk factors of melanoma include both genetic and environmental factors. Among genetic factors, the mutation in CDKN2A have been associated with melanoma

(MacKie, Hauschild, & Eggermont, 2009). Males have higher rate than the female, probably due to hormonal differences (MacKie et al., 2009; Scarbrough et al., 2014). The ultraviolet radiation exposure, including artificial and natural, presents the major environmental risk factor for melanoma (Gefeller, Fiessler, Radespiel-Troger, Uter, & Pfahlberg, 2016; MacKie et al., 2009). In addition, some case-control studies also showed that the pesticide exposure may contribute to the risk of melanoma (MacKie et al., 2009; Pukkala et al., 2002).

2.3. Association between melanoma and glioma.

Several published reports support the familial association between glioma and melanoma, known as the melanoma-astrocytoma syndrome (Azizi et al., 1995; Kaufman et al., 1993; Paunu et al., 2002; Scarbrough et al., 2014). At the population level, the association between melanoma and glioma was suggested by the analysis of the SEER database in the United States (Scarbrough et al., 2014). Although this association could be treatment-related, i.e. as reflecting increased risk of the second malignancy as a result of cancer therapy, the previous analysis of the SEER data did not confirm this hypothesis (Scarbrough et al., 2014).

The common antigen expression and genetic alterations between melanoma and glioma have been supported by other studies studies (Killela et al., 2013; Kuan et al., 2011; Solomon et al., 2008). An inverse association atopic conditions with melanoma parallels similar inverse association between atopic conditions and glioma, suggesting a common genetic predisposition related to immunological factors (Linos et al., 2007).

CHAPTER III

METHODOLOGY

3.1 Data Source

The nationwide population-based study was started in 1996. The data were obtained from the Taiwan National Health Insurance (NHI) research database which has been routinely collected by the National Health Research Institute (NHRI). Up to 99% of 23 million Taiwanese population have been covered by the health insurance, making the insurance database an appropriate source of data for population-based studies. In this study, the data used represent a random sample of one million individuals from the NHI database for 1998 to 2010. The sample was selected by the NHRI from the total population, and the distribution of the sample was shown no difference compare with the total population.

3.2 Definition of glioma and melanoma

Patients with glioma were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 191, 192.0-192.3, 192.8, 192.9, 225 and 237.5. Melanoma was identified using ICD-9-CM code 172, 173, 190.0, 190.9, 192.1, 216.X (X=0, 3-7, 9), 224, 223.2, 235.1, 235.2, 237.6, 238.2, 238.3, 238.8. Both conditions were identified in the claims database between 1 January 1998 and 31 December 2010. Patients less than age 20 were excluded from the database.

3.3 Study variables

Glioma identified by the selected ICD-9 code was our main outcome variable. Age, gender, and melanoma will be included in the data analysis as independent variables. Age was defined at baseline. For glioma patients, age at diagnosis was calculated from the initial day of registry in the database and specific age of diagnosing glioma or melanoma among

those who were 20 years of age or older. Age was also stratified by ten year interval, with the oldest age category being 80 years of age and older.

3.4 Statistical analysis

All statistical analyses were performed in SAS, version 9.2. Distribution of glioma and melanoma cases by age and gender were described. A Cox proportional hazard regression analysis was used to estimate the hazard ratios (HRs), and the accompanying 95% confidence intervals (CIs) associated with each of the independent variable. HRs of glioma associated with melanoma were adjusted for age and gender. The value of $P=0.05$ was considered significant.

CHAPTER IV

RESULTS

The current analysis included 675,121 patients after exclusion of those under 20 years old. We identified 23,959 melanoma cases and 2219 glioma cases diagnosed between 1998 and 2010. The follow-up time for each participant ranged from 0 to 13 person-years.

Age distribution for melanoma and glioma cases are presented in Table 1. Table 1 shows that the number of melanoma cases increases with age peaking at the fourth decade with slight decline at fifty and older (Table 1). And the number of glioma cases increased with age peaking at the fifth decade with slight decline at sixty and older (Table 1). The gender distribution showed that more females have melanoma (50.41%) and glioma (55.16%). Also, among glioma patients with prior melanoma approximately 63% were females. The risk of glioma adjusted for gender increased with age, with the hazard ratio peaking at age group age from 60 to 69 and decrease after 70 years and older (Figure 1).

The hazard ratio of developing glioma in melanoma patients was significantly higher among patients without melanoma (HR=6.18, 95%CI=5.57-6.85), after adjusted gender and age (Table 2). The hazard ratio for developing glioma was lower for males, with the relative risk being 0.78 (95% CI = 0.714-0.844), after adjustment for age and history of melanoma (Table 2).

Table 1.

Age and gender distribution of glioma, melanoma, and glioma with prior melanoma cases. Cases were identified between 1998 and 2010.

	Melanoma	All gliomas	All gliomas with prior melanoma
Age			
20-29	1685 (6.75%)	86 (3.88%)	6 (2.32%)
30-39	4999 (20.03%)	297 (13.38%)	29 (11.2%)
40-49	5941 (23.8%)	430 (19.38%)	46 (17.76%)
50-59	4984 (19.97%)	434 (19.56%)	51 (19.69%)
60-69	3318 (13.29%)	447 (20.14%)	47 (18.15%)
70-79	2795 (11.2%)	384 (17.31%)	59 (22.78%)
80+	1237 (4.96%)	141 (6.35%)	21 (8.11%)
Total	24959	2219	259
Gender			
Male	12378 (49.59%)	995 (44.84%)	96 (37.07%)
Female	12581 (50.41%)	1224 (55.16%)	163 (62.93%)

*For “Melanoma” and “glioma”, age category is determined by age at disease diagnosis.

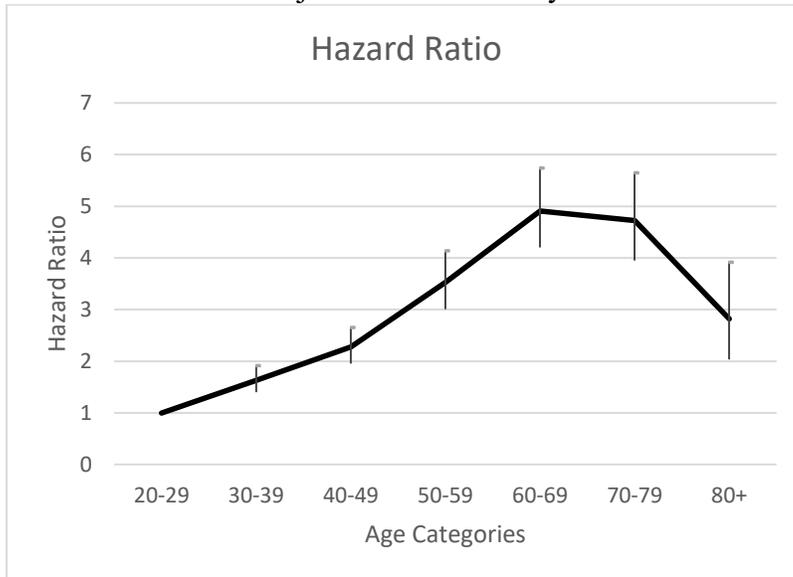
*For “prior melanoma”, age category is determined by age at all glioma diagnosis.

Table 2. Association between history of melanoma and glioma risk

Risk factor	Hazard Ratio	95% Confidence Limits
History of melanoma (yes/no)	6.39	5.77-7.08
Gender (male vs. female)	0.78	0.71-0.84
Age at baseline (years)	1.03	1.03-1.03
Age at baseline (10 years)	1.34	1.31-1.37

Figure 1

The hazard ratio of glioma in different age-groups as compare to age 20-29. The hazard ratio estimates were adjusted for the history of melanoma and gander.



Risk factor	Hazard Ratio	95% Confidence Limits
20-29	1 (ref)	
30-39	1.63	1.4-1.91
40-49	2.28	1.95-2.65
50-59	3.53	3.01-4.14
60-69	4.91	4.2-5.74
70-79	4.72	3.95-5.64
80+	2.82	2.04-3.91

CHAPTER V

DISCUSSION AND CONCLUSION

The main finding of this analysis is increased the hazard ratio of developing glioma in melanoma patients as compared to patients without melanoma history in this sample of the Taiwanese population: HR=6.18, 95%CI=5.57-6.85 (Table 2). These results confirms the earlier finding in the US population (Scarborough et al., 2014). Similarly to previously published studies, our analysis shows increasing risk of glioma up to age 70 (Scarborough et al., 2014). However, unlike previous studies we found lower risk of glioma among males, whereas being a male has been an established demographic risk factor for glioma (Qi, Shao, Zhang, Hui, & Wang, 2013; Scarborough et al., 2014). Also, lower proportion of males we found among melanoma patients, whereas previous studies consistently showed increased risk of melanoma among males (Qi et al., 2013; Scarborough et al., 2014). It was suggested that males have a greater risk of glioma than females due to hormonal differences between genders (Qi et al., 2013; Scarborough et al., 2014).

The age distribution of both melanoma and glioma cases were as expected but the gender distributions of both malignancies were different from expected, i.e. females have the higher proportion than males. It is possible that although the selection of the study participants from the Taiwanese population was conducting using random procedure, the selected participants are different from the general population. Another explanation could be difference in risk factors for both malignancies in different populations. For example, ethnicity certainly differ between Taiwan and United States (Chien et al., 2016).

The strength of our study is that the national insurance database was nation-wide all the participation were recorded their health condition every time they go to the hospital

and patient's historical record (NHIA, 2010). The major limitation of this study is using a sample of the Taiwanese population as opposed to the entire population. Although the selection of the one million study participants was conducted using random sampling, this does not completely exclude selection bias.

Overall, the data in the study show the relationship between melanoma and glioma. Our result provide direction for a future study in glioma analysis in the total Taiwan population and eastern population.

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