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Reduced Immunoglobulin E and Allergy among Adults with Glioma Compared with Controls

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ABSTRACT

We and others have reported previously that adults with glioma are 1.5- to 4-fold less likely than controls to report a variety of allergic conditions. The consistent nature of this relationship calls for a biological explanation so that preventative or therapeutic modalities can be explored. We enrolled 403 newly diagnosed adult glioma cases in the San Francisco Bay Area over a 3-year period using a population-based cancer registry and 402 age/gender/ethnicity frequency-matched controls identified via random digit dialing. We assessed total, food-specific, and respiratory-specific IgE in available case ($n = 228$) and control ($n = 289$) serum samples. IgE levels were associated with gender, age, smoking status, and ethnicity among cases and/or controls. Among the cases, IgE levels were not associated with aspects of glioma therapy including radiation, chemotherapy, or tumor resection. Total IgE levels were lower in cases than controls: age/gender/ethnicity/education/smoking-adjusted odds ratio (OR) for elevated *versus* normal total IgE was 0.37 [95% confidence interval (CI), 0.22–0.64]. For the food panel, OR was 0.12 (95% CI, 0.04–0.41). For the respiratory panel, OR was 0.76 (95% CI, 0.52–1.1). Among respiratory allergies, late age of onset (>12 years) but not IgE levels defined a group with strong associations with risk (OR, 0.50; 95% CI, 0.33–0.75). These results corroborate and strengthen our findings of an inverse association between allergic reactions and glioma by showing a relationship with a biomarker for allergy and cancer for the first time. Furthermore, the results indicate a complex relationship between allergic disease and glioma risk that varies by allergen and allergic pathology.

INTRODUCTION

The etiology of adult glioma is currently unknown, apart from a small number of cases arising from strong genetic predisposition alleles such as *APC* and *TSC* as well as ionizing radiation exposures (1). This leaves the majority of sporadic brain tumors unexplained, although current epidemiologic studies have shown weak evidence for constitutional polymorphisms, mutagen sensitivity, infectious and dietary agents, occupations, and non-ionizing radiation (1). Our lack of understanding of the causes of glioma precludes any preventative or control measures for this disease.

Recent results from several epidemiologic studies in the United States and Europe have implicated immune factors in glioma risk. The most consistent immune factor is allergy (and perhaps infectious and autoimmune diseases), in which four studies (three case-control and one cohort) have reported an *inverse* association between self-reported allergies and brain cancer (Table 1; refs. 2–5). A possible explanation of these studies is that tumor immunosurveillance may operate more efficiently in those individuals who have allergies or that allergies are correlated with another constitutional, environmental, or developmental factor that reduces brain tumor risk (2).

The term "allergy" represents a spectrum of diseases that all have immunologic mechanisms; however, subjects can mistake other morbidities for allergy, for example, biochemical intolerance to lactose or amines (6). Indeed, in our previous analysis, the greatest differences between cases and controls for allergen sensitivity was among various food allergens (2), in which metabolic intolerances or atopic and nonatopic allergic mechanisms can play a role (7). A biological marker may provide more specificity and help reduce bias inherent in subjective questionnaires. IgE is the class of antibody responsible for atopic allergic diseases and represents a quantifiable "intermediate phenotype" for allergy. In this study, we assess IgE levels in conjunction with self-reported allergy, with a goal to confirm the allergy questionnaire result and identify an immunologic pathophysiology related to glioma.

MATERIALS AND METHODS

Study Participants. Study subjects were recruited by population-based methods in six San Francisco Bay Area counties from May 1997 to April 2000. Cases were identified via rapid case ascertainment methods using the Northern California Cancer Registry as described previously (2). Controls were selected through random digit dialing and frequency matched to cases by age, ethnicity, and gender. Subjects or their proxies completed a detailed in-person interview including history of allergies (2). Pathological material was retrieved for all resected brain cancers and reviewed and classified by a single neuropathologist (Kenneth Aldape, MD Anderson, Houston, TX). Blood and sera were collected either at the time of interview or at a later time. Participants were asked a separate blood draw questionnaire at that time about currently used medications and chemotherapy and radiation therapy. For analytical purposes, medications were classified as follows: (*a*) chemotherapeutic, (*b*) DNA/RNA polymerase poison (*e.g.,* antiretrovirals), (*c*) antibiotic or antiviral, (*d*) nonsteroidal anti-inflammatory and analgesic, (*e*) antihistamine, antileukotriene, or other allergy medication, and (*f*) other medications. Also, high-dose steroids (dexamethasone) were considered separately.

IgE levels were assessed using a standardized clinical instrument designed for this purpose: Pharmacia Diagnostics (Kalamazoo, MI) UniCAP fluorescent "sandwich" assay (8). Briefly, 40 μL of serum were incubated on the mix of allergens or anti-IgE antibodies bound to solid-phase ImmunoCAP. Incubations with enzyme-labeled antibodies against the heavy chain (constant) for the total IgE test or the light chain (variable) for the specific allergen tests were followed by incubations of developer and stop solutions. The respiratory IgE panel (Phadiotop) included 15 allergens that identify 97% of atopic allergy to respiratory allergens. The food panel (fx5) included six allergens that comprise most food allergies (peanut, tree nut, shellfish, milk, egg, and codfish).

IgE quantities were used in two manners: first, clinical categories were considered. For total IgE, IgE levels of >100 kilounits/liter are clinically "elevated," IgE levels of 25 to 100 kilounits/liter are "borderline," and IgE levels of <25 kilounits/liter are "normal;" for food and respiratory IgE, levels of <0.35 kilounit/liter are termed "negative," and levels of >0.35 kilounit/liter are termed "positive." Continuous measures were determined by measuring fluorescence against the standard curve with known quantity inputs. Measures of IgE that fell below the lower limit were adjusted to the 0.35 kilounit/liter threshold for statistical purposes. Descriptive statistics and odds ratios (ORs)

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Note: Supplementary data for this article can be found at Cancer Research Online (http://cancerres.aacrjournals.org).

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Table 1 *Association of reported history of allergy, infection, and autoimmune disease on the occurrence of primary brain tumors in four studies*

Study type	Immune factor	Diagnosis	Risk ratio (95% CI)	Reference
Case/control	Allergy	Glioma	0.5 (0.3–0.7)	Wiemels *et al.* (2)
Case/control	Allergy	Glioma	0.6 (0.5–0.7)	Schlehofer *et al.* (3)
		Meningioma	0.9 (0.7–1.2)	
Case/control	Infections	Glioma	0.7 (0.6–0.9)	Schlehofer *et al.* (3)
		Meningioma	0.7 (0.5–1)	
Case/control	Allergy	Glioma	0.7 (0.5–0.9)	Brenner *et al.* (5)
Case/control	Autoimmune disease	Glioma	0.5 (0.4–0.7)	Brenner *et al.* (5)
Case/control	Autoimmune disease	Meningioma	0.6 (0.4–0.9)	Brenner *et al.* (5)
Retrospective cohort	Allergy	Glioma	0.5 (0.2–1.1)	Schwartzbaum *et al.* (4)

were computed with SAS software (SAS Institute, Inc., Cary, NC). Graphics and other statistics were implemented in *R* or GraphPad (San Diego, CA).

RESULTS

Study Population. The population of the current study was a subset of our previous study (2). The cases studied here largely represent the "self-reported" (*i.e.*, the interview was conducted directly with the glioma patient) group from the previous publication; only 19 of the 289 cases in the current study are from proxy-reported individuals (*i.e.*, the interview was conducted with next of kin due to morbidity or mortality of the glioma patient). The average time from date of diagnosis to the date of blood draw was 135 days (median ± SE, 112 ± 5 days). Cases from whom sera were obtained were younger and less likely to be diagnosed with glioblastoma histology than the overall case group, and controls donating sera were older on average than controls who chose not to donate serum samples (Supplementary Table 1). Among the cases only, household income was significantly associated with provision of sera (Supplementary Table 1).

IgE Measurements. Total IgE levels ranged from <2.0 kilounits/liter (the lower limit of the assay) to over 5,000 kilounits/liter. Total IgE levels among the controls had a mean of 142 kilounits/liter (SD, 468 kilounits/liter) and a median of 32 kilounits/liter. Total IgE measurements were repeated in 245 subjects, with 231 (94%) repeat samples producing data within 10% of the original, and 197 (80%) repeat samples producing data within 5% of the original. No subjects were reclassified to a different categorical class as a result of retesting; the first test result was used for all analyses. The controls had detectable IgE in 162 of 289 individuals (56%), and of these, a subset 66 of 289 individuals (23%) had elevated IgE levels. When the data were logarithmically transformed, they adequately fit a normal distribution ($P > 0.15$ by the Kolmogorov Smirnov test for controls; Fig. 1), and subsequent comparisons were made using log-transformed data. Among the cases, total IgE levels were normally distributed for those above the lower limit of the assay (Fig. 1); however, the data set was skewed in the overall distribution ($P < 0.01$, Kolmogorov Smirnov test) due to the larger number of subjects that fell below the limit of detection of the assay (Fig. 1). Food IgEs were positive in 32 of 289 controls (11%) and 3 of 224 cases (1.3%), and respiratory IgEs were positive for 115 of 289 controls (40%) and 84 of 224 cases (38%; Supplementary Table 2). Because these two measures detected more than half of the individuals as "negative," tests for normal distribution of continuous data were not performed.

IgE and Demographic Variables within Case and Control Groups. Among the controls, total IgE levels were significantly higher in nonwhites as compared with whites and in males as compared with females (Supplementary Table 2). The trends were similar for cases; differences were significant for gender and smoking and close to significant for ethnicity for total IgE levels (Supplementary Table 2). Among the cases, respiratory IgE levels were significantly associated with age (Supplementary Table 2). History of beer, wine, or hard alcohol consumption ($P = 0.7$ and 0.3 for cases and controls; data not shown) or college graduation ($P = 0.70$ and 0.52, cases and controls; Supplementary Table 2) did not significantly affect IgE levels among the cases and controls.

Among cases, total IgE levels did not differ significantly among various histologic diagnoses ($P = 0.48$; Supplementary Table 2) and were each lower than the IgE level in all controls. We also did not detect a significant effect of history of chemotherapy, radiation, and surgical therapy on total IgE levels (Supplementary Table 3). In addition, IgE levels did not vary by season of collection for study participants (data not shown; $P = 0.08$)

IgE and Medication Use. Sixty-four percent (173 of 270) of controls and 97% (206 of 213) of cases reported taking some medication at the time of the blood draw. The rest of the medication groups, including those taking steroids such as dexamethasone, did not differ significantly from "no medication" individuals for both

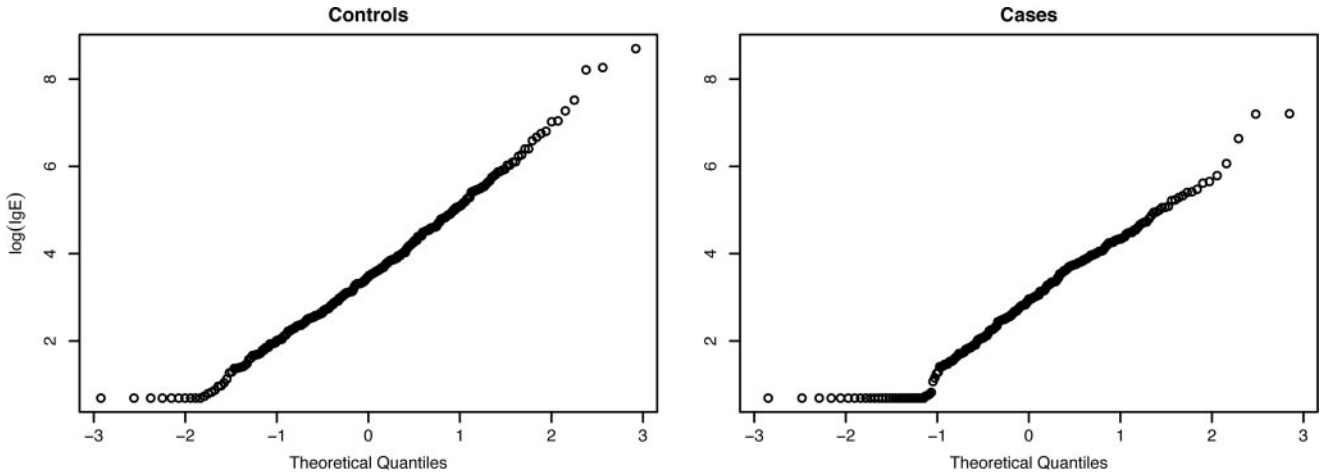

Fig. 1. Quantile plots demonstrating a log-normal distribution of total IgE among the controls and cases when data are log-transformed.

cases and controls (Supplementary Table 4); for controls, differences became nonsignificant after removing the one individual taking dexamethasone. We did not detect a significant overall effect of recent medication use on either IgE levels (Supplementary Table 4) or IgE/glioma case-control comparisons (see below). In addition, IgE and length of time from diagnosis to blood draw (which relates to length of treatment time) did not significantly correlate (Pearsons $r^2 = -0.05$; $P = 0.46$).

Case and Control Comparisons for IgE. No notable differences were observed between unadjusted ORs of IgE measures and case/control status and those adjusted for gender, ethnicity (white/nonwhite), college education (graduate/not), smoking (current/past/never), and age (as a continuous variable). When clinical categorical classifications of IgE were considered, IgE levels were uniformly lower among cases compared with controls (Table 2; Fig. 2). These differences were statistically significant for total IgE and food IgE (Table 2; Fig. 2). When IgE was considered as a continuous variable, the OR per log unit of total IgE was 0.73 [95% confidence interval (CI), 0.64–0.84; $P < 0.001$]. This relationship was not significantly affected when the 74 cases and 1 control taking dexamethasone were removed from the analysis (OR, 0.77; 95% CI, 0.66–0.89; Supplementary Table 5).

IgE Levels Compared with Self-Reported Allergy. Concordance between IgE and reported allergy was not high (Table 3). Concordance bordering on "intermediate agreement" by κ statistic was found for respiratory allergens and respiratory IgE (0.32 for controls and 0.44 for cases). Concordance between reported food allergens and food IgE was 74% for controls and 82% for cases due to the large number of concordant "negatives" (those who were negative for reporting food allergy as well as food-related IgE), but κ statistics were −0.03 and 0.08 due to the high rate of individuals who were positive for reporting food-related allergy or had IgE, but not both ("discordant positives;" Table 3).

Notably, the case/control association for elevated *versus* normal total IgE was similar among those who report no allergy [OR adjusted for age, gender, ethnicity, education, and smoking = 0.19 (95% CI, 0.04–0.86); $P = 0.03$] and those reporting any allergy [adjusted OR = 0.43 (95% CI, 0.24–0.77); $P = 0.01$].

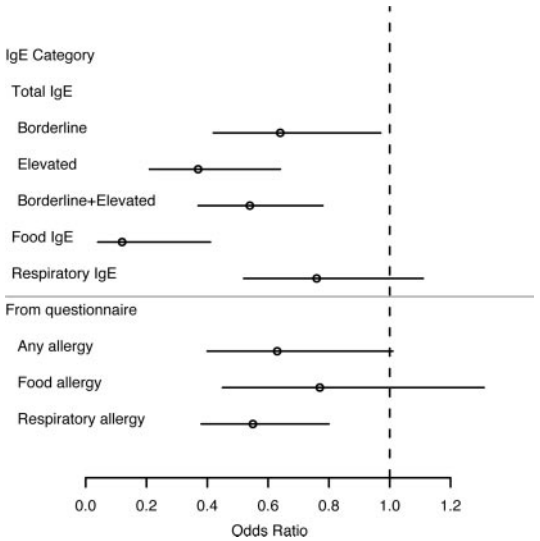

Fig. 2. Case-control ORs for IgE levels and for self-reported allergy, all expressed as categorical data. ORs are adjusted for gender, ethnicity, age, smoking status, and college education and shown with 95% CIs.

Respiratory Allergy and Age of Onset. The disparate result between total/food IgE and respiratory allergy was explored further by stratification of respiratory allergies into early age of onset (≤12 years) *versus* later age of onset (≥13 years). Those with reported early-onset allergies had higher IgE levels and were significantly more likely to be positive for respiratory IgE ($P < 0.001$; Table 4). When cases and controls were stratified into reported early- and late-onset of allergies, there were negligible changes on case/control differences by total IgE (data not shown). However, when self-reported allergy was considered alone, it was apparent that the case/control ORs were somewhat stronger for those with late-onset allergies (age ≥ 13 years; Table 4, right hand column), which were less likely to be IgE-related (Table 4, left hand columns).

Table 2 *Multivariate case/control ORs for IgE levels and history of allergy: San Francisco Bay Area Adult Glioma Study, 1997–2000*

Model		*N*			
		Cases	Controls	OR * (95% CI)	*P*
	Total				
1	IgE data				
	ln(IgE) †	226 ‡ (2.9 ± 0.10)	289 (3.5 ± 0.9)	0.73 (0.64–0.84)	<0.001
2	Normal	130	127	1.0	
	Borderline	70	96	0.64 (0.42–0.96)	0.03
	Elevated	26	66	0.37 (0.22–0.64)	<0.001
3	Questionnaire data				
	No allergies	49	45	1.0	
	1–3 allergies	126	167	0.69 (0.42–1.1)	0.13
	4+ allergies	51	77	0.50 (0.28–0.88)	0.02
	Respiratory				
4	IgE data				
	Nonelevated respiratory IgE	140	174	1.0	
	Elevated respiratory IgE	84	115	0.76 (0.52–1.1)	0.16
5	Questionnaire data				
	No respiratory allergies	123	129	1.0	
	At least 1 respiratory allergy	101	160	0.56 (0.39–0.81)	0.002
	Food				
6	IgE data				
	Nonelevated food IgE	221	255	1.0	
	Elevated food IgE	3	32	0.12 (0.04–0.41)	<0.001
7	Questionnaire data				
	No food allergies	187	225	1.0	
	At least 1 food allergy	37	62	0.70 (0.44–1.1)	0.14

* Each model was adjusted for gender, ethnicity, education, smoking, and age.
† Ln(IgE) was expressed as a continuous variable. Numbers in parentheses are least square means ± SE. All other variables are categorical.
‡ Two cases, for whom smoking information was missing, were dropped from the model.

Table 3 *Concordance between IgE level and reported allergies: San Francisco Bay Area Adult Glioma Study, 1997–2000*

	Cases				Controls			
	Reported allergies				Reported allergies			
	None	Any *	% Concordance	κ †	None	Any *	% Concordance	κ †
Total IgE								
Normal	35	96			23	104		
Bord/Elev	14	83	52	0.11	22	140	56	0.05
Total	228				289			
Food IgE								
Negative	185	38			203	52		
Positive	3	0	82	−0.03	22	10	74	0.08
Total	226				287			
Respiratory IgE								
Negative	102	39			101	73		
Positive	23	62	73	0.44	28	87	65	0.32
Total	226				289			

Abbreviations: Bord, borderline; Elev, elevated.
* Any reported allergy (for total IgE), any reported food allergy (for food IgE), and any reported respiratory allergy (respiratory IgE).
† $\kappa \geq 0.75$, excellent agreement; $\kappa = 0.40–0.75$, intermediate agreement, $\kappa \leq 0.40$, poor agreement.

DISCUSSION

The term allergy describes a spectrum of pathophysiologies with varied symptoms and mechanisms. Using a detailed questionnaire, we previously found that allergy and its associated symptoms were reported significantly less frequently among glioma cases compared with a population-based control group. Despite a detailed assessment of different allergens using our questionnaire, we could not identify a specific allergen, symptom, or severity score that distinguished a particular allergic pathology that was deficient among the glioma cases (2). However, we did detect more significant associations with increased numbers of reported allergens (*i.e.*, a "dose-response;" ref. 2). A common manifestation of allergy is atopy, which is generally defined as a type I immediate hypersensitivity reaction mediated by IgE. Our current report demonstrates that IgE levels are strongly inversely associated with glioma and, in particular, IgE to dietary allergens (Table 2; Fig. 2). The associations between IgE and glioma were weaker for respiratory allergens; instead, reported respiratory allergy history showed a stronger association with case/control status than IgE levels, especially among those individuals with a late age of allergy onset (≥13 years of age; Table 4).

The two primary variables we consider, self-reported allergy and laboratory-determined IgE, are subject to potential but different biases. First, glioma cases may be less likely to report allergy due to lapse in recall induced by the disease. Evidence that helps to rebut this potential bias comes from a recent cohort study in which participants were asked about allergies years prior to diagnosis of glioma (4). This study found associations between allergies and glioma that were consistent with three other published case/control studies (Table 1). We find an additional argument against self-reporting bias in our data, in which early-onset reported respiratory allergies are significantly more correlative with IgE levels than late-onset allergies (Table 4). Whereas self-reporting telescoping bias might be expected to bias IgE levels in the other direction (*i.e.*, later age of onset allergies may be easier to remember), the result matches the known pathological differences of asthma when classified by age of onset. Early-onset allergies are more likely to be IgE-related than late-onset allergies, which are mediated more often by "non-allergic," tissue-localized mechanisms (9).

Another potential bias might arise from depression of IgE by the glioma itself or treatments of the tumor. Brain tumors are well known to have effects on the immune system [primarily the depression of cell-mediated immunity and humoral defects (10, 11)]. We are, however, unaware of any study examining IgE in glioma patients, but total serum IgG levels and those to specific herpes viruses were normal in other studies (12, 13). We found no significant effect on IgE levels by several variables that we measured: type of surgical intervention, radiation therapy, chemotherapy, medication use (Supplementary Tables 3 and 4), and time from surgical intervention to blood draw. Also, concordance between self-reported lifetime history of allergies and IgE measurements was similar between the cases and the controls (Table 3), thus showing that glioma-induced IgE suppression was not likely to account for case/control differences in IgE. Furthermore, in

Table 4 *Effect of age at onset of allergies on respiratory IgE levels and glioma: San Francisco Bay Area Adult Glioma Study, 1997–2000*

	Total IgE					Respiratory IgE			History of respiratory allergy ¶		
	N	ln(IgE) *	SE ln(IgE)	*P* *	Geometric mean †	No. positive	% positive	*P* ‡	No. of cases	No. of controls	OR § 95% CI
Cases											
Age at onset of Resp allergy				<0.001				<0.001			
No Resp allergy	123	2.9	0.16		17.9	22	17.9		123	129	1.00
Age ≤ 12 y	37	3.9	0.25		50.7	29	78.4		37	37	0.77 (0.45–1.3)
Age ≥ 13 y	64	3.3	0.20		28.1	33	51.6		64	122	0.50 (0.33–0.75)
Total	224								224	288	
Controls											
Age at onset of Resp allergy				0.06				<0.001			
No Resp allergy	129	3.7	0.17		40.4	28	21.7				
Age ≤ 12 y	37	4.4	0.27		80.1	27	73.0				
Age ≥ 13 y	122	4.0	0.17		52.6	59	48.4				
Total	288										

Abbreviation: Resp, respiratory.
* Least square means and *P* values for total IgE from a general linear model using continuous IgE value as outcome, adjusted for age, gender, ethnicity, education, and smoking.
† Least square geometric mean calculated as $e^{\text{mean ln(IgE)}}$.
‡ *P* values from logistic model using dichotomous IgE value as outcome and adjusted for variables listed above.
§ Controlled for age, gender, ethnicity, education, and smoking.
¶ History of respiratory allergy considered only, with no adjustment for IgE levels.

both cases and controls, the known modifiers of IgE levels (*i.e.*, gender, smoking, ethnicity, and age of allergy onset) were associated with IgE levels, with some associations reaching statistical significance. The detection of significant effects of IgE levels from these known modulating factors validates our measurement of IgE levels and demographic variables. Age at time of blood draw was less of a factor because age-related differences in IgE levels are most pronounced between young children and adults, and our study did not include children. We did not have the data to consider other potential modifiers of IgE levels, including allergen avoidance and changes in a subject's daily activities.

The cases from whom serum was available were significantly younger than the overall average age of cases (about 4.7 years younger) due to higher mortality at higher ages (data not shown). The controls with serology were older than other controls because younger controls were less likely to consent to provide blood (Supplementary Table 1). The direction of bias for these factors is not known; however, age adjustments (along with gender and smoking) in multivariable analyses did not significantly change any of our results (data not shown), and so this bias is likely to be small.

IgE testing represents one of several tests available to a clinician in diagnosing allergic diseases. Whereas IgE is a useful test, it does not identify allergic or even atopic disease with great precision and needs to be supplemented by other assays such as skin-prick testing for overall definition of allergy, especially in older adults (14, 15). IgEs are labile in serum with a half-life measured in days. Despite this fact, serum levels of antibody against a unique, pointed allergen challenge (without repeated challenge) have a half-life of 3–7 years (16, 17) due to the long life of antibody-producing plasma cells. In addition, persons exhibiting high levels of IgE early in life are highly prone to developing adult atopic allergies (particularly respiratory), indicating that a point measurement of IgE in adulthood is not an unreasonable measure of historical IgE levels (18–20), a point supported by our data (Table 4).

Despite the challenges of defining allergy and IgE levels, we have found significant associations between a general aspect of immune function and the presence of a cancer of the nervous system. Our study is ultimately not concerned with defining allergy but rather with developing a biomarker and understanding a mechanism by which a component of the immune system can influence brain tumor risk. Total IgE showed stable and robust association with the occurrence of glioma. However, both self-report and IgE levels are subject to biases, and it is not possible with the current information to determine which provides the more accurate assessment of an immunologic mechanism that may prevent glioma. Given that IgE levels were not highly concordant with self-reported allergy and that both were strongly inversely associated with glioma, it is possible that they both relate to a third unmeasured factor that may be a component of the immune system. Self-reported allergies are among the most consistent associations reported in the field of brain cancer epidemiology (Table 1); IgE antibodies provide us additional concrete evidence for this association, but they have not provided a mechanistic basis.

Our strongest association with glioma was IgE for food allergens, for which modest frequencies of individuals (11% of controls and 1% of cases; Supplementary Table 2) were positive. Given the low prevalence of IgE for food allergens among cases, the magnitude of this OR is highly unstable. Food allergies were reported for 62 of 287 controls (22%) and 37 of 224 cases (17%; Table 2), which compares favorably with the 12% to 20% found in the literature (21, 22). However, there was very little concordance among positive IgE tests and self-reported food allergy. Among the 62 controls who reported allergies, 10 individuals were positive for IgE (16%), which compares with the value of 40% reported in the literature (6). Among the cases, none of the 3 positive IgE patients reported an allergy, and 38 others that reported a food allergy were negative for IgE. Much of this discordance among cases and controls (self-report false positives) is probably due to nonimmunologic food intolerance, an allergy that was outgrown, or extended allergen avoidance (23). Other discordance (self-report false negatives) is the result of food sensitization that may not be noticeable as an allergy by individuals. For instance, 8% to 12% of adults are positive for food allergen IgE, but only 1% to 2.5% are truly allergic by food challenge tests (24). Our low concordance κ measures match closely with a recent study using skin prick test with perceived food allergy (23).

Whereas food allergen IgE is much more strongly associated with glioma than reported food allergies, the strongest associations for the respiratory allergies are seen among reported allergies rather than IgE (Table 2; Fig. 2) and, in particular, late-onset respiratory allergies (Table 4). Early-onset disease is more likely "allergic/extrinsic," or IgE-mediated, whereas late-onset disease is associated with "nonallergic/intrinsic" pathology that is not dependent on IgE (9, 25). This seemingly contradictory result (to food allergy) indicates that measurement of IgE levels may be one or more steps removed from an immunologic process that affects brain tumor risk. Whether this process is the same among people who demonstrate food IgEs and report respiratory allergies cannot be determined with the current data but will be a primary goal of future research. One feature common among food allergies and late-onset respiratory allergies is an apparent role for eosinophils; late-onset asthmatics have higher eosinophil counts than early-onset asthmatics and a higher rate of eosinophilia (9). Food allergies are commonly associated with eosinophilic gastritis (7). Animal models of glioma suppression by the allergic cytokine interleukin (IL)-4 include the presence of activated eosinophils (26, 27). Whereas the cytokines IL-4, IL-5, and IL-13 are generally specific to Th2-allergic type reactions, IL-13 is uniquely elevated to a high level among nonallergic asthmatics (25, 28) and is produced by activated eosinophils, among other cells (29). Interestingly, IL-13 receptors are expressed by gliomas, leading to a targeted therapy using this receptor for toxin delivery (30, 31).

The brain is traditionally thought of as an "immune privileged" organ due to the presence of the blood–brain barrier, which restricts the passage of large molecules and cells from the brain, as well as the absence of typical lymphatic drainage for antigen processing (32). However, we now think of the brain as immunocompetent due to the capacity of intrathecal nervous system antigens to stimulate systemic immune recognition and the presence of activated T and B cells as well as antigen-processing cells within the brain such as the microglia (33). The immune response of intracerebral antigens is distinctive from the rest of the organism in part due to the brain's sensitive and fragile architecture, which would not endure a vigorous cell-mediated delayed-type hypersensitivity inflammatory response. Brain cancer is typically associated with an immune infiltrate consisting of T cells, macrophages, and microglial cells with active inflammation (10, 11). This immune reaction is not necessarily a sign of effective tumor rejection and may not be typical of a "healthy" antitumor immune response. The brain tumor secretes strong immunomodulatory cytokines such as transforming growth factor β and prostaglandin E_2 to suppress Th1 and associated delayed-type hypersensitivity responses, which appear to be active but largely ineffectual. The nature of what constitutes a "protective" immune system against tumors at the earliest stages of disease is unknown, but the paucity of subjects with allergy and elevated IgE among our case group suggests that those individuals without the capacity for allergy (via genetic, developmental, or environmental influences) may also have lower capacity for tumor immunosurveillance.

A larger impact of this study is the introduction of an immunologic

allergy biomarker in the study of the etiology of cancer. Robust associations between case and control status were found using IgE and self-reported allergy, particularly among food allergies, and we found evidence that non–IgE-related allergic mechanisms (*i.e.*, late-onset respiratory allergies) may play a role in cancer etiology. A large body of research now indicates that allergies may play a role in a diverse group of cancers including lymphoma, leukemia, pancreatic cancer, and other solid tumors (34–38). The sophistication with which we currently examine genetic susceptibility, diet, and chemical exposures is not matched by a consideration of immunologic processes that impact cancer risk, which begs the development of a conceptual framework and panel of biomarkers to study this topic.

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