

Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies

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Several studies have shown a decrease in glioma risk associated with a personal history of allergic conditions and the medications used to treat the symptoms. However, few studies have been able to examine risk within histological subgroups of glioma. Case-control data from M. D. Anderson Cancer Center and University of California, San Francisco were pooled to conduct the analysis stratified by histological subtype. A risk prediction model considering inflammation-related variables and antihistamine use was built using logistic regression. Of the subtypes examined, long-term antihistamine use was associated with increased risk of anaplastic gliomas, especially when length of use was considered in conjunction with history of asthma or allergy. Anaplastic cases with no history of asthma or allergy were 2.94 times more likely than controls to report antihistamine use for 10 years or more; whereas anaplastic cases with a history of asthma or allergy were 2.34 times more likely than controls to report antihistamine use for 10 years or more. Furthermore, anti-inflammatory medication use was associated with a protective effect against glioblastoma (OR = 0.80; 95% CI: 0.65, 0.99), especially among individuals with no history of asthma or allergies. No statistically significant effects of anti-inflammatory drugs or antihistamines were evident for the other histological subtypes. Thus, modulation of the immune system by the use of common drugs, such as antihistamines or nonsteroidal anti-inflammatory drugs, may contribute to the development of certain types of brain tumors.

Gliomas account for approximately three-fourths of all primary malignant brain tumors, and, despite extensive study into their etiology, there are few established risk factors.¹ Epidemiological studies of gliomas are difficult to conduct both because gliomas are rare, making recruitment difficult for large studies of risk factors, and because the classification of “glioma” is a broad grouping that includes several component histologies. These histologic types exhibit characteristic racial/ethnic and gender distributions, and may have distinct molecular profiles, according to recent gene expression studies.^{2,3} If the subtypes are actually etiologically heterogeneous, real differences in risk factors may be missed by combining subtypes in epidemiologic studies.⁴ For these reasons, pooled studies from multiple research centers are necessary to acquire enough cases to provide analyses of more detailed case groups, especially when examining rare exposures.

One current topic of interest in brain tumor epidemiology is the effect of immune responses on glioma risk. Recent studies suggest an association of self-reported allergy or asthma with lower glioma risk.^{5–15} Furthermore, some studies have reported associations between glioma risk and use of over-the-counter medications associated with inflammation, particularly nonsteroidal anti-inflammatory drugs (NSAIDs) and antihistamines.^{9,16} These drugs act to alleviate symptoms associated with histamine release after allergen exposure. We speculated that use of these medications would be more common among persons prone to allergies and more likely to be associated with a decreased risk, as has been reported in previous studies.^{10,11,15} We used data from case-control studies on adult glioma in the greater Houston, TX area and the San Francisco Bay area to examine the relationships between these medications and glioma risk by histologic subtype.

Key words: glioma, glioblastoma, epidemiology, histamine antagonists, anti-inflammatory agents

Abbreviations: CI: confidence interval; GBM: glioblastoma; MDACC: The University of Texas M. D. Anderson Cancer Center; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; RDD: random-digit dialing; UCSF: University of California, San Francisco

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Material and Methods

Data collected by M.D. Anderson Cancer Center (MDACC) as part of the Harris County Brain Tumor Study and by the University of California, San Francisco (UCSF) as part of the Bay Area Adult Glioma Study (Series 2 and 3) were pooled to increase sample sizes in three histologic subgroups: high-grade (ICD-O codes 9440-9442), anaplastic glioma (ICD-O codes 9401, 9392, 9451, 9380, 9382) and low-grade glioma (ICD-O codes 9450, 9400, 9411, 9420, 9421, 9380, 9382, 9383, 9391, 9506).

MDACC subjects

Cases (≥ 18 years) were newly diagnosed between January 2001 and July 2008 with glioma (ICD-O-3 codes 9380-9481) and resided in the following Texas counties surrounding Houston: Austin, Brazoria, Chambers, Colorado, Fort Bend, Galveston, Harris, Jefferson, Liberty, Montgomery, Orange, San Jacinto, Walker, Waller and Wharton. Cases were interviewed before radiotherapy or chemotherapy but typically after surgery. Proxies were interviewed for subjects unable to participate because of disability or death. For all cases, diagnosis was confirmed by a neuropathologist at MDACC. Controls, frequency-matched to cases by age (within 5 years), sex and ethnicity (White, Black, Hispanic, other) were English-speaking residents of the same Texas counties obtained through standard random-digit dialing (RDD).^{17,18} Overall response rates were 77% for cases and 53% for controls.

UCSF subjects

Cases (≥ 20 years) were newly diagnosed with a histologically confirmed glioma (ICD-O-3 codes 9380-9481) between May 1997 to August 1999 (Series 2) and November 2001 to September 2004 (Series 3). They resided in six counties around the San Francisco Bay Area (Alameda, Contra Costa, Marin, San Mateo, San Francisco and Santa Clara) and were identified using the Northern California Rapid Case Ascertainment program. Controls resided in the same six counties as the cases and were identified using RDD. They were frequency matched to cases on age (within five years), sex and race/ethnicity (White, Black, Hispanic, Asian or other).^{14,19} Overall response rates were 75% for cases and 73% for controls.

MDACC interviews

Structured in-person or telephone interviews using questionnaires and show-cards were conducted with consenting cases (or proxies) and controls. Neither cases nor controls were told of the study hypotheses during the interview. Subjects answered questions about demographic characteristics, personal and family medical history (including personal history of asthma or allergies) and occupational and environmental exposures. Information on all medications taken during the past 10 years was also obtained, as previously described.⁹ The two medications of interest for the analysis were NSAIDs, linked with reduced risk in other cancers, and antihistamines,

often taken for allergies, which have been shown to confer a reduced risk for gliomas. Briefly, participants were shown or read aloud a list of these drugs (generic and brand names) and asked whether, at anytime during the 10 years before diagnosis (or interview), they had taken these drugs on a regular basis (*i.e.* at least weekly) for at least six consecutive months. If the respondent reported regular use, the interviewer asked the specific name of the drug(s) and the duration of regular use; dosage was not obtained.

UCSF interviews

In-person or telephone interviews with cases (or proxies) and controls used a structured questionnaire and show cards. The questionnaire asked extensive information about family and personal medical history including asthma and allergies, demographics, occupational history and environmental exposures, as previously described.¹⁴ The interviewer also asked for information on all medication use, including antihistamines and NSAIDs, as detailed elsewhere.¹⁶ Briefly, subjects were shown a list of drugs including generic and brand names and asked whether, during the past 10 years (or 10 years prior to diagnosis for cases), they had taken a total of 600 or more pills of any of these drugs. If so, the respondent was then asked how many times per day, week, month or year the drug had been taken during those 10 years. They were also asked the year of first use and total number of months or years of use for each category of medication; however, specific dosages were not requested.

Statistical analyses

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Whether the medication was ever used regularly, as well as the duration of use (< 10 years *vs.* ≥ 10 years), was examined in separate models. Variables that were significantly related to case status in univariable analysis were evaluated for inclusion in the final multivariable model, which was also adjusted for the frequency-matched variables (age, gender and race/ethnicity). Reference categories were those who reported no regular use of that medication. Proxy-reported data did not appreciably alter our findings and were not excluded from the analyses. To be considered a confounder, the characteristic had to be associated with the outcome in the unexposed, associated with the exposure among the controls, and must have changed the point estimate by more than 10% after adjustment. (All analyses were performed using Stata version 10.0 (Stata Corp, College Station, TX). All *p*-values are two-sided ($\alpha = 0.05$).

Results

In the pooled dataset, we obtained complete interview data from 1,534 controls and 1,339 cases, including 294 (22%) proxy-reports of which 34 were from MDACC (8.6% of MDACC cases), 134 were from UCSF Series 2 (33.4% of Series 2 cases) and 126 were from series 3 (23.2% of Series 3

Table 1. Participant characteristics, overall and by histological subtype

	Controls (<i>n</i> = 1,534)	GBM cases (WHO Grade IV) (<i>n</i> = 806)	Anaplastic cases (WHO Grade III) (<i>n</i> = 219)	Low-grade cases (WHO Grade II) (<i>n</i> = 230)	All cases ¹ (<i>n</i> = 1,339)
Age in years ² Mean(SD ³)	52.7 (15)	59.1 (13)	49.3 (15)	42.8 (13)	53.5 (15)
Gender² <i>n</i> (%)					
Male	803 (52)	470 (58)	125 (57)	117 (51)	756 (56)
Female	731 (48)	336 (42)	94 (43)	113 (49)	583 (44)
Race² <i>n</i> (%)					
White	1,207 (79)	654 (81)	171 (78)	170 (74)	1,054 (79)
African-American	82 (5)	29 (4)	5 (2)	16 (6)	56 (4)
Hispanic	137 (9)	64 (8)	21 (10)	23 (11)	115 (9)
Other	108 (7)	59 (7)	22 (10)	21 (9)	114 (9)
Education <i>n</i> (%)					
<High school	60 (4)	66 (8)	20 (9)	10 (4)	104 (8)
High school	346 (23)	240 (29)	54 (25)	62 (27)	376 (28)
Some college	318 (21)	150 (19)	45 (21)	40 (17)	252 (19)
Bachelors degree or higher	810 (53)	347 (43)	100 (46)	118 (51)	604 (45)
Ever cigarette use, <i>n</i> (%)	960 (63)	470 (59)	129 (59)	121 (53)	766 (57)
Ever alcohol use, <i>n</i> (%)	1,417 (92)	677 (84)	185 (84)	192 (84)	1,124 (84)
Family history of cancer, <i>n</i> (%)	969 (63)	540 (67)	133 (61)	115 (50)	840 (63)
Family history of brain tumor, <i>n</i> (%)	79 (5)	69 (9)	22 (10)	13 (6)	109 (8)
Inflammation-related events					
History of asthma/allergy, <i>n</i> (%)	1,007 (66)	449 (56)	121 (55)	145 (63)	776 (58)
History of chicken pox, <i>n</i> (%)	1,248 (81)	535 (75)	155 (75)	168 (75)	925 (69)
History of antihistamine use, <i>n</i> (%)	168 (11)	59 (7)	28 (13)	21 (9)	114 (9)
History of anti-inflammatory use, <i>n</i> (%)	490 (32)	250 (31)	63 (29)	60 (26)	388 (29)

¹All cases category also includes 73 glioma cases designated as “other” histologic grade and 11 cases where histologic grade was missing.

²Matching variables. ³Standard deviation.

GBM, glioblastoma multiforme.

cases). Overall, controls were more highly educated, more likely to have used alcohol and tobacco and more likely to report a positive history of the inflammation-related variables than cases (Table 1). These differences were also consistent within each of the three datasets, MDACC and UCSF Series 2 and 3 (not shown). However, there was some heterogeneity present across the three series. MDACC cases (mean: 49.8 years $\pm$ 0.68) were significantly younger than UCSF cases [means: 55.8 $\pm$ 0.78 and 54.6 $\pm$ 0.68 for series 2 and 3, respectively] ($p < 0.001$). Furthermore, MDACC cases were significantly more likely to have attended at least some college and to have a positive history of cigarette smoking. Thus, to account for such differences in the distributions of certain demographics between the three study series, we adjusted all logistic regression models for series.

Antihistamine use was significantly associated with a 64% increased risk (OR = 1.64; 95% CI: 1.03, 2.61) for anaplastic tumors (WHO Grade III), adjusting for relevant covariates (Table 2). NSAID use was significantly associated with a 20%

reduction in risk (OR = 0.80; 95% CI: 0.65, 0.99) of glioblastoma [GBM; WHO Grade IV] (Table 2). History of asthma/allergy was protective against risk across all histologic grades and overall. Among individuals with no history of asthma/allergy, participants who reported ≥ 10 years of antihistamine use had a significant 2.94-fold increase in risk of anaplastic tumors (95% CI: 1.04, 8.34) [Table 3]. A similar association was also observed among those participants with a history of asthma/allergy (OR = 2.34; 95% CI: 1.20, 4.57). Using NSAIDs for < 10 years was significantly protective against overall glioma risk, among those with no history of asthma/allergy (Table 3).

To ensure that our results did not differ substantially in a particular study series, we conducted a posthoc analysis in which we ran the logistic regression models within each series. Although there was a certain degree of heterogeneity present, the confidence intervals for the point estimates of interest were largely overlapping, which indicates that these measures of association were not notably different from each other.

Table 2. Results of multivariable logistic regression models¹

	GBM cases (n = 806)		Anaplastic cases (n = 219)		Low grade cases (n = 230)		All cases ² (n = 1,339)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Antihistamine use ³	0.89	0.63, 1.25	1.64	1.03, 2.61	1.00	0.60, 1.67	1.02	0.78, 1.34
Anti-inflammatory use ³	0.80	0.65, 0.99	1.05	0.75, 1.47	1.15	0.82, 1.62	0.90	0.75, 1.07
History of asthma/allergy	0.46	0.36, 0.58	0.43	0.30, 0.62	0.68	0.46, 0.99	0.51	0.42, 0.62
Family history of brain tumors	1.84	1.28, 2.64	2.13	1.24, 3.67	1.25	0.65, 2.38	1.79	1.31, 2.46
History of chickenpox	0.69	0.54, 0.86	0.61	0.42, 0.88	0.56	0.39, 0.80	0.67	0.55, 0.82

¹All models adjusted for age, race, sex, education, study series and all other covariates in the table. ²All cases category includes 73 glioma cases designated as "other" histologic grade and 11 cases where histologic grade was missing. ³Refers to regular use during the 10 years prior to diagnosis or interview, which is defined as: having ever taken 600+ pills (UCSF) or having used the drugs for at least once a week for a minimum of 6 months (MDACC).

GBM, glioblastoma multiforme.

Discussion

We found that cases with anaplastic glioma were more than two-times as likely as controls to report regular long-term use of antihistamines, regardless of asthma/allergy history. Among individuals with no asthma/allergy history, short-term NSAID use (<10 years) was inversely associated with glioma across all subtypes and overall (significant for GBMs and all cases). Because glioma subtypes are different in terms of clinical course and are also likely to be etiologically distinct, examining them separately is vital to identifying relevant risk factors for each.⁴ Thus, pooled analyses, such as this one, are necessary for obtaining an adequate sample size of each tumor type.

Although NSAID use has been found to be protective against various cancers in several previous studies,²⁰ very few have examined its impact specifically on the different histological subtypes of glioma.^{1,16} A previous study examining a subset of the glioblastoma multiforme cases included in this pooled analysis found a significant inverse association with regular anti-inflammatory use.¹⁶ This study was the first to examine NSAID use in relation to glioblastoma risk. The current analysis, which includes more than three times as many cases, corroborates the findings of the previous study and contributes the additional knowledge that the strongest protective effect of NSAIDs against GBM may be among those with no history of asthma or allergies.

Results from previous studies on antihistamine use and glioma risk have been inconsistent. One multinational study reported a 30% reduction in risk of adult glioma with antihistamine use.¹¹ Two related studies found small nonsignificant reductions in glioma risk associated with any antihistamine use by participants reporting a history of atopic conditions.^{12,15} Recently, Scheurer *et al.* found an overall increase in glioma risk among long-term users of antihistamines in a subset of the MDACC patients included in this analysis; that report prompted the current pooled analysis.⁹

These previous reports could differ from the current findings for three reasons. First, the definition of long-term antihistamine use is inconsistent between studies. Some reported

ever/never use without considering total length of use. Second, differences in formulations of these drugs between different populations could lead to exposures to varying doses. Approval of new over-the-counter drugs differs by country, thus formulations tend to be different not only over time but also geographically. Third, the heterogeneity of tumor types included in these studies could have also affected the results. All previous reports included all subtypes of gliomas in their analyses, whereas the current pooled analysis examined histological subtypes separately to allow the differences in effects by histologic group to be detected.

We believe this is the first report to investigate the association between adult glioma and antihistamine use accounting for different histologic subtypes of glioma. By pooling two similar datasets, we were able to obtain risk estimates stratified by histology, which showed a strong effect only among the anaplastic tumors. Although the use of self-reported medication information is a limitation of our study, there is no other valid source for this information, as most of these drugs are nonprescription. We were also unable to collect dosage data and reason for antihistamine use. Self-reported dosage information would likely be unreliable given that the exposures of interest occurred years before the interview date. While antihistamines can be used for indications other than alleviation of allergy symptoms (*i.e.* sleep aids), the use of these drugs as a result of an undiagnosed glioma is unlikely. Antihistamines are not usually taken for the relief of common brain tumor symptoms (*e.g.*, seizures, drowsiness and vision changes).

Although a growing body of literature points to a role of the immune system in prevention or promotion of gliomas,^{1,21} continued work is still needed in the identification of specific immunomodulatory medications, like antihistamines, as risk factors for glioma. Many of these medications readily cross the blood-brain barrier and act as selective inverse agonists to receptors found on the surface of glial cells. Histamine H₁ receptors can stimulate proliferation and trigger numerous inflammation pathways known to be important in carcinogenesis, such as NF- κ B and arachidonic acid.^{22,23}

Table 3. Adjusted¹ odds ratios for length of antihistamine and anti-inflammatory use, stratified by history of asthma or allergy, among all glioma cases, GBM cases, anaplastic cases and low-grade cases

Antihistamine use	Controls (n = 1,534)		GBM cases (n = 806)		Anaplastic cases (n = 219)		Low-grade cases (n = 230)		All cases ² (n = 1,339)	
	n		n	Odds ratio (95% CI)	n	Odds ratio (95% CI)	n	Odds ratio (95% CI)	n	Odds ratio (95% CI)
No history of asthma or allergy										
No use	485		343	Reference	90	Reference	79	Reference	535	Reference
<10 Years of use	25		10	0.63 (0.27, 1.46)	2	0.49 (0.11, 2.19)	3	0.80 (0.22, 2.88)	15	0.65 (0.32, 1.30)
≥10 Years of use	15		4	0.51 (0.16, 1.59)	6	2.94 (1.04, 8.34)	2	1.30 (0.27, 6.14)	12	0.98 (0.44, 2.20)
Any history of asthma or allergy										
No use	880		404	Reference	101	Reference	128	Reference	688	Reference
<10 Years of use	55		14	0.88 (0.47, 1.65)	6	1.32 (0.49, 3.55)	5	0.93 (0.34, 2.53)	28	0.96 (0.59, 1.58)
≥10 Years of use	70		31	1.24 (0.76, 2.01)	14	2.34 (1.20, 4.57)	11	1.33 (0.63, 2.79)	59	1.40 (0.94, 2.07)
Anti-inflammatory use³										
No history of asthma or allergy										
No use	375		245	Reference	68	Reference	64	Reference	396	Reference
<10 Years of use	93		42	0.55 (0.35, 0.88)	7	0.44 (0.19, 1.03)	6	0.56 (0.22, 1.39)	56	0.55 (0.37, 0.82)
≥10 Years of use	58		43	0.65 (0.39, 1.07)	14	1.08 (0.53, 2.20)	5	0.55 (0.20, 1.49)	62	0.71 (0.46, 1.09)
Any history of asthma or allergy										
No use	673		287	Reference	78	Reference	98	Reference	510	Reference
<10 Years of use	124		43	0.78 (0.41, 1.50)	12	1.63 (0.82, 3.25)	8	0.94 (0.40, 2.18)	65	0.94 (0.65, 1.34)
≥10 Years of use	210		108	1.13 (0.71, 1.79)	28	1.28 (0.77, 2.14)	33	1.39 (0.86, 2.22)	178	1.04 (0.81, 1.34)

¹All models adjusted for age, race, sex, education, study series, family history of brain tumors, and history of chickenpox and controlled for all other covariates in the table. ²All cases category includes 73 glioma cases designated as "other" histologic grade and 11 cases where histologic grade was missing. ³Individual numbers may not sum to column totals due to missing values. GBM, glioblastoma multiforme.

Furthermore, compounds that interfere with normal H₁ receptor activity can result in immune-stimulatory or -suppressive behavior, as well as affect cell proliferation and stability.²⁴ For example, a recent report showed that melanoma cells rich in H₁ receptors undergo intensive DNA damage and apoptosis in the presence of antihistamines.²⁵ These mechanisms of cellular damage could be relevant in glial cells, which also exhibit high concentrations of H₁ receptors.

The present findings support an increased risk for glioma, specifically anaplastic tumors, in adults who used antihistamines for ≥ 10 years. However, small sample sizes in some groups after stratification lessened the precision of our point estimates. Although there is biological plausibility behind our results, more laboratory evidence related to antihistamine use and glioma development would enhance support for our findings. Furthermore, the specificity of the effect to anaplastic tumors needs further biological explanation that is

unavailable with our current knowledge about the biology and pharmacology of these medications in glial cells.

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