DOI: 10.1093/jnci/djr361
Advance Access publication on October 18, 2011.

ARTICLE

Prediagnostic Plasma IgE Levels and Risk of Adult Glioma in Four Prospective Cohort Studies

Federico C. F. Calboli, David G. Cox, Julie E. Buring, J. Michael Gaziano, Jing Ma, Meir Stampfer, Walter C. Willett, Shelley S. Tworoger, David J. Hunter, Carlos A. Camargo Jr, Dominique S. Michaud

Manuscript received March 30, 2011; revised August 9, 2011; accepted August 18, 2011.

Correspondence to: Dominique S. Michaud, ScD, Department of Epidemiology, Division of Biology and Medicine, Brown University, Box G-S121-2, 121 S Main St, Providence, RI 02912 (e-mail: dominique_michaud@brown.edu).

Background Increased levels of serum immunoglobulin E (IgE) because of allergies have been inversely associated with risk of glioma in observational studies. Despite consistency across studies examining history of allergies and glioma, questions remain as to whether those are causal associations. An inverse association between serum IgE and risk of glioma was reported in a large case–control study, but reverse causality and treatment effects remain potential explanations for those findings.

Methods We combined data from four prospective cohort studies and used a nested case–control design to examine the association between allergy and glioma. We included glioma case subjects who were confirmed from medical or pathology records or from death certificates, and with prediagnostic blood available. We matched three control subjects per case subject, and the final numbers for analyses were 169 case subjects and 520 control subjects. Total IgE, food allergen–specific IgE, and respiratory allergen–specific IgE levels were measured using a highly sensitive fluorescent assay. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression analysis. Stratified analyses were conducted by age and birth cohorts.

Results Borderline elevated total IgE levels (25–100 kU/L) showed a statistically significant inverse association with glioma (OR = 0.63, 95% CI = 0.42 to 0.93), but no association was noted between elevated IgE (>100 kU/L) and glioma (OR = 0.98, 95% CI = 0.61 to 1.56) compared with clinically normal IgE levels (<25 kU/L). The association between glioma and total IgE was consistent for both men and women. Non-statistically significant inverse associations were noted for elevated IgE levels among individuals born before year 1930 (OR = 0.67, 95% CI = 0.34 to 1.34) and when restricting analyses to highly fatal (deceased within 2 years of diagnosis) glioma case subjects (OR = 0.64, 95% CI = 0.34 to 1.19) compared with individuals with clinically normal IgE levels. No associations were observed for either food allergen–specific or respiratory allergen–specific IgE levels.

Conclusions Overall, our prospective findings are consistent with recent retrospective studies and support an association between total IgE levels and glioma. However, this association requires further elucidation.

J Natl Cancer Inst 2011;103:1588–1595

Gliomas are tumors that arise from glial cells, representing the majority of all primary malignant brain tumors. Although primary brain tumors are uncommon, they are associated with substantial morbidity and mortality. The 5-year survival rates for malignant tumors are 29% for men and 32% for women (1). Between 1975 and 2006, the US age-adjusted incidence rate for primary malignant brain tumors was 6.6 per 100 000 person-years (2).

Several epidemiological studies have supported an inverse association between self-reported history of allergies and the risk of glioma; a meta-analysis showed that risk was reduced by 39% in people with a history of allergies compared with people with no history of allergies (relative risk = 0.61, 95% confidence interval [CI] = 0.55 to 0.67) (3). Overall, the consistent associations between allergies and brain tumors shown in several studies are in marked contrast to the many inconsistent associations that have been reported for other potential occupational and environmental risk factors of brain tumors (4). The degree of consistency in these findings suggests that an etiologic basis for allergies is possible. Immune regulation in the central nervous system appears to be mediated through the immunoglobulin E (IgE) response to allergens (5), making it more humoral (antibody mediated) in nature than cell mediated, perhaps to minimize damage to the tissue architecture of the central nervous system from the vigorous inflammatory nature of a cell-mediated assault (6). Therefore, the inherent tendency of atopic individuals to react to antigens (including tumor-derived antigen) with a type 2 helper T response may provide those individuals with a more efficient immune response against the development of brain tumors.

To examine the association between specific and total IgE levels in prediagnostic blood and subsequent risk of glioma, we pooled data from four large prospective cohorts: the Physicians' Health Study (PHS), the Nurses' Health Study (NHS), the Women's Health Study (WHS), and the Health Professionals Follow-Up Study (HPFS). To our knowledge, this is the first prospective study to examine the relationship between total plasma IgE levels allergy and glioma risk.

CONTEXT AND CAVEATS

Prior knowledge

Several epidemiological studies have shown that a history of allergies is associated with decreased risk of glioma. Allergens induce an increase in serum IgE, which may modulate the immune regulation in the central nervous system. There are no prospective studies that examined the association between total IgE levels and glioma.

Study design

A nested case–control design was used to analyze 169 glioma case subjects and 520 matched control subjects from four US prospective cohort studies with available prediagnostic blood. Total IgE, food allergen–specific IgE, and respiratory allergen–specific IgE were measured, and association with glioma was analyzed by logistic regression.

Contribution

Compared with clinically normal IgE levels (<25 kU/L), borderline elevated total IgE levels (25–100 kU/L) were inversely associated with glioma, but elevated IgE levels (>100 kU/L) showed no association. When analysis was restricted to highly fatal case subjects (died within 2 years of diagnosis) or earlier birth cohorts (born before 1930), an inverse association was observed with elevated IgE levels compared with normal levels, although the association was not statistically significant. Food allergen–specific and respiratory allergen–specific IgE levels showed no association with glioma.

Implications

This study suggests that total IgE levels are associated with glioma, but further research is necessary to confirm and understand the complex nature of the association.

Limitation

Relatively small number of case subjects and limited statistical power for subanalyses.

From the Editors

Methods

Study Populations

We analyzed data collected from four independent cohorts. These cohorts have been described in detail elsewhere (7–10). Briefly, the PHS was a randomized trial to assess the efficacy of aspirin in the reduction of cardiovascular mortality and the efficacy of β-carotene in the reduction of cancer incidence. The trial started in 1982 and includes 22 071 male physicians. The subjects, aged 40–84 years, with no history of cardiovascular disease or cancer, were assigned randomly in a 2 × 2 factorial design to receive aspirin, β-carotene, or placebo. The study participants are now followed as an observational cohort. The NHS is a prospective study of risk factors for cancer, cardiovascular disease, and diabetes. The study began in 1976 and includes121 700 female US registered nurses, aged 30–55 years, who completed and returned an initial questionnaire. The WHS was a randomized trial. The trial started in 1991 and included a total of 39 876 female health professionals. The subjects aged 45 years or older were originally assigned randomly in a 2 × 2 factorial design to receive aspirin, vitamin E, or placebo to examine the effects on vascular events. The trial ended in 2009, and the study is now an observational cohort study. The HPFS includes 51 529 US male health professionals, aged 40–75 years, who completed an initial lifestyle questionnaire and a comprehensive dietary assessment in 1986. This cohort has been followed over time to examine lifestyle and dietary associations with major disease outcomes.

All cohort subjects are frequently contacted (yearly in the WHI and PHS and biennially in the HFPS and NHS I and II) to ascertain outcomes. The follow-up rate for the cohorts for incidence of cancer was greater than 95% of the total possible person-years. Deaths of cohort subjects are usually reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index (NDI) is searched biennially for nonrespondents; this method has been shown to have a sensitivity of 98% (11). This study was approved by the Human Research Committee of the Brigham and Women's Hospital.

Case Ascertainment

Yearly or biennially, all participants from these cohorts were asked whether they had been diagnosed with any cancer, heart disease, or other medical conditions during the previous year(s). Medical records and pathology reports were obtained from hospitals after permission was received from case subjects. Similarly, medical records and pathology reports were requested for deceased glioma case subjects identified through the NDI or from other sources. Approximately 88% of potential case subjects (ie, self-reported or deceased case subjects with glioma) were subsequently confirmed with medical, pathology, or cancer registry data. We only included glioma case subjects who were confirmed from medical or pathology records, or from a death certificate. We included all glioma brain tumors; these included astrocytoma, glioblastoma, oligodendroglioma, ependymoma, and mixed glioma subtypes.

History of Asthma

Self-reported history of asthma was reported in three of the four cohorts (NHS, WHS, HPFS); the question at baseline in HPFS (1986) asked whether the participant had ever had asthma, and the question at baseline in the WHS (at enrollment) and NHS (1988) asked specifically if the participants had ever been diagnosed with asthma (by a physician). No baseline data were collected on history of asthma in the PHS cohort.

Blood Collection

Between August 1982 and December 1984, blood samples were collected from 14 916 PHS participants as part of the initial trial, by sending venipuncture kits to the 22 071 participants (return rate 68%). Blood samples were drawn into EDTA tubes. Samples were

centrifuged, aliquoted, and stored in liquid nitrogen freezers at −82°C as either whole blood or plasma. Blood samples were collected from 32 825 NHS cohort subjects from May 1989 through September 1990. Blood collection kits were sent to 59 923 nurses who had indicated that they would be willing to send a blood sample (return rate 55%). Upon arrival in the laboratory, the blood samples were centrifuged, and the samples were divided into eight aliquots and stored in liquid nitrogen freezers. Blood samples were collected from WHS participants from September 1992 to May 1995 as part of the initial trial, after sending a blood collection kit to 39 848 participants who indicated willingness to provide a blood specimen. A total of 28 133 individuals returned a sample (return rate 71%), collected in both EDTA tubes and citrate tubes. Once the samples were received, they were stored in liquid nitrogen freezers. In 1993 and 1994, blood specimens were collected from men in HPFS; a venipuncture kit was sent to all living participants who agreed to provide blood (number not known); 18 225 of whom returned the specimens on ice using an overnight courier. Multiple aliquots of plasma, buffy coat for DNA analyses, and red cells were stored in liquid nitrogen freezers for use in future assays.

IgE Measurement

All identified and confirmed incident glioma case subjects who had provided blood samples at baseline were selected for this study (N = 181). For each case subject, we identified three control subjects (N = 542) among the cohort participants who returned blood samples, who did not have cancer, and who were alive at the time the matched case subject was diagnosed; only two control subjects were matched with one case subject where the matching criteria could not be met. The control subjects were chosen at random and matched with each case subject on year of birth, cohort (which automatically matches the sex, because each cohort consists of either men or women), month of blood sample collection, and ethnic background. In addition, in the PHS and WHS cohorts, control subjects were matched to each case subject based on their original intervention group (ie, aspirin, β-carotene, vitamin E, or placebo). Blood samples were removed from the freezers and sent to the Channing Laboratory (Boston, MA) as case–control sets in a random sequence. Laboratory personnel were blinded to the case–control status of all samples. The laboratory used the Pharmacia Diagnostics AB (Uppsala, Sweden) UniCAP fluorescent assay (12), which has been specially designed to assay circulating serum IgE levels for use in clinical settings. This commercial assay, which is a sandwich fluorescent immunoassay, has been shown to be reproducible and precise when used by different laboratories (13). ImmunoCAP Phadiotop (Pharmacia Diagnostics AB) assay was used to test for respiratory-specific allergens, which included 15 allergens and could identify 97% of atopic allergy to respiratory allergens. Food allergens were tested against a mixture of food-specific allergens, which included peanut, wheat, fish, milk, egg white, and soybean. Total serum IgE is commonly used to make a clinical diagnosis of atopic disease and has a sensitivity of 93% and a specificity of 89% when compared with clinical symptoms (14). Samples with a coefficient of variation (CV) percentage greater than 10% were remeasured. The average CV from this study was 1.6% for total IgE, 2.3% for the respiratory-specific allergens, and 6.1% for the food-specific allergens.

Serum IgE levels are stable over a long period (when stored at −20°C); a previous study found no degradation of IgE antibodies over an 8-year period (14). In addition, total and specific IgE levels in sera stored for 32–37 years at −20°C were shown to be equal or greater than the levels of IgE in sera stored for 5 years (15).

For total IgE, we used the clinical cut points of greater than 100 kU/L for elevated IgE levels and 25–100 kU/L for borderline elevated clinically ambiguous IgE levels; less than 25 kU/L is considered clinically normal. According to Pharmacia Diagnostics AB, IgE levels for the food and respiratory panels are considered negative if the assay showed a level of less than 0.35 kU/L and positive if the level is 0.35 kU/L or more. The measured fluorescence scored against a standard curve with known quantity inputs was used to determine a continuous measure of IgE (per manufacturer instructions).

Statistical Analysis

Because of failure to measure IgE at the laboratory or insufficient volume available for some samples, the final analysis included 169 case subjects and 520 control subjects. Each cohort was analyzed both individually and pooled together. The three allergy measurements (total IgE, food allergen–, and respiratory allergen–specific IgE) were log transformed to normalize them. We used conditional logistic regression analyses to examine the associations between the concentration measurements of total IgE, food and respiratory allergens, and risk of glioma. We conducted subanalyses stratifying on median age (>58 or <58 years; range 40–85 years) and birth cohort (before or after birth year 1930; range = 1901–1948) and tested for interaction by including cross-product terms (three categories for total IgE [normal, borderline elevated, and elevated] multiplied by stratified categories [age and birth cohort]) in the logistic regression models. We conducted *t* tests or one-way analysis of variance tests to compare levels of IgE across groups. The kappa statistic was used to calculate concordance between categories of self-reported history of asthma (yes or no) and two categories of total IgE measures (<25 or ≥25 kU/L). All tests of statistical significance were two-sided, and *P* values less than .05 were considered statistically significant. All analyses were performed using SAS 9.1 (SAS Inc, Cary, NC).

Results

Case subjects (N = 169) and control subjects (N = 520) in this study were obtained from four cohort studies, representing different populations. Mean age at diagnosis for glioma was similar across cohorts, and the majority of case subjects (90%–100%) were white of European descent (Table 1). Mean age at blood collection was slightly higher in the HPFS cohort compared with other cohorts. Total IgE levels, after log transformation, varied across the four cohorts. Among control subjects, 38% (PHS) to 52% (NHS) of individuals had clinically normal levels (<25 kU/L), 39% (NHS and PHS) to 43% (WHS) had borderline elevated levels (25–100 kU/L), and 9% (NHS) to 23% (PHS) had elevated levels (>100 kU/L) of total IgE. We observed a statistically significant difference ($P < .001$) in the distribution of total IgE between women (NHS and WHS) and men (HPFS and PHS), but not between cohorts of the same sex ($P = .95$ for women, and $P = .80$ for men;

Table 1. Characteristics of case subjects and control subjects in the four US prospective cohorts*

Characteristic	Case subjects (n = 169)		Control subjects (n = 520)	
	No.	Mean (SD)	No.	Mean (SD)
NHS (women)				
ln (total IgE), kU/L	47	3.1 (1.4)	155	3.0 (1.3)
Age at blood draw, y	47	57.8 (5.9)	155	57.8 (6.1)
Race (white), %	47	100	155	100
Age at diagnosis, y	47	66.4 (5.5)	—	—
WHS (women)				
ln (total IgE), kU/L	20	2.6 (2.8)	60	3.0 (2.1)
Age at blood draw, y	20	57.6 (9.7)	60	57.6 (9.5)
Race (white), %	20	90	60	90
Age at diagnosis, y	20	62.4 (10.3)	—	—
HPFS (men)				
ln (total IgE), kU/L	34	3.0 (2.2)	102	3.6 (1.4)
Age at blood draw, y	34	63.7 (9.4)	102	63.7 (9.2)
Race (white), %	34	94	102	94
Age at diagnosis, y	34	70.0 (10.1)	—	—
PHS (men)				
ln (total IgE), kU/L	68	3.7 (1.7)	203	3.6 (1.6)
Age at blood draw, y	68	56.3 (9.5)	203	56.4 (9.5)
Race (white), %†	37	94.6	200	97.5
Age at diagnosis, y	68	68.0 (10.6)	—	—

* The blood collection periods of all cohorts were as follows: NHS, 1989–1990; WHS, 1992–1995; HPFS, 1993–1994; PHS, 1982–1984. IgE = immunoglobulin E; HPFS = Health Professionals Follow-up Study; NHS = Nurses' Health Study; PHS = Physicians' Health Study; WHS = Women's Health Study; — = control subjects do not have an age at diagnosis as they did not develop cancer.

† Data missing on 31 case subjects and three control subjects.

data not shown). For food allergens, the distribution of IgE levels ranged between a minimum of 0.35 kU/L and a maximum of 10.2 kU/L; no difference in distribution of values was observed between men and women. For respiratory allergens, we observed a difference ($P = .02$) in distribution of IgE levels between the sexes (data not shown).

Mean total IgE levels were statistically significantly higher among 43 control subjects who had reported a history of asthma at baseline (and/or history of allergies in the HPFS) than among 274 control subjects without a history (with vs without asthma history, ln mean = 3.83, SD = 1.78, vs ln mean = 3.09, SD = 1.84, respectively; $P = .01$; data not shown). The PHS cohort did not have data on history of asthma or allergies and, therefore, was not included in this analysis. Median overall survival among all case subjects (N = 169) was worst for IgE levels less than 25kU/L (8.5 months [5-95 percentile = 1–180 months]); survival was 9 months (5-95 percentile = 0–180 months) for IgE levels 25–100 kU/L, and 13 months (5-95 percentile = 0–180 months) for IgE levels greater than 100 kU/L (data not shown).

Overall, we found no statistically significant associations between allergy measurements and risk of glioma. However, there was an inverse association of borderline statistical significance ($P = .07$) for total IgE levels higher than clinically normal levels and risk of glioma (total IgE ≥25 vs<25 kU/L, odds ratio [OR] = 0.72, 95% CI = 0.51 to 1.04) compared with IgE levels lower than clinically normal levels (data not shown in tables). A statistically significant inverse association was noted for borderline elevated IgE levels and risk of glioma (total IgE 25–100 vs <25 kU/L, OR = 0.63, 95% CI = 0.42 to 0.93), but no association between elevated IgE levels and risk of glioma (total IgE >100 vs <25 kU/L, OR = 0.98, 95% CI = 0.61 to 1.56) was noted compared with normal IgE levels (Table 2). The food allergen–specific and respiratory allergen–specific IgE levels were not associated with risk of glioma (Table 2).

We examined the association between IgE levels and risk of glioma stratified by sex to see if the association was similar for men and women (Table 3). Among men, we observed a statistically significant inverse association for borderline elevated IgE level and glioma risk (total IgE 25–100 vs <0.25 kU/L, OR = 0.58, 95% CI = 0.34 to 0.99) compared with normal IgE levels. Among women, a non-statistically significant inverse association was noted for borderline elevated IgE level and glioma risk (total IgE 25–100 vs <0.25 kU/L, OR = 0.68, 95% CI = 0.37 to 1.24) compared with normal IgE levels. Similar to the overall findings (Table 2), elevated IgE levels or food- and respiratory-specific IgEs were not associated with risk of glioma in men or women.

Each cohort was examined separately to assess the associations between total IgE levels and risk of glioma (Table 4). In two cohorts (WHS and HPFS), we found inverse associations for both borderline elevated and elevated IgE levels compared with normal levels. However, the analysis was based on small numbers of study subjects (WHS, n = 20 subjects; HPFS, n = 34 subjects). The associations in the other two cohorts (NHS and PHS) were similar to the results of the four cohorts combined (shown in Table 2).

Data on self-reported history of asthma at baseline or during follow-up was available on three of the four cohorts (WHS, NHS, and HPFS); using these three cohorts, a non-statistically significant inverse association was observed between self-reported asthma and risk of glioma (OR = 0.60, 95% CI = 0.21 to 1.70). Including history of self-reported asthma with total IgE levels in the same logistic regression model did not change the associations substantially. Concordance between self-reported asthma and IgE levels in this study was 48% (concordance statistic, $\kappa = .04$).

Table 2. Associations between prediagnostic plasma immunoglobulin E (IgE) levels and glioma in four US prospective cohorts*

IgE level†	Case subjects, No.	Control subjects, No.	OR (95% CI)
Total IgE, kU/L			
Mean ln (IgE) (SD)	3.24 (1.78)	3.34 (1.91)	
ln (IgE)	169	520	0.97 (0.88 to 1.07)‡
Normal, <25	84	220	1.0 (referent)
Borderline elevated, 25–100	50	209	0.63 (0.42 to 0.93)
Elevated, >100	35	91	0.98 (0.61 to 1.56)
Normal, <25	84	220	1.0 (referent)
Above normal, ≥25	85	300	0.72 (0.51 to 1.03)
Food allergen–specific IgE, kU/L			
Negative (≤0.35)	156	481	1.0 (referent)
Positive (>0.35)	13	39	1.03 (0.54 to 1.98)
Respiratory allergen–specific IgE, kU/L			
Negative (≤0.35)	112	357	1.0 (referent)
Positive (>0.35)	57	163	1.12 (0.77 to 1.62)

* The four cohorts were Nurses' Health Study (NHS), Women's Health Study (WHS), Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS). CI = confidence interval; OR = odds ratio. Conditional logistic regression was used to analyze the matched nested case–control dataset.

† Total IgE levels were measured using the Pharmacia Diagnostics UniCAP fluorescent immunoassay; cut points were based on clinically defined cut points. Respiratory allergen–specific IgE was measured using the ImmunoCAP Phadiotop and food allergen–specific IgE was measured using a mixed food allergen assay from Pharmacia Diagnostics AB; recommended cut points were provided by Pharmacia Diagnostics AB.

‡ ORs for continuous variable (for increase by 1 ln total IgE).

We examined the association between total IgE levels and glioma among case subjects who died within 2 years of diagnosis (highly fatal), given that these subjects most likely represent primary glioblastoma multiforme case subjects (n = 116). When restricting the analysis to case subjects who died within 2 years of diagnosis, a non-statistically significant inverse association was observed for borderline elevated and elevated IgE levels and risk of glioma (total IgE 25–100 vs 25 kU/L, OR = 0.80, 95% CI = 0.50 to 1.27; total IgE >100 vs 25 kU/L, OR = 0.64, 95% CI = 0.34 to 1.19) compared with normal levels. Similarly, a non-statistically significant inverse association was observed between food-specific IgE levels and glioma risk (>0.35 vs ≤0.35 kU/L, OR = 0.73, 95% CI = 0.31 to 1.73) comparing positive (>0.35 kU/L) with negative levels (≤0.35 kU/L), when restricting the analysis to these case subjects (data not shown). We also examined the association between total IgE and glioblastoma (n = 103 case subjects); when analysis was restricted to glioblastoma case subjects, a similar non-statistically significant inverse association was detected (total IgE 25–100 vs <25 kU/L, OR = 0.69, 95% CI = 0.42 to 1.13; total IgE >100 vs <25 kU/L, OR = 0.82, 95% CI = 0.43 to 1.58) (data not shown).

Further analyses were conducted to include a lag analysis between blood collection and date of diagnosis. The associations between total IgE levels and risk of glioma were similar for glioma

Table 3. Associations between prediagnostic plasma immunoglobulin E (IgE) levels and glioma by sex*

	Women			Men		
IgE level†	Case subjects, No.	Control subjects, No.	OR (95% CI)	Case subjects, No.	Control subjects, No.	OR (95% CI)
Total IgE, kU/L						
ln (IgE)	67	215	0.99 (0.86 to 1.13)‡	102	305	0.95 (0.83 to 1.08)‡
Normal, <25	38	107	1.0 (referent)	46	113	1.0 (referent)
Borderline elevated, 25–100	21	87	0.68 (0.37 to 1.24)	29	122	0.58 (0.34 to 0.99)
Elevated, >100	8	21	0.94 (0.37 to 2.38)	27	70	0.95 (0.54 to 1.66)
Food allergen–specific IgE, kU/L						
Negative (≤0.35)	61	200	1 (referent)	95	280	1.0 (referent)
Positive (>0.35)	6	15	1.32 (0.49 to 3.54)	7	24	0.86 (0.36 to 2.07)
Respiratory allergen–specific IgE, kU/L						
Negative (≤0.35)	47	164	1 (referent)	65	192	1 (referent)
Positive (>0.35)	20	51	1.38 (0.75 to 2.54)	37	112	0.98 (0.62 to 1.56)

* Results for women are based on the two female cohorts: Nurses' Health Study (NHS) and Women's Health Study (WHS). Results for men are based on the two male cohorts: Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS). Conditional logistic regression was used to analyze the matched nested case–control dataset after stratifying data by sex. CI = confidence interval; OR = odds ratio.

† Total IgE levels were measured using the Pharmacia Diagnostics AB UniCAP fluorescent immunoassay; cut points were based on clinically defined cut points. Respiratory allergen–specific IgE was measured using the ImmunoCAP Phadiotop and food allergen–specific IgE was measured using a mixed food allergen assay from Pharmacia Diagnostics AB; recommended cut points were provided by Pharmacia Diagnostics AB.

‡ ORs for continuous variable (for increase by 1 ln total IgE).

Table 4. Associations between prediagnostic plasma immunoglobulin E (IgE) levels and glioma by cohort study*

Cohort, total IgE level in kU/L†	Case subjects, No.	Control subjects, No.	OR (95% CI)
NHS			
ln (IgE)	47	155	1.03 (0.85 to 1.25)‡
Normal, <25	27	80	1.0 (referent)
Borderline elevated, 25–100	13	61	0.64 (0.31 to 1.34)
Elevated, >100	7	14	1.57 (0.52 to 4.71)
WHS			
ln (IgE)	20	60	0.98 (0.63 to 1.52)‡
Normal, <25	11	27	1.0 (referent)
Borderline elevated, 25–100	8	26	0.73 (0.23 to 2.31)
Elevated, >100	1	7	0.32 (0.03 to 3.28)
HPFS			
ln (IgE)	34	102	0.80 (0.63 to 1.01)‡
Normal, <25	19	36	1.0 (referent)
Borderline elevated, 25–100	9	43	0.34 (0.12 to 0.97)
Elevated, >100	6	23	0.49 (0.17 to 1.44)
PHS			
ln (IgE)	68	203	1.04 (0.87 to 1.24)‡
Normal, <25	27	77	1.0 (referent)
Borderline elevated, 25–100	20	79	0.74 (0.39 to 1.42)
Elevated, >100	21	47	1.24 (0.63 to 2.44)

* Conditional logistic regression was used to analyze the matched nested case–control dataset by cohort. CI = confidence interval; HPFS = Health Professionals Follow-up Study; NHS = Nurses' Health Study; OR = odds ratio; PHS = Physicians' Health Study; WHS = Women's Health Study.

† Total IgE levels were measured using the Pharmacia Diagnostics AB UniCAP fluorescent immunoassay; cut points were based on clinically defined cut points.

‡ ORs for continuous variable (for increase by 1 ln total IgE).

case subjects diagnosed within 5 years (total IgE ≥25 vs <25 kU/L, OR = 0.57, 95% CI = 0.29 to 1.14) and those diagnosed 5 or more years after blood collection (total IgE ≥25 vs <25 kU/L, OR = 0.79, 95% CI = 0.53 to 1.20). This indicates that IgE levels were not likely influenced by the onset of the disease.

We analyzed our data after stratifying on median birth year (1930) because allergen exposures in childhood have changed substantially over time and prevalence of allergies has increased. We noted inverse associations between borderline elevated and elevated IgE levels and glioma risk, compared with normal IgE levels, among those born between 1901–1930, although the associations were not statistically significant (total IgE 25–100 vs <25 kU/L, OR = 0.77, 95% CI = 0.45 to 1.31; total IgE >100 vs <25 kU/L, OR = 0.67, 95% CI = 0.34 to 1.34; IgE levels as continuous variable, P_{trend} = .21); whereas the associations for those born between 1930–1948 were similar to our findings shown in Table 2. The test for interaction between total IgE and birth year was not statistically significant ($P_{interaction}$ = .06) (data not shown). Among older individuals (≥58 years), a non-statistically significant inverse association was observed between total IgE levels and risk of glioma (total IgE >100 vs <25 kU/L, OR = 0.51, 95% CI = 0.24 to 1.06); a non-statistically significant positive association was noted for individuals younger than 58 years (total IgE >100 vs <25 kU/L, OR = 1.79, 95% CI = 0.91 to 3.54). The interaction between total IgE and age was not statistically significant ($P_{interaction}$ = .08).

Discussion

We analyzed the association between allergies and risk of subsequent glioma by measuring the IgE levels in participants of four US prospective cohort studies. We did not observe a statistically significant association between total IgE level and risk of glioma, although a more detailed examination of the data revealed a lower risk for "borderline elevated" total IgE levels (25–100 kU/L) than with "elevated" total IgE levels (>100 kU/L), compared with clinically normal total IgE levels (<25 kU/L). This observation was consistent across three of the four cohorts and for both men and women. We observed a non-statistically significant inverse association between total IgE and glioma when restricting our analysis to case subjects that had died within 2 years of diagnosis (highly fatal). No associations between food allergen–specific IgE and respiratory allergen–specific IgE levels and glioma were noted.

To date, most studies examining the relation between allergies and brain tumors have used self-reported history of asthma or allergies (3). No particular allergen or allergy has been identified as being uniquely associated with risk of brain cancer, and an inverse dose–response relationship has been reported with increasing number of allergies and brain cancer (16). The most common manifestation of allergic response is a type I immediate hypersensitivity reaction mediated by IgE. The relationship between blood levels of total IgE and brain cancer has been previously evaluated in a traditional case–control study (17), which was later updated with additional data (18). In the updated analysis, Wiemels et al. (18) reported a statistically significant inverse association for borderline IgE (25–100 kU/L, OR = 0.66, 95% CI = 0.48 to 0.90) and a non-statistically significant inverse association for elevated IgE (>100 kU/L, OR = 0.79, 95% CI = 0.55 to 1.12). The authors speculate, given the attenuation of the association in the updated analysis compared with the strongly inverse association in the earlier findings for elevated IgE levels (>100 kU/L, OR = 0.37, 95% CI = 0.22 to 0.64), that the introduction of the treatment drug temozolomide confounded the association (given that the drug

lowers total IgE levels) (18). An alternative explanation, provided by the authors, is that a cohort effect could explain the different results; the first case–control study had a median birth year of 1939 compared with 1948 for the second series of case subjects and control subjects. Although we had limited power to examine this, we also noted that the associations were more consistently inverse for total IgE and risk in the earlier birth cohorts.

We observed an inverse association among highly fatal case subjects of glioma. Although not statistically significant, this finding suggests that the immune relation with allergies is etiologically relevant for primary glioblastomas or those with a specific genetic profile. For example, glioma case subjects with the enzyme cytosolic isocitrate dehydrogenase 1 (IDH1) mutation status have a defined methylation profile and higher survival (19). Thus, the relation between allergies and glioma may be more apparent among subtypes of aggressive tumors that would have to be defined by genetic profile.

A number of factors have to be taken in consideration in the analysis of our results. Early-onset allergies are thought to be more likely to be IgE mediated than late onset allergies, which are often mediated by tissue-specific mechanisms (20). Although serum antibodies have a long half-life, it is difficult to determine the precise date of exposure to allergens; thus, it is conceivable that some individuals who experienced repeated immune challenges might have reverted to baseline IgE levels by the time of sampling. In addition, although a clear inverse association between self-reported history of allergies and brain cancer has been observed consistently, concordance between self-reported allergies and total IgE levels is relatively low; 56% were consistently positive in a previous study (17) and 48% in this study.

The strength of our study included the measurement of total IgE levels in prediagnostic blood; consequently, our results could not have been influenced by treatment of glioma and unlikely to have been influenced by disease. This has been a concern in previous studies where blood samples were collected after the diagnosis and treatment of glioma (18). In addition, we were able to examine total IgE levels at different time periods to evaluate whether the lag between blood collection and diagnosis affected the association.

Limitations of this study include a relatively small sample size of only 169 case subjects. However, obtaining prospective data on glioma is a challenge given the low incidence of this cancer, and these results are based on the pooling of four large cohort studies. We had limited power to detect a statistically significant association for subanalyses; our observation of a non-statistically significant inverse association between total IgE levels and highly fatal glioma (survival less than 2 years) will need to be confirmed in larger studies.

Overall, our results confirm the previously reported pattern of association between total IgE and brain cancer. The associations between total IgE levels and risk of glioma in this study and the large case–control study by Wiemels et al. (18) support an inverse association among earlier birth cohorts, which has attenuated in more recent birth cohorts because of the changes in allergy patterns over time (increasing prevalence). This study supports more research to clarify the complex relationship between allergies, total IgE levels, and risk of glioma.

References

1. CBTRUS (2010). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004–2006. Source: Central Brain Tumor Registry of the United States, Hinsdale, IL. www.cbtrus.org.
2. SEER Cancer Statistics Review 1975-2007. http://seer.cancer.gov/csr/1975_2007/index.html.
3. Linos E, Raine T, Alonso A, et al. Atopy and risk of brain tumors: a meta-analysis. *J Natl Cancer Inst.* 2007;99(20):1544–1550.
4. Wrensch M, Minn Y, Chew T, et al. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro Oncol.* 2002;4(4):278–299.
5. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med.* 2001;344(1):30–37.
6. Harling-Berg CJ, Park TJ, Knopf PM. Role of the cervical lymphatics in the Th2-type hierarchy of CNS immune regulation. *J Neuroimmunol.* 1999;101(2):111–127.
7. Stampfer MJ, Buring JE, Willett W, et al. The 2 x 2 factorial design: its application to a randomized trial of aspirin and carotene in U.S. physicians. *Stat Med.* 1985;4(2):111–116.
8. Belanger CF, Hennekens CH, Rosner B, et al. The Nurses' Health Study. *Am J Nurs.* 1978;78(6):1039–1040.
9. Buring JE, Hennekens CH; for The Women's Health Study Research Group. The Women's Health Study: summary of the study design. *J Myocardial Ischemia.* 1992;4:27–29.
10. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet.* 1991;338(8765):464–468.
11. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol.* 1994;140(11):1016–1019.
12. Walker PR, Calzascia T, Dietrich PY. All in the head: obstacles for immune rejection of brain tumours. *Immunology.* 2002;107(1):28–38.
13. Szeinbach SL, Barnes JH, Sullivan TJ, et al. Precision and accuracy of commercial laboratories' ability to classify positive and/or negative allergen-specific IgE results. *Ann Allergy Asthma Immunol.* 2001;86(4):373–381.
14. Paganelli R, Ansotegui IJ, Sastre J, et al. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. *Allergy.* 1998;53(8):763–768.
15. Henderson CE, Ownby D, Klebanoff M, et al. Stability of immunoglobulin E (IgE) in stored obstetric sera. *J Immunol Methods.* 1998;213(1):99–101.
16. Wiemels JL, Wiencke JK, Sison JD, et al. History of allergies among adults with glioma and controls. *Int J Cancer.* 2002;98(4):609–615.
17. Wiemels JL, Wiencke JK, Patoka J, et al. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Res.* 2004;64(22):8468–8473.
18. Wiemels JL, Wilson D, Patil C, 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.
19. Christensen BC, Smith AA, Zheng S, et al. DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma. *J Natl Cancer Inst.* 2011;103(2):143–153.
20. Miranda C, Busacker A, Balzar S, et al. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol.* 2004;113(1):101–108.

Funding

This work was supported by the National Institutes of Health (R01 CA114205 to DSM, R01 CA047988 and R01 HL043851 to JEB, P01 CA097193 to JMG, P01 CA087969 to Dr Susan Hankinson, P01 CA055075 to WCW).

Notes

The authors are solely responsible for the study design, data collection, analysis and interpretation of the data, writing the article, and decision to submit the article for publication.

Affiliations of authors: Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, UK (FCFC, DGC, DSM); INSERM U1052, Lyon Cancer Research Center, Centre Léon Berard, Lyon, France (DGC); Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA (JEB, JMG); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (JM, MS, WCW, SST, DJH, CAC); Department of Epidemiology (MS, WCW, SST, DJH) and Department of Nutrition (MS, WCW, DJH), Harvard School of Public Health, Boston, MA; Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA (CAC); Department of Epidemiology, Division of Biology and Medicine, Brown University, Providence, RI (DSM).