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A Pooled Multisite Analysis of the Effects of Atopic Medical Conditions in Glioma Risk in Different Ethnic Groups

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Abstract

Background—The incidences of atopic conditions (allergies, asthma or eczema) and glioma vary by ethnicity. Atopic conditions are inversely associated with gliomas. We conducted a pooled multi-site study investigating the associations of atopic conditions with glioma in different race/ethnicity groups.

Methods—Using glioma cases and healthy controls, unconditional logistic regression was conducted to assess the associations of atopic conditions with glioma separately in White, Black, Asian and Hispanic subpopulations. Odds ratios (ORs) and 95% confidence intervals were calculated.

Results—Glioblastoma multiforme (GBM) cases were less likely than controls to report a history of atopic conditions in Whites (OR=0.46, [95% CI 0.38–0.54]) and Asians (OR=0.27, [95% C, 0.10–0.73]). The same trend was seen when looking at glioma cases of all histologies. An inverse association was not seen in Blacks for GBM or all histologies combined.

Conclusions—The inverse association between glioma and atopic conditions may vary by ethnicity due to a difference in the biology of atopic conditions in different ethnicities but may be due to chance because of the limitations of small non-White sample sizes.

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Keywords

Allergies; Atopic Conditions; Glioma

Introduction

The broad category of glioma represents 30% of all primary brain tumors. Glioblastoma multiforme (GBM), a highly aggressive form of glioma, accounts for 54% of gliomas. Less than 5% of GBM patients are still alive at 5 years after diagnosis [1]. The etiology of glioma is not well established. The only environmental factor consistently associated with increased glioma risk is exposure to ionizing radiation [2,3]. Thus, identifying other risk factors for this cancer is crucial.

An inverse association of glioma risk with atopic medical conditions has been consistently reported in the literature, with odds ratios/relative risks ranging from 0.5 to 0.7 [4–8]. A meta-analysis using several of these studies gave a combined relative risk of 0.61 (95% CI, 0.55–0.67) for allergy, 0.68 (95% CI, 0.58–0.80) for asthma, and 0.69 (95% CI, 0.58–0.82) for eczema [7]. Previous studies using the data presented here have also confirmed that allergies, asthma and other IgE related medical conditions appear to be inversely associated with glioma risk [7–9].

The association between atopic conditions and glioma may be complex, as studies assessing the association of atopic conditions in conjunction with other possible risk factors show mixed results. A recent study showed that antihistamine use was significantly associated with glioma risk among individuals reporting a history of allergies/asthma but not in those without this history. In this same study, in individuals without allergies/asthma, a history of chickenpox was strongly protective against glioma risk, whereas among individuals with allergies/asthma, the odds ratio was in the opposite direction, though statistically insignificant [10]. Additionally, associations may not be consistent among histological types. A pooled case-control study found that risk of oligodendrogliomas was not reduced due to allergies alone [11]. Finally, timing of atopic conditions may also have an impact on glioma risk. A recent brain tumor study found that inverse associations with asthma and hay fever strengthened with increasing age of allergy onset and weakened with longer time since onset [12].

Glioma incidence rates vary by ethnicity, with Whites holding the highest rates [13,14]. Studies have investigated whether there is a genetic component to the differences between ethnicities in glioma biology with conflicting results [14–16]. The prevalence of atopic conditions also varies between ethnicities, though the causes of these differences are unclear [17]. There are studies suggesting there are associations between gene polymorphisms and the presence of atopic conditions [18–20]. Thus, the associations between atopic conditions and different ethnicities may be biologically based. However, these associations may also be due to environment rather than being inherently due to ethnicity [21–22]. Whether or not the association between atopic conditions and glioma varies by ethnicity was recently evaluated. This study found no differences in rate ratios between Blacks and Whites. It should be noted

that this study included brain tumors other than glioma, though the majority were stated to be gliomas. Additionally, this study excluded females [23].

To evaluate the associations between atopic conditions and glioma in Whites, Blacks, Hispanics and Asians in a study sample with adequate statistical power, we created pooled data obtained from three separate institutions and populations.

Materials and Methods

Data were obtained from three separate case-control studies of glioma risk factors conducted by the University of Illinois at Chicago (UIC)/Duke, the University of Texas MD Anderson Cancer Center (MDACC), and the University of California, San Francisco (UCSF). Institutional Review Board approvals were obtained from all institutions.

Study Population

UIC/Duke—Hospital-based glioma cases were identified from Duke and North Shore University Health System (NSUHS) during the period of August 2003 – April, 2008 with a pathologically confirmed new diagnosis (ICDO-3 sites C70.0–C72.9 and C75.1–C75.3) of GBM (ICDO-3 histology codes 9440–9442), astrocytoma (9400–9411 and 9420–9421), or oligodendroglioma (9450–9460). Patients who were aged 18 years or older, English speaking, and United States residents were eligible for recruitment. After screening (n=1712), 1039 were determined as eligible to participate. Seven hundred forty-one patients consented to participate (participation rate=71%). Among those who consented, 429 (41% of eligible) completed the self-report surveys as of August 18, 2008. Clinic-based controls were recruited from patients seen at Duke University (96% from orthopedic clinics and 4% from other clinics) and NSUHS (from neurology clinics). Clinic controls were aged 18 years or older, had to reside in the United States, and could not have had a brain tumor or history of a neurodegenerative disease, and were frequency matched to cases by age (10-year interval), gender, and race/ethnicity. Subjects who consented to participate were asked to complete a web-based or telephone survey that included information on demographics, personal and family medical history, as well as occupational, residential, dietary, and numerous potential environmental exposures.

MD ANDERSON CANCER CENTER—Using population-based methods, cases consisted of adults over the age of 18 years with newly diagnosed, pathologically confirmed glioma (ICD-O-3 codes 9380-9481) identified in the MDACC Neuro-Oncology clinic between January 2001 and January 2006 who live in several counties around Houston, Texas. Controls were obtained through a contracting company by random-digit dialing in the same geographic areas as the cases and were frequency-matched to cases on age (within 5 years), race/ethnicity and sex. The participation rate was 77% for cases and 53% for controls. Questionnaires were used to conduct detailed in-person or telephone interviews for cases, their proxies or controls through which data on demographic factors, health characteristics, medications, reproductive factors and familial attributes [24].

UCSF—Study subjects were recruited by population-based methods in the San Francisco Bay Area from 1997–2004. Cases included all individuals diagnosed with pathologically

confirmed glioma (ICD codes 9380 to 9481) and were identified via rapid case ascertainment methods using the Northern California Cancer Registry. All cases and controls were 20 years of age or older. Population based controls were selected through random digit dialing and frequency matched to cases by age, race, and gender. Subjects or their proxies completed a detailed in-person interview including history of allergies. Data were also collected on demographic factors, health characteristics, medications and reproductive factors [20.25]. The participation rate was 75% for cases and 73% for controls.

Pooled Study Population—The UIC/Duke data included 697 cases and 614 controls. 4 cases and 1 control from this dataset were deleted from the analysis due to missing responses for presence of an atopic condition. The final UIC/Duke data used for the pooled analysis had 693 cases and 613 controls. The UCSF data included 939 cases and 934 controls. 4 cases and 3 controls from this dataset were deleted from the analysis due to missing responses for presence of an atopic condition. The final UCSF data used for pooled analysis included 935 cases and 931 controls. The MDACC data included 622 cases and 662 controls. No cases or controls were excluded from the MDACC data. 72 % of the UCSF case data (n=673) was obtained through self-report, and 91.4 % of the MD Anderson case data (n=569) was obtained through self-report.

The UIC/Duke contributions were as follows: Cases: 93.1% white (n=645), 2.3% Black (n=16), and 4.6% Other (n=32), Controls: 87.0% White (n=533), 8.0% Black (n=49), and 5.1 % Other (n=31). The MD Anderson contributions were as follows: Cases: 86.0% white (n=535), 3.9% Black (n=24), 8.0% Hispanic (n=50), 1.1% Asian (n=7) and 1.0% Other (n=6), Controls: 87.7% White (n=579), 6.7% (n=44), 3.3% Hispanic (n=22), 1.5% Asian (n=10) and 1.0 % Other (n=7). The UCSF contributions were as follows: Cases: 78.2% white (n=731), 3.6% Black (n=34), 8.0% Hispanic (n=75), 7.1% Asian (n=66) and 3.1% Other (n=29), Controls: 78.5% White (n=731), 4.3% Black (n=40), 7.6% Hispanic (n=71), 7.9% Asian (n=73) and 1.7% Other (n=16).

The pooled analysis contained a total of 2250 cases and 2206 controls. Analysis was repeated for 1298 GBM cases versus 2206 controls.

Statistical Methods

Subjects were asked about the presence of various medical conditions, including allergies, asthma and eczema. There were some differences between institutions in the definitions of atopic conditions. Specifically, institutions differed in whether they asked about history of eczema. MD Anderson and UCSF asked about a personal history of asthma or allergies, while UIC/Duke asked about a history of allergies, asthma and eczema (Table 1).

Additionally, both the studies from MD Anderson and UIC/Duke inquired about medical personnel-diagnosed atopic conditions (allergies, asthma or eczema). In the UCSF series, atopic conditions including allergies were self-reported in the survey, which resulted in a much higher prevalence of allergies in this population.

We conducted analyses using SAS version 9.1 (SAS Institute, Cary, NC). Data from UIC/Duke, UCSF and MDACC were analyzed separately and as a pooled dataset (data for

individual institutions not shown). Using the Breslow-Day test for homogeneity, effect modification was assessed to ensure that the effect of atopic conditions on glioma did not differ by institution. Additionally, data from UCSF and MD Anderson were analyzed separately for case data that was acquired through self-report, and data from all proxy and self-report cases combined to ensure that inclusion of proxy reports did not alter results (data not shown). Associations between cases and controls were tested using a Chi-Square statistic for categorical variables and a t-test for continuous variables. Age-, institution-, gender- and race-adjusted odds ratios and their 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. Heterogeneity between races was assessed using Cochrane's Q test. Additionally, interaction between race and atopic conditions was assessed using an interaction term in the logistic regression model for comparisons between any two races. Statistical significance was assessed using a two sided test at the alpha=.05 level for all studies.

Results

The prevalence of atopic conditions was as follows: For UCSF, 75.9% (n=710) of cases reported an atopic condition and 85.9 % (n=800) of controls reported an atopic condition. For MD Anderson, 16.3% (n=101) of cases reported an atopic condition and 33.8 % (n=223) of controls reported an atopic condition. For UIC/Duke, 36.6% (n=251) of cases reported an atopic condition and 50.8% (n=308) of controls reported an atopic condition (Table 1). However, even with the differences in definitions, all three datasets fundamentally assessed presence of atopic conditions and the inverse association between glioma and atopic conditions in the three studies was consistent. None of the differences precluded the ability to combine the datasets. A Breslow-Day test of homogeneity showed no differences between institutions (data not shown). Data were analyzed for each institution separately and variables from each study were evaluated and recoded to a common dataset for use in a pooled analysis.

As shown in Table 2, the pooled dataset resulted in 2250 cases of all histologies, 1298 GBM cases and 2206 controls. Cases were younger than controls (mean ages 51.54 and 53.30, respectively). There was also a difference in gender distribution; 43.38% of cases and 50.82% of controls were female. The same trends were seen when comparing GBM cases with healthy controls. The majority of cases (84.62%) and controls (83.23%) in the pooled dataset were White.

Table 3 shows the magnitude of the associations between atopic conditions and glioma for each institution, controlling for age, race, gender, as well as the pooled estimate controlling for age, race, gender and institution. Atopic conditions were consistently protective in all glioma histologies combined and GBM alone in all the individual institutions, as well as in the pooled estimate. For the combined data for all gliomas, the presence of an atopic condition was less likely to be reported by cases than controls (OR= 0.49, [95% CI, 0.43–0.57]). A very similar effect was seen when limiting the analysis to GBM cases (OR= 0.47, [95% CI, [0.40–0.55]).

Table 4 shows the magnitude of the associations between atopic conditions and GBM separately and for all glioma histologies combined by race/ethnicity controlling for age, gender, and institution. There was no association seen between atopic conditions and all gliomas (OR= 0.96, [95% CI, 0.50–1.84]) for Blacks. The association seen between atopic conditions and all gliomas for Hispanics (OR=0.81, [95% CI, 0.42–1.57]) was not statistically significant. The estimate was similar when limiting the analysis to GBM cases. In Whites, the presence of an atopic condition was less likely amongst all glioma cases than controls (OR= 0.47, [95% CI, 0.41–0.55]), and for GBM cases (OR= 0.46, [95% CI, [0.38–0.54]). In Asians, presence of an atopic condition was less likely amongst all glioma cases than controls (OR= 0.32, [95% CI, 0.14–0.75]), or amongst GBM cases compared to controls (OR= 0.27, [95% CI, [0.10–0.73]). The Cochrane's Q test across all races showed that the difference of the association between atopic conditions and glioma across all race groups are not significant. The interaction between race and atopic conditions was significant when comparing Blacks to Whites (p=0.02) and Blacks and Asians (p=0.04) (data not shown).

DISCUSSION

In this study, atopic conditions were less prevalent among cases than controls. However, this inverse association did not hold true across all ethnicities. This study adds to the evidence that atopic conditions may be protective for glioma but suggests that the inverse association may be influenced by additional factors such as ethnicity [4–6, 26–29]. Specifically, in this study, the inverse association was seen with Whites and Asians, but not with Blacks. The inverse association in Hispanics was not statistically significant. Despite many studies describing an inverse association between atopic conditions and glioma, not all studies have confirmed this association. A study by Cicuttini et al. showed no statistically significant association between glioma and either asthma (OR=0.8, 95% CI: 0.5–1.2) or eczema (OR=0.9, 95% CI: 0.5–1.4) [30]. However, this study did not specify racial distribution in their study population. Our findings may explain some of the inconsistencies between studies.

Genetic differences between Blacks and other ethnicities is one possible explanation for the lack of the inverse association between atopic conditions and glioma, as glioma development is associated with common germline alterations with limited penetrance [31]. These low-penetrance germline alterations may be difficult to identify but could theoretically be associated with ethnicity. It is also worth considering the differential burden of atopic conditions in different ethnicities. Blacks have a higher burden of atopic disease, and it is unknown what role this may play in glioma etiology [32]. Finally, even with the pooled data, the sample size of non-Whites was small. Thus, there is a chance that differences between races are simply due to chance. Further research is needed to distinguish the relationship between atopic conditions and glioma in Blacks.

The strengths of this analysis include the availability of a large number of variables for study, several of which are poorly studied with respect to glioma. Additionally, the ability to pool studies greatly increased sample size. While there were differences in the types of

controls used across the studies (clinic controls versus random-digit-dialed population controls), the association was consistent across all sites.

There were some limitations in our study that are important to address. Even with a larger pooled study, the actual numbers of subjects in each non-White ethnic group were small, resulting in limited statistical power in each ethnic group. For example, the lack of a statistically significant inverse association in Hispanics may be due to small sample size. As it is difficult for any single institution to gather a sufficient number of cases for glioma analyses, a major goal of the Brain Tumor and Epidemiology Consortium (BTEC) is to enhance collaborative research [33]. Our study enabled a larger sample size through pooling data.

There were also differences between institutions in the requirement of physician diagnosis of allergies vs. self-report. The prevalence of allergies was particularly high in the UCSF population (75.9% of cases and 85.9% of controls), and this may be due to the broad definition of allergies used in this study population, as well as the fact that subjects from a subset of the UCSF population reported only self-reported allergies, as opposed to the diagnosis by a medical professional used in all the other studies. It is important that the same definition of allergies was used within each study, minimizing bias in the pooled analysis.

An additional issue was the use of clinic controls in the UIC/Duke, who may have been more likely to have other medical conditions, as opposed to population controls. A specific issue was that subjects with neurodegenerative disease were excluded from the study, but those with other medical conditions including autoimmunity were not. Finally, the use of proxy and self-report survey responses in the UCSF and MD Anderson data may have had an effect on results, though we analyzed data both including and omitting cases, and saw only small differences. Regardless, self-reported data is always at risk for being affected by differential recall bias in cases vs controls.

Despite these limitations, these data add to the evidence of a reduced risk for malignant glioma, showing cases have lower prevalence of atopic conditions than controls. This association appears strongest in the Whites and Asians. A better understanding of these observations and the mechanisms underlying these observations is needed.

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Table 1

Description of Study Populations and Prevalence of Atopic Conditions [a]

	Definition of Atopic Conditions	Prevalence of Atopic Conditions In cases	Prevalence of Atopic Conditions In Controls
UCSF	Personal history of asthma or allergies	710/935 (75.9%)	800/931 (85.9 %)
UIC/Duke	History of allergies, asthma and eczema)	101/693 (16.3%)	223/613 (33.8 %)
MDACC	Personal history of asthma or allergies	251/622 (36.6%)	308/662 (50.8%)

[a] UCSF, UIC/Duke and MDACC and Pooled Study of all Institutions Combined

Table 2

Distribution of Demographic Characteristics for All Glioma Cases and Controls From Three US Studies [a]

	Healthy Controls N=2206	GBM[b] N=1298	All Gliomas N=2250
Mean Age (SD)	53.30 (14.98)	56.7 (12.93)	51.54 (14.68)
Gender-female (%)	1121 (50.82)	517 (39.83)	517 (39.83)
Race (%)			
White	1836 (83.23)	1119 (86.21)	1904 (84.62)
Black	132 (5.98)	41 (3.16)	74 (3.29)
Hispanic	101 (4.58)	74 (5.70)	131 (5.82)
Asian	90 (4.08)	38 (2.93)	81 (3.60)
Other	45 (2.04)	25 (1.93)	59 (2.62)

[a] UCSF, UIC/Duke and MDACC and Pooled Study of all Institutions Combined

[b] GBM is glioblastoma

Table 3

Associations Between Atopic Conditions and Gliomas: Individual and Pooled Data From Three US Studies [a]

Atopic Conditions				
	UIC/Duke OR (95% CI)*	**MD Anderson OR (95% CI)[b]**	**UCSF OR (95% CI)[b]**	**All Institutions Combined OR (95% CI)[c]**
GBM	0.59 (0.45, 0.77)	0.35 (0.25, 0.50)	0.47 (0.36, 0.61)	0.47 (0.40, 0.55)
All Gliomas	0.59 (0.47, 0.74)	0.39 (0.30, 0.51)	0.52 (0.41, 0.66)	0.49 (0.43, 0.57)

[a] UCSF, UIC and MDACC and Pooled Study of all Institutions Combined

[b] Adjusted for age, race, and gender

[c] Adjusted for age, race, gender and institution

Table 4

Associations Between Atopic Conditions and Gliomas By Ethnicity: Pooled Data From Three US Studies [a]

GBM												
	Black			**Hispanic**			**White**			**Asian**		
History of Atopic Conditions[c]	Cases N=41 N (%)	Controls N=132 N (%)	OR (95% CI)[b]	Cases N=74 N (%)	Controls N=101 N (%)	OR (95% CI)[b]	Cases N=1119 N (%)	Controls N=1836 N (%)	OR (95% CI)[b]	Cases N= 38 N (%)	Controls N=90 N(%)	OR (95% CI)[b]
	22 (53.66)	67 (50.76)	0.90 (0.47,2.23)	31 (41.89)	58 (57.43)	0.71 (0.32,1.56)	515 (46.02)	1111 (60.51)	**0.46 (0.38, 0.54)**	23 (60.53)	72 (80.00)	**0.27 (0.10,0.73)**
All Gliomas												
History of Atopic Conditions[c]	Cases N=74 N (%)	Controls N=132 N (%)	OR (95% CI)[b]	Cases N= 131 N (%)	Controls N=101 N (%)	OR (95% CI)[b]	Cases N= 1904 N (%)	Controls N= 1836 N (%)	OR (95% CI)[b]	Cases N= 81 N (%)	Controls N=90 N (%)	OR (95% CI)[b]
	40 (54.05)	67 (50.76)	0.96 (0.50,1.84)	58 (44.27)	58 (57.43)	0.81 (0.42,1.57)	883 (46.38)	1111 (60.51)	**0.47 (0.41, 0.55)**	53 (65.43)	72 (80.00)	**0.32 (0.14,0.75)**

[a] UCSF, UIC/Duke and MDACC

[b] Adjusted for age, gender and institution

[c] Includes asthma, allergies or eczema