Published in final edited form as:
Cancer Epidemiol. 2013 December ; 37(6): . doi:10.1016/j.canep.2013.08.004.

Antihistamine Use and Immunoglobulin E Levels in Glioma Risk and Prognosis

E. Susan Amirian[a,b], **Deborah Marquez-Do**[a], **Melissa L. Bondy**[a,b], and **Michael E. Scheurer**[a,b]

E. Susan Amirian: amirian@bcm.edu; Deborah Marquez-Do: deboraha@bcm.edu; Melissa L. Bondy: mbondy@bcm.edu

[a]Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA

[b]Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Abstract

Objective—An inverse association between personal history of allergies/asthma and glioma risk has been fairly consistently reported in the epidemiologic literature. However, the role of regular antihistamine use remains controversial due to a small number of studies reporting contradictory findings. We evaluated the association between regular use of oral antihistamines and glioma risk, adjusting for a number of relevant factors (e.g., immunoglobulin E levels and history of chickenpox).

Methods—We used a subset of the Harris County Case-Control Study, which included 362 pathologically-confirmed glioma cases and 462 cancer-free controls, to evaluate this association using unconditional multivariable logistic regression. These models were run among the overall study population and stratified by allergy status. Cox regression was utilized to examine whether antihistamine use was associated with mortality among all cases and separately among high-grade cases.

Results—Antihistamine use was strongly associated with glioma risk among those with a positive allergy/asthma history (OR: 4.19, 95% CI: 2.06–8.51), but not among those with a negative history (OR: 1.59, 95% CI: 0.95–2.67). There were no significant associations between antihistamine use and survival among cases.

Conclusion—The current study implies that regular antihistamine use may increase glioma risk. However, several larger studies are necessary before definitive conclusions can be drawn.

Keywords

brain neoplasms; risk factors; epidemiology; survival; case-control studies; hypersensitivity; immunoglobulin E

Corresponding Author: Michael E. Scheurer, One Baylor Plaza MS:BCM305, Houston, TX 77030, Scheurer@bcm.edu, Phone: 1-713-798-5547, Fax: 1-713-798-8711.
Contact information for co-authors: E.S.A. & D.M.D. phone: 1-713-798-7480, M.L.B. phone: 1-713-798-2953
Fax number for all authors: 1-713-798-8711, Mailing address for all authors: One Baylor Plaza MS:BCM305, Houston, TX 77030

Conflict of Interest Statement
The authors declare no conflicts of interest.

1. Introduction

Glioma is a highly fatal disease with few confirmed risk factors [1, 2]. However, recent studies have associated glioma susceptibility with factors that either modulate the immune response or serve as a surrogate for immune dysfunction (e.g., polymorphisms in immune genes, immunoglobulin E (IgE) levels, atopic conditions, antihistamine use) [3–19]. A meta-analysis of numerous case-control and two cohort studies has indicated that there is an inverse association between history of atopy/allergies and glioma risk that is unlikely to be due to chance alone [20]. Cumulatively, such findings on allergy status, in combination with the existing literature on other immunomodulatory factors, strongly support the involvement of immune hyperactivity or atopy in predicting glioma susceptibility. By contrast, the effects of regular use of antihistamines, which are commonly taken to counteract symptoms associated with allergies and atopic conditions, remain unclear.

Although a possible link between cancer risk and the use of antihistamines has long been suspected [21], results from epidemiological studies investigating such associations have not yet reached a consensus [11, 12, 22–28]. In addition to their immunomodulatory capabilities, another reason for suspecting the potential involvement of common antihistamines in carcinogenic processes is their structural similarity to N,N-diethyl-2-[4-(phenylmethyl)phe- noxy]ethanamine • HCl (DPPE), which is an intracellular histamine antagonist related to tamoxifen that has been shown to promote tumor growth [26]. Also of concern, particularly with regard to brain tumor etiology, is that antihistamines, many of which are capable of crossing the blood-brain barrier, may induce nitrosatable exposures in the brain [11, 25]. Therefore, the potential impact of long-term antihistamine use strongly warrants clarification, because, in addition to their interference with histamine-regulated pathways, there are several other mechanisms by which these medications could potentially influence cancer risk. The purpose of this study was to evaluate the impact of regular oral antihistamine use in a population of 362 pathologically-confirmed glioma cases and 462 cancer-free controls from the Harris County Case-Control Study (HCCCS).

2. Methods

2.1 Study Population & Data Collection

Detailed information on the HCCCS can be found elsewhere [11]. Briefly, newly diagnosed, histologically-confirmed glioma (ICD-O-3 codes 9380-9481) cases over the age of 18 were identified between 2001 and 2006 by hospital physicians in and around Harris County, Texas. A study neuropathologist conducted central review of pathology specimens to confirm glioma diagnosis. Cancer-free controls were obtained through random-digit dialing using standard methods [29, 30], and were frequency-matched to cases on age (± 5 years) and sex. The ability to speak English was an eligibility criterion. Participation rates for the parent study were 77% and 53% for cases and controls, respectively. Despite efforts to frequency match at recruitment, the study population had to be re-matched on sex in the analysis phase. This was likely due to the higher incidence of glioma among males [31], in conjunction with a higher availability of female controls. Thus, only a subset of available controls was utilized in the final analyses.

Data on demographic factors, health characteristics, and familial attributes were obtained through structured questionnaires, which were administered as in-person or telephone interviews. Interviews with the cases were conducted before radiotherapy or chemotherapy, but normally after surgery. Information on allergies and/or asthma, history of chicken pox, and oral antihistamine use was self-reported during the interviews. With regard to the medication use data, subjects were provided a list of drugs (i.e. generic and brand names of antihistamines) and were asked whether they had taken any of the drugs on a regular basis

for at least six consecutive months before diagnosis or time of interview (for cases and controls, respectively). If the participant reported regular use, they asked the specific name of the drug(s) and the duration of regular use. No dose information was collected. Response rates to the medication questions among cases and controls were not significantly different between in-person or telephone interviews. Additionally, samples of venous blood (20mL) were collected from each participant (for cases, before chemotherapy or radiation therapy). The parent study was approved by the MD Anderson Cancer Center Institutional Review Board (IRB) and written informed consent was obtained from all participants. The current analysis was also approved by the Baylor College of Medicine IRB.

2.2 Serology

IgE levels were determined from the participants' blood samples taken at the time of enrollment into the study. Standardized IgE enzyme-linked immunosorbent assay (ELISA) kits (Calbiotech, Spring Valley, CA) were utilized to determine IgE levels, according to manufacturer's instructions. This assay provides a quantitative assessment of IgE in serum on the basis of a standard curve with six standard values. Laboratory personnel were blinded to case-control status during the laboratory analyses.

2.3 Statistical Analysis

Cases and controls were compared on matching characteristics and other relevant attributes using χ^2 tests. Unconditional logistic regression models were used to calculate odds ratios and 95% confidence intervals (CI) for the associations between glioma status and regular oral antihistamine use, adjusting for potential confounders (which were chosen *a priori*). History of chickenpox was included in our models as a potential confounder because a growing body of literature indicates that varicella-zoster exposure may be relevant to glioma risk [32–35] and may also potentially impact the risk for atopic conditions [36, 37]. The regression models were run both among the overall study population and stratified by self-reported allergy/asthma status, as antihistamines are sometimes taken regularly for indications other than allergic conditions (i.e., as sleep aids or antiemetics). All multivariable models included matching characteristics, in order to control for residual confounding, and post-hoc analyses were conducted with all available controls to assess how much re-matching on sex in the analysis phase of our study affected logistic regression results.

IgE levels were included in the models dichotomously (≥ or < 250 international units [IU] per mL), because the impact of controlling for IgE levels at enrollment was similar whether adjusted for dichotomously, continuously, or as a three-level variable [data not shown]. Several possible cut-points for IgE levels were explored, with some dichotomizing male and female "normal" levels differently. However, despite the use of several exploratory cut-points, the minute extent to which adjustment for IgE impacted the odds ratio for antihistamine use was not affected, and the odds ratio for IgE never reached statistical significance.

Cox proportional hazards regression models were utilized to assess whether regular oral antihistamine use was associated with mortality risk among all cases, and separately, among high-grade (WHO grade IV) glioma cases. Cancer-directed treatment was not adjusted for, as treatment-related variables are unlikely to be associated with history of antihistamine use reported at enrollment, and therefore, would not act as data-based confounders. Survival analyses could not be stratified by self-reported allergy/asthma status due to the small numbers of cases resulting in inadequate statistical power (only 53 total cases with positive history of allergies/asthma). Log-log plots were used to evaluate the proportional hazards assumption; no violations were noted. All p-values were two-sided with a 0.05 level of

significance, and all statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

3. Results

The distribution of matching characteristics and other attributes among glioma cases (n=362) and cancer-free controls (n=462) is presented in Table 1. There were no statistically significant differences between cases and controls in sex, age, or IgE levels. However, significantly higher proportions of controls reported positive histories for allergies/asthma and chickenpox, compared to cases.

Approximately 19% of cases (n=67) and 15% of controls (n=70) reported regular antihistamine use. Of the 53 cases who reported a positive history of allergies/asthma, 27 (51%) reported regular antihistamine use; whereas among the 162 controls reporting allergies, 41 (25%) reported regular use. Among cases with a negative history of allergies/asthma, 13% (n=40) reported regular antihistamine use, compared to almost 10% (n=29) of controls without allergies/asthma.

In the overall logistic regression model (Table 2), regular oral antihistamine use was significantly associated with glioma status (OR: 2.15, 95% CI: 1.42–3.25), adjusting for allergies/asthma, history of chickenpox, IgE levels, sex, age, and race. By contrast, self-reported allergies/asthma and chickenpox were both inversely associated with glioma risk (OR: 0.28, 95% CI: 0.20–0.41, and OR: 0.49, 95% CI: 0.34–0.71, respectively). When stratified by allergy/asthma status, antihistamine use remained strongly associated with glioma risk among those with a positive allergy/asthma history (OR: 4.19, 95% CI: 2.06–8.51), but not among those with a negative history (OR: 1.59, 95% CI: 0.95–2.67). In the group that did not report having allergies/asthma, history of chickenpox was significantly protective against glioma risk (OR: 0.39, 95% CI: 0.26–0.60), but this association did not hold among those who did report having allergies/asthma (OR: 1.81, 95% CI: 0.58–5.70). When the study population was restricted to only high-grade glioma cases and cancer-free controls, the results of both the overall and the stratum-specific logistic regression analyses remained similar [data not shown].

In our post-hoc analysis, in which all, rather than a subset, of available controls were used, we found the trends in the logistic regression results to be relatively similar to those reported above. Specifically, regular oral antihistamine use was significantly associated with glioma status in the overall study population (adjusted OR: 2.02; 95% CI: 1.36–3.00) and among individuals with a history of allergies/asthma (adjusted OR: 3.58; 95% CI: 1.82–6.97), but not among individuals without allergies/asthma (adjusted OR: 1.51; 95% CI: 0.92–2.48). Confidence intervals for estimates from the full population overlapped with those from the re-matched population, but the point estimates were slightly attenuated when all controls were included in the models. However, the estimates provided in the Table 2 from the re-matched study population may be better adjusted for the effects of residual confounding by sex than those from the post-hoc analysis.

Regular oral antihistamine use was not predictive of glioma survival (HR: 0.95, 95% CI: 0.65–1.38), controlling for allergy/asthma status, history of chickenpox, IgE levels, sex, age, and race (Table 3). Only sex and age were significantly associated with mortality hazard, both in the overall case population and among high-grade cases.

4. Discussion

In this study, we found that regular oral antihistamine use was significantly associated with glioma risk among individuals reporting a history of allergies/asthma, despite adjustment for

IgE levels and other relevant covariates. Although antihistamine use was also associated with glioma status in the overall population, this association is likely explained by the deleterious effect found among the stratum of individuals with a positive allergy/asthma history. Another interesting, though incidental, finding of our study was that the effects of having a positive history of chickenpox were modified by allergy/asthma status. Among individuals without allergies/asthma, a history of chickenpox was strongly protective against glioma risk, whereas among individuals with allergies/asthma, the effect estimate was in the opposite direction, though not statistically significant. Similar associations were not observed for glioma survival. Regardless, these associations cumulatively provide additional evidence in support of the hypothesis that the balance between Th1- and Th2-regulated immunity could potentially influence glioma susceptibility.

A possible link between cancer risk and the use of antihistamines has long been suspected [21], although results from epidemiological research investigating such associations have been inconsistent [11, 12, 22–28]. However, there are far fewer studies focused on the use of antihistamines specifically in relation to glioma risk, and from these studies, no clear consensus on the role of these medications has emerged [11, 12, 28, 38]. A recent study by McCarthy et al. found a protective association of borderline statistical significance between antihistamine use and high-grade glioma risk (OR: 0.75, 95% CI: 0.57–0.99) [28]. In a post-hoc analysis, we re-ran our model, restricting to high-grade cases and cancer-free controls, and could not replicate their findings, even after excluding allergy/asthma status from our model in order to more closely resemble their model (OR: 1.18, 95% CI: 0.74–1.90). Differences between our study and theirs that may help explain the discrepant results include adjustment for different potential confounders (i.e., history of chickenpox, IgE levels) and the use of hospital- versus population-based controls.

In addition to the analyses presented here, our group has also previously reported adverse associations between regular antihistamine use and glioma risk in different, though somewhat overlapping, subsets of the HCCCS population [11, 12]. By contrast to our previous work, in this study we were able to incorporate data on IgE levels in an attempt to adjust for chronic allergic inflammation in our regression models. IgE (or reaginic antibody) levels are often markedly higher among individuals with allergies than in individuals without atopic conditions, although a few more recent studies have observed some discordance between self-reported allergies and IgE levels [14, 16, 39, 40]. Nonetheless, it is typically very challenging to obtain data on IgE levels during the etiologic time period of interest (serum half-life of 2 days), and the levels can still provide a general proxy for an imbalance towards Th2-immunity or a susceptibility to atopy [40]. In our study, adjustment for IgE levels did not substantively alter the effect of regular antihistamine use on glioma risk. However, this is not entirely unexpected, as IgE is usually produced in the sensitization phase of an allergic reaction, whereas histamine is not released until the activation phase during which basophils and mast cells degranulate.

Our study is subject to some limitations. The results of some of our stratified analyses are based on small numbers and must be validated by larger studies before definitive conclusions can be drawn. Furthermore, our study may have some misclassification of allergy/asthma history, as this was self-reported, and information on type of allergy (i.e., food, dust, animal, etc.) was not available for additional subanalyses. Also, because our questionnaire asked about regular use of antihistamines for at least six consecutive months, individuals who only took antihistamines during peak allergy seasons (e.g., 3–4 months in the spring) would not have been classified as regular antihistamine users in our analyses. However, if such seasonal antihistamine use is associated with increased glioma risk, classifying these individuals as unexposed would have biased our results towards the null. Finally, our study may also be subject to selection bias, as the participation rate among

controls was low, which may, in part, be attributable to the use of random-digit dialing for control recruitment.

Most medications classified as antihistamines work by competitively inhibiting histamine by binding to either its H1 or H2 receptors without activating the subsequent pathways [41]. The contribution of histamine to cellular proliferation is primarily dependent on the amount of histamine present, and seems to be tumor type specific [42–44]. In fact, histamine may have a broad range of varying effects in different tumor microenvironments. For example, histamine has been shown to inhibit phagocytic production of reactive oxygen metabolites (ROMs) that contribute to tumor-induced immunosuppression [45, 46]. ROMs trigger oxidative inhibition of T-cells and NK-cells, reducing their cytotoxicity toward tumor cells. By inhibiting ROM production, histamine may be indirectly promoting tumor necrosis. Furthermore, activation of either the H1 or H2 histamine receptors results in down- or up-regulation of tumor growth, respectively [42, 43]. In a similar manner, histamine can act as an immunosuppressor when interacting with H2 receptors, or as an immune stimulator when interacting with H1 receptors [43]. Partly due to these dual-natured reactions, how chronic use of medications that interrupt the interaction of histamine with its receptors will influence the risk of oncogenesis is likely to be extremely complex and may potentially depend on the cell type of interest [42, 44]. The current study adds preliminary evidence to the existing literature on antihistamine use and glioma risk, but cannot clarify the mechanisms at play. Given the intricacy of the biological interactions involved, several larger cross-disciplinary studies are necessary before conclusions can be drawn. Future studies should be designed to incorporate medication dosage information and should be sufficiently powered to be able to analyze the effects of first- and second-generation antihistamines separately. Such larger analyses are currently being planned by the Glioma International Case-Control Study (GICC) investigators, in order to further clarify the relationships between antihistamine use and glioma risk.

Acknowledgments

This study was funded by grants from the National Cancer Institute (K07CA131505 to M.E.S. and R01CA070917 to M.L.B.).

References

1. Fisher JL, Schwartzbaum JA, Wrensch M, Wiemels JL. Epidemiology of brain tumors. Neurol Clin. 2007; 25(4):867–890. vii. [PubMed: 17964019]
2. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. Nat Clin Pract Neuro. 2006; 2(9):494–503.
3. Schwartzbaum JA, Huang K, Lawler S, Ding B, Yu J, Chiocca EA. Allergy and inflammatory transcriptome is predominantly negatively correlated with CD133 expression in glioblastoma. Neuro-Oncology. 2010; 12(4):320–327. [PubMed: 20308310]
4. Backes DM, Siddiq A, Cox DG, Calboli FC, Gaziano JM, Ma J, et al. Single-nucleotide polymorphisms of allergy-related genes and risk of adult glioma. J Neurooncol. 2013
5. Schwartzbaum JA, Xiao Y, Liu Y, Tsavachidis S, Berger MS, Bondy ML, et al. Inherited variation in immune genes and pathways and glioblastoma risk. Carcinogenesis. 2010; 31(10):1770–1777. [PubMed: 20668009]
6. Davis FG, Al-Alem U. Allergies and adult gliomas: cohort results strengthen evidence for a causal association. J Natl Cancer Inst. 2011; 103(21):1562–1563. [PubMed: 22010179]
7. Calboli FC, Cox DG, Buring JE, Gaziano JM, Ma J, Stampfer M, et al. Prediagnostic plasma IgE levels and risk of adult glioma in four prospective cohort studies. J Natl Cancer Inst. 2011; 103(21): 1588–1595. [PubMed: 22010181]

8. Wiemels JL, Wiencke JK, Kelsey KT, Moghadassi M, Rice T, Urayama KY, et al. Allergy-related polymorphisms influence glioma status and serum IgE levels. Cancer Epidemiol Biomarkers Prev. 2007; 16(6):1229–1235. [PubMed: 17548690]
9. Brenner AV, Butler MA, Wang SS, Ruder AM, Rothman N, Schulte PA, et al. Single-nucleotide polymorphisms in selected cytokine genes and risk of adult glioma. Carcinogenesis. 2007; 28(12): 2543–2547. [PubMed: 17916900]
10. Amirian E, Liu Y, Scheurer ME, El-Zein R, Gilbert MR, Bondy ML. Genetic variants in inflammation pathway genes and asthma in glioma susceptibility. Neuro-Oncology. 2010; 12(5): 444–452. [PubMed: 20406895]
11. Scheurer ME, El-Zein R, Thompson PA, Aldape KD, Levin VA, Gilbert MR, et al. Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. Cancer Epidemiol Biomarkers Prev. 2008; 17(5):1277–1281. [PubMed: 18483351]
12. Scheurer ME, Amirian ES, Davlin SL, Rice T, Wrensch M, Bondy ML. Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies. International Journal of Cancer. 2011; 129(9):2290–2296.
13. Schwartzbaum J, Ding B, Johannesen TB, Osnes LT, Karavodin L, Ahlbom A, et al. Association between prediagnostic IgE levels and risk of glioma. J Natl Cancer Inst. 2012; 104(16):1251–1259. [PubMed: 22855780]
14. Wiemels JL, Wrensch M, Sison JD, Zhou M, Bondy M, Calvocoressi L, et al. Reduced allergy and immunoglobulin E among adults with intracranial meningioma compared to controls. Int J Cancer. 2011; 129(8):1932–1939. [PubMed: 21520030]
15. Lachance DH, Yang P, Johnson DR, Decker PA, Kollmeyer TM, McCoy LS, et al. Associations of high-grade glioma with glioma risk alleles and histories of allergy and smoking. Am J Epidemiol. 2011; 174(5):574–581. [PubMed: 21742680]
16. Turner MC, Krewski D, Armstrong BK, Chetrit A, Giles GG, Hours M, et al. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. Cancer Causes Control. 2013; 24(5):949–960. [PubMed: 23443320]
17. Wiemels JL, Wilson D, Patil C, Patoka J, McCoy L, Rice T, et al. IgE, allergy, and risk of glioma: update from the San Francisco Bay Area Adult Glioma Study in the temozolomide era. Int J Cancer. 2009; 125(3):680–687. [PubMed: 19408307]
18. Zhou M, Wiemels JL, Bracci PM, Wrensch MR, McCoy LS, Rice T, et al. Circulating levels of the innate and humoral immune regulators CD14 and CD23 are associated with adult glioma. Cancer Res. 2010; 70(19):7534–7542. [PubMed: 20719886]
19. Schlehofer B, Siegmund B, Linseisen J, Schuz J, Rohrmann S, Becker S, et al. Primary brain tumours and specific serum immunoglobulin E: a case-control study nested in the European Prospective Investigation into Cancer and Nutrition cohort. Allergy. 2011; 66(11):1434–1441. [PubMed: 21726235]
20. Linos E, Raine T, Alonso A, Michaud D. Atopy and Risk of Brain Tumors: A Meta-analysis. Journal of the National Cancer Institute. 2007; 99(20):1544–1550. [PubMed: 17925535]
21. Brandes LJ, Warrington RC, Arron RJ, Bogdanovic RP, Fang W, Queen GM, et al. Enhanced cancer growth in mice administered daily human-equivalent doses of some H1-antihistamines: predictive in vitro correlates. J Natl Cancer Inst. 1994; 86(10):770–775. [PubMed: 7909571]
22. Erber E, Lim U, Maskarinec G, Kolonel LN. Common immune-related risk factors and incident non-Hodgkin lymphoma: the multiethnic cohort. Int J Cancer. 2009; 125(6):1440–1445. [PubMed: 19444913]
23. Kelly JP, Rosenberg L, Palmer JR, Rao RS, Strom BL, Stolley PD, et al. Risk of breast cancer according to use of antidepressants, phenothiazines, and antihistamines. Am J Epidemiol. 1999; 150(8):861–868. [PubMed: 10522657]
24. McCredie M, Maisonneuve P, Boyle P. Antenatal risk factors for malignant brain tumours in New South Wales children. Int J Cancer. 1994; 56(1):6–10. [PubMed: 8262678]
25. McKean-Cowdin R, Pogoda JM, Lijinsky W, Holly EA, Mueller BA, Preston-Martin S. Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. Int J Epidemiol. 2003; 32(2): 211–217. [PubMed: 12714539]

26. Nadalin V, Cotterchio M, Kreiger N. Antihistamine use and breast cancer risk. Int J Cancer. 2003; 106(4):566–568. [PubMed: 12845653]
27. Selby JV, Friedman GD, Fireman BH. Screening prescription drugs for possible carcinogenicity: eleven to fifteen years of follow-up. Cancer Res. 1989; 49(20):5736–5747. [PubMed: 2571410]
28. McCarthy BJ, Rankin K, Il'yasova D, Erdal S, Vick N, Ali-Osman F, et al. Assessment of type of allergy and antihistamine use in the development of glioma. Cancer Epidemiol Biomarkers Prev. 2011; 20(2):370–378. [PubMed: 21300619]
29. Harlow BL, Davis S. Two one-step methods for household screening and interviewing using random digit dialing. Am J Epidemiol. 1988; 127(4):857–863. [PubMed: 3354550]
30. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol. 1984; 120(6):825–833. [PubMed: 6334439]
31. Dubrow R, Darefsky AS. Demographic variation in incidence of adult glioma by subtype, United States, 1992–2007. BMC Cancer. 2011; 11:325. [PubMed: 21801393]
32. Wrensch M, Weinberg A, Wiencke J, Masters H, Miike R, Barger G, et al. Does prior infection with varicella-zoster virus influence risk of adult glioma? Am J Epidemiol. 1997; 145(7):594–597. [PubMed: 9098175]
33. Wrensch M, Weinberg A, Wiencke J, Miike R, Barger G, Kelsey K. Prevalence of antibodies to four herpesviruses among adults with glioma and controls. Am J Epidemiol. 2001; 154(2):161–165. [PubMed: 11447050]
34. Wrensch M, Weinberg A, Wiencke J, Miike R, Sison J, Wiemels J, et al. History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. Am J Epidemiol. 2005; 161(10):929–938. [PubMed: 15870157]
35. Sjostrom S, Hjalmars U, Juto P, Wadell G, Hallmans G, Tjonneland A, et al. Human immunoglobulin G levels of viruses and associated glioma risk. Cancer Causes Control. 2011; 22(9):1259–1266. [PubMed: 21717196]
36. Silverberg JI, Kleiman E, Silverberg NB, Durkin HG, Joks R, Smith-Norowitz TA. Chickenpox in childhood is associated with decreased atopic disorders, IgE, allergic sensitization, and leukocyte subsets. Pediatr Allergy Immunol. 2012; 23(1):50–58. [PubMed: 22017482]
37. Silverberg JI, Norowitz KB, Kleiman E, Silverberg NB, Durkin HG, Joks R, et al. Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: a case-control study. J Allergy Clin Immunol. 2010; 126(2):300–305. [PubMed: 20624648]
38. Wigertz A, Lonn S, Schwartzbaum J, Hall P, Auvinen A, Christensen HC, et al. Allergic conditions and brain tumor risk. Am J Epidemiol. 2007; 166(8):941–950. [PubMed: 17646205]
39. Carosso A, Bugiani M, Migliore E, Anto JM, DeMarco R. Reference values of total serum IgE and their significance in the diagnosis of allergy in young European adults. Int Arch Allergy Immunol. 2007; 142(3):230–238. [PubMed: 17108704]
40. Hoppin JA, Jaramillo R, Salo P, Sandler DP, London SJ, Zeldin DC. Questionnaire predictors of atopy in a US population sample: findings from the National Health and Nutrition Examination Survey, 2005–2006. Am J Epidemiol. 2011; 173(5):544–552. [PubMed: 21273397]
41. Suh JD, Kennedy DW. Treatment options for chronic rhinosinusitis. Proc Am Thorac Soc. 2011; 8(1):132–140. [PubMed: 21364231]
42. Cianchi F, Vinci MC, Masini E. Histamine in cancer: the dual faces of the coin. Cancer Biol Ther. 2008; 7(1):36–37. [PubMed: 18347416]
43. Medina MA, Quesada AR, Nunez de Castro I, Sanchez-Jimenez F. Histamine, polyamines, and cancer. Biochem Pharmacol. 1999; 57(12):1341–1344. [PubMed: 10353253]
44. Medina VA, Rivera ES. Histamine receptors and cancer pharmacology. Br J Pharmacol. 2010; 161(4):755–767. [PubMed: 20636392]
45. Agarwala SS, Sabbagh MH. Histamine dihydrochloride: inhibiting oxidants and synergising IL-2-mediated immune activation in the tumour microenvironment. Expert Opin Biol Ther. 2001; 1(5): 869–879. [PubMed: 11728221]
46. Hellstrand K, Hansson M, Hermodsson S. Adjuvant histamine in cancer immunotherapy. Semin Cancer Biol. 2000; 10(1):29–39. [PubMed: 10888269]

Table 1

Population characteristics by glioma status.

	Glioma Cases (n=362) n(%)	Controls (n=462) n(%)	p-value[a]
Sex			0.05
Male	204 (56.4)	228 (49.4)	
Female	158 (43.7)	234 (50.7)	
Age			0.09
<50 years	198 (54.7)	225 (48.7)	
≥50 years	164 (45.3)	237 (51.3)	
Median (SD)	49 (13.8)	50 (13.1)	
Race			0.03
Non-Hispanic White	305 (84.3)	413 (89.4)	
Other	57 (15.8)	49 (10.6)	
Self-Reported History of Chickenpox			<.0001
Yes	267 (73.8)	400 (86.6)	
No	95 (26.2)	62 (13.4)	
IgE Levels			0.31
≥250 IU per mL	24 (6.6)	23 (5.0)	
<250 IU per mL	338 (93.4)	439 (95.0)	
Self-Reported Allergies/Asthma			<.0001
Yes	53 (14.6)	162 (35.1)	
No	309 (85.4)	300 (64.9)	
WHO Glioma Grade			
II	97 (26.8)		
III	70 (19.3)		
IV	195 (53.9)		

Note. IU per mL= International Units per milliliter

[a]Chi-squared test comparing cases to controls.

Table 2

Multivariable unconditional logistic regression models of the effects of regular oral antihistamine use on glioma risk, both in the overall HCCCS[a] study population and stratified by self-reported history of allergies/asthma.

	Logistic regression[b] Odds Ratios (95% CI)[c]		
	Overall	**Allergies/Asthma**	
	(n=824)	**Yes (n=215)**	**No (n=609)**
Regular Antihistamine Use			
Yes	**2.15 (1.42–3.25)**	**4.19 (2.06–8.51)**	1.59 (0.95–2.67)
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Self-Reported Allergies/Asthma			
Yes	**0.28 (0.20–0.41)**	-	-
No	1.00 (reference)	-	-
Self-Reported History of Chickenpox			
Yes	**0.49 (0.34–0.71)**	1.81 (0.58–5.70)	**0.39 (0.26–0.60)**
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
IgE Levels			
≥250IU per mL	1.45 (0.77–2.74)	1.76 (0.53–5.84)	1.45 (0.68–3.13)
<250 IU per mL	1.00 (reference)	1.00 (reference)	1.00 (reference)

Note. IU per mL= International Units per milliliter

[a] Harris County Case-Control Study

[b] All odds ratios are also adjusted for matching variables (age, sex, and race).

[c] Bolding indicates statistical significance.

Table 3

Cox proportional hazards regression models of the effect of regular oral antihistamine use on mortality risk, both among all glioma cases and among high-grade glioma cases.

	Cox proportional hazards regression	
	HR (95% CI) [a]	
	Overall (n=362)	**High-Grade Glioma Only (n=195)**
Regular Antihistamine Use		
Yes	0.95 (0.65–1.38)	1.07 (0.68–1.67)
No	1.00 (reference)	1.00 (reference)
Self-Reported Allergies/Asthma		
Yes	0.76 (0.50–1.14)	0.86 (0.55–1.35)
No	1.00 (reference)	1.00 (reference)
Self-Reported History of Chickenpox		
Yes	0.97 (0.71–1.34)	1.08 (0.74–1.57)
No	1.00 (reference)	1.00 (reference)
IgE Levels		
≥250 IU per mL	0.81 (0.47–1.40)	0.97 (0.54–1.76)
<250 IU per mL	1.00 (reference)	1.00 (reference)
Sex		
Male	**1.41 (1.08–1.85)**	**1.50 (1.08–2.09)**
Female	1.00 (reference)	1.00 (reference)
Age		
≥ 50 years	**3.22 (2.45–4.23)**	**2.02 (1.44–2.83)**
< 50 years	1.00 (reference)	1.00 (reference)
Race		
Non-Hispanic White	1.00 (reference)	1.00 (reference)
Other	0.66 (0.43–1.01)	0.63 (0.39–1.04)

Note. IU per mL= International Units per milliliter

[a] Bolding indicates statistical significance.