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Original article

Exploring the association between melanoma and glioma risks

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ABSTRACT

Purpose: Gliomas are one of the most fatal malignancies, with largely unknown etiology. This study examines a possible connection between glioma and melanoma, which might provide insight into gliomas' etiology.
Methods: Using data provided by the Surveillance, Epidemiology, and End Results program from 1992 to 2009, a cohort was constructed to determine the incidence rates of glioma among those who had a prior diagnosis of invasive melanoma. Glioma rates in those with prior melanoma were compared with those in the general population.
Results: The incidence rate of all gliomas was greater among melanoma cases than in the general population: 10.46 versus 6.13 cases per 100,000 person-years, standardized incidence ratios = 1.42 (1.22–1.62). The female excess rate was slightly greater (42%) than that among males (29%). Sensitivity analyses did not reveal evidence that radiation treatment of melanoma is responsible for the detected gap in the rates of gliomas.
Conclusions: Our analysis documented increased risk of glioma among melanoma patients. Because no common environmental risk factors are identified for glioma and melanoma, it is hypothesized that a common genetic predisposition may be responsible for the detected association.

Introduction

Gliomas are tumors of neuroepithelial tissue, arising from glial cell lineage, and make up the largest percentage of all malignant central nervous system (CNS) tumors (77%) [1–3]. These cancers are rare, having a population-based incidence rate in the United States of approximately six cases per 100,000 person-years for adult glioma [1–6]. However, although these tumors are rare, they present one of the most fatal malignancies. Most subtypes of glioma tend to be aggressive and difficult to treat, with median survival below 2 years, especially in those aged 60 years and older [1]. Understanding glioma, etiology would provide a key to prevention and advancement in treatment [7]. However, despite several decades of etiologic research, the epidemiology of glioma has provided very few clues. Besides demographic factors such as gender (male), race (Caucasian), and age, the only established nongenetic risk factor for glioma is high-dose radiation [1,4,8,9]. An emerging line of etiologic glioma research studies connections between glioma and other disorders. For example, there is now a reported inverse association between the risk of glioma and a history of atopic conditions, such as allergies, asthma, and eczema [10]. Such connections between different conditions may be helpful in elucidating common etiologic components. In this regard, a suspected association between melanoma and glioma represents a possibility to discover a common etiologic link between the two disorders and thereby to provide insight into glioma etiology.

An association between melanoma and glioma was first suggested by the observation of a familial association between melanoma and gliomas [11–13], which was later confirmed by the description of the melanoma-astrocytoma syndrome, involving deletions at genetic loci coding for a number of important cell cycle control proteins [14]. There were also two later analyses, further supporting the connection between glioma and melanoma: (i) melanoma occurred more frequently than expected among first-degree relatives of glioma patients [15] and (ii) the families with glioma had a significant excess of melanoma cases [16]. We also found an association between self-reported history of melanoma and the high-grade glioma in the analysis of a case-control study; this was an unpublished incidental finding, as the main analysis explored gene–environment interactions [17]. Because we could not validate the self-reported history of melanoma in this previous study, we turned to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database, to test the hypothesis that glioma rates are greater among melanoma cases compared with those in the general population.

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Materials and methods

Data source

For this study, population-based data from the National Cancer Institute's SEER program were used, which cover approximately 26% of the United States' population [18]. Seventeen SEER registry databases were used, including data from 1992 to 2009, released on April 2010, but excluding cases impacted by Hurricane Katrina in Louisiana [19]. This study was limited to adult glioma (age >20 years).

Definition of glioma, glioblastoma, and melanoma cases and selection criteria

Glioma cases were defined using information provided by the Central Brain Tumor Registry of the United States [20]. Data for glioma cases were collected over the period of 1992–2009, using the ICD-O-3 site codes (C70.0–C72.9) and histology codes 9380-9460 for all gliomas and only the histology codes of 9440, 9441, and 9442 for glioblastoma (GB). Invasive melanoma cases were collected through the period of 1992–2009, using site codes (C44.0–C44.9) and ICD-O-3 histology codes 8720-8790. Only cases with confirmed histology of invasive melanoma and glioma were included in the analysis.

In analysis of other prior cancers, besides melanoma, ICD-O-3 site codes were used to define the other prior cancer sites in the database, for cohort selection. The International Classification of Diseases (ICD)-O-3 site codes used for breast cancer were C50.0–C50.9, for colon cancer the codes used were (C18.0, C18.2–C18.9, and C19.9), and the site code C61.9 was used for prostate cancer.

Starting in 1992, any individual with an incidence of invasive melanoma was entered into a cohort and followed until an incidence of glioma (in which event they were labeled as a case of "glioma with prior melanoma"), or until censoring (death or reaching the end of the study follow-up period, 2009). After an individual's entry into the study cohort, if multiple primaries occurred during follow-up, besides glioma, the individual was still counted as a case as long as they also had an incidence of glioma.

The time period for this analysis starting at 1992 was selected to avoid an increase in glioma detection because of the introduction of magnetic resonance imaging technology into the clinic [6]; previously published analysis by Dubrow and Darefsky demonstrated a lack of increase in observed glioma incidence since 1992 [21].

Study variables

Race was recoded as a three-leveled variable: white, black, and other. Age-specific incidence rates were calculated for those with ages between 20 and 84 years. The upper limit for age inclusion was 84 years, because SEER population data do not specify age beyond 85 years of age. Therefore, the age-standardized rates could not be calculated for the unconditional incidence of glioma, melanoma, and GB, among those in ages above 84.

Model and statistical analysis

All modeling and statistical analyses were performed in SAS, version 9.2 (SAS, Cary, NC). To calculate the rates of glioma, conditional on the incidence of a prior incidence of melanoma, invasive melanoma cases were included into a cohort and followed until the incidence of glioma or until censoring (reaching the end of the study period or death). Incidence of melanoma would qualify an individual for inclusion into the melanoma cohort, including melanoma diagnosis not being the first primary cancer. Any subsequent incidence of glioma was then counted as a case. The empirical age-specific rates (λ_a) were calculated as a ratio of the numbers of cases (n_a) to person-years (P_a) at risk: $\lambda_a = n_a/P_a$. The standard error (SE) was calculated as $\sigma_E = \sqrt{\lambda_a(1-\lambda_a)/P_a}$. The age-adjusted rates (or directly standardized incidence rates) are calculated for age 20–84 years as $\lambda = \sum_{a=20}^{84}\lambda_a P_{a,\mathrm{std}}\left(\sum_{a'=20}^{84}P_{a',std}\right)^{-1}$, where $P_{a,\mathrm{std}}$ are the age-specific counts of the standard population. The standard error for the age-adjusted rate is estimated assuming that the numbers of events observed in each age group are independent [22].

The population in the SEER areas was used for calculation of the unconditional rates, that is, glioma rates in the general population. Furthermore, we considered this population as standard and used for standardization of glioma rates in the melanoma cohort. It is important that we used the same population both for the denominator in calumniation of unconditional glioma rates and for age-standardization of glioma rates in the melanoma cohort, as this insures comparability of the rate in the general population and in the melanoma cohort. To estimate proportion of excess glioma cases in the melanoma cohort, standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) were calculated as described previously [22]. SIRs were age-standardized and stratified by gender; race adjustment or stratification was not applicable as no glioma cases were identified among the melanoma cohort in non–white racial categories. To compare glioma rates in the melanoma cohort in the sensitivity analysis, we calculated t-statistics (a ratio of the rate difference and SE for this difference evaluated as the square root of the sum of their standard errors squared) and applied t test. Because the estimates of rates were obtained based on the large number of cases, respective t distributions with large degrees of freedom were well approximated by normal distributions.

Results

In this analysis, we identified 51,088 glioma cases and 242,471 invasive melanoma cases diagnosed between 1992 and 2009. Among the glioma cases, 29,702 (58.1%) were GB. In the melanoma cohort, 192 incident glioma cases and 114 (59.4%) incident GB cases were identified. The follow-up time ranged from 0 to 17.9 person-years, with a median follow-up time of 4.08 person-years.

Similar trends were observed in age and gender distributions for melanoma and glioma cases of all categories; specifically, the number of cases increased with age peaking at the seventh decade with slight decline at age 70 years or older (Table 1). The gender distribution of melanoma, unconditional glioma, and GB cases were similar (40% female), with only a slightly lower observed proportion of females in the glioma with prior melanoma cohort (34%). These results were expected, because both gliomas and melanomas are known to be less common in females than in males. White population accounted for most melanoma and all glioma and GB cases (~90%) and all (100%) of all glioma and GB cases with prior melanoma (Table 1).

As expected, the incidence rates (per 100,000 person-years) of melanoma, all gliomas, and GB increased with age (Table 2). Whereas the increase in melanoma rates was monotonic, the rates of all gliomas and of GB decreased after age 80. Also expected [21] were greater rates of glioma among men: specifically, men had approximately 1.4-fold greater incidence rate of all gliomas and of GB compared with women. Racial differences in melanoma and glioma were also in agreement with previous studies: rates of melanoma, all gliomas, and GB were greater among whites [21,23]. In summary, the results presented in Tables 1 and 2 display the expected findings, serving as an important quality control check for this analysis.