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ARTICLE

Association Between Prediagnostic IgE Levels and Risk of Glioma

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Background Previous nested case–control studies suggest that a prediagnostic biomarker of allergy, IgE, is inversely associated with the risk of glioma, but these findings are inconsistent. The purpose of our study was to assess this association and determine how long before glioma diagnosis it may be observed.

Methods We conducted a nested case–control study using serum specimens from the Janus Serum Bank cohort in Norway. Blood donors who were subsequently diagnosed with glioma (n = 594 case subjects), between January 1, 1974 to December 31, 2007, were matched with subjects without glioma (n = 1177 control subjects) for date of blood collection, 2-year age interval at blood collection, and sex. Respiratory allergen-specific and total IgE levels in the serum were measured using fluorescent assays. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression models stratified on sex and glioblastoma, the most common glioma subtype. Data were stratified on time from blood collection to tumor diagnosis to assess how long before glioma diagnosis the association could be observed.

Results Among women, testing positive for allergen-specific IgE (>0.35 kU_A/L) was associated with decreased risk of glioblastoma compared with testing negative (≤0.35 kU_A/L; OR = 0.46, 95% CI = 0.23 to 0.93). Among both sexes combined, testing positive for total IgE (>100 kU/L) was associated with decreased risk of glioma compared with testing negative (≤100 kU/L; OR = 0.75, 95% CI = 0.56 to 0.99), and simultaneously testing positive for allergen-specific IgE and total IgE was associated with a borderline statistically significantly decreased risk of glioblastoma and glioma compared with simultaneously testing negative for these types of IgE. Testing positive for total IgE at least 20 years before diagnosis was associated with decreased risk of glioma compared with testing negative (OR = 0.54, 95% CI = 0.30 to 0.99).

Conclusion An inverse association between IgE levels and risk of glioma was detected; the association was present at least 20 years before tumor diagnosis.

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Allergy consists of a group of heterogeneous diseases with different underlying mechanisms. However, common allergies including eczema, hay fever, and allergic asthma, characterized by immediate hypersensitivity reactions, are mediated by IgE, which is produced and regulated by the B cells as well as T helper type 2 (Th2) and type 17 (Th17) cells (1–3). Allergic symptoms result from cross-linking of IgE to an allergen on the surface of mast cells, leading to the release of granules including histamine and other inflammatory substances. Two broad classes of IgE participate in the allergic response, allergen-specific IgE, which recognizes specific components of an allergen, and total IgE, which recognizes these components and, in addition, includes antibodies of unknown specificity and function (4). Levels of allergen-specific IgE are used, together with allergic symptoms, to diagnose allergies. However, there are allergies, such as contact allergies, that do not involve IgE (5), and conversely, elevated levels of either allergen-specific or total IgE are not necessarily associated with allergic symptoms (6,7).

Many observational studies have been conducted to determine whether having a history of allergy is associated with a reduced risk of cancer (8,9). Findings from most of these studies are conflicting, with varying results both within and among cancer sites. In contrast, the inverse association between self-reported allergy and glioma has been consistently observed in case–control studies (10–12). In addition, there are two recent nested case–control studies (13,14), in which prediagnostic IgE concentration was used as a biomarker of allergy. In the first study, Schlehofer et al. (13) found an association between those testing positive for respiratory allergen-specific IgE (>0.35 kU_A/L) and decreased risk of glioma compared with those testing negative (≤0.35 kU_A/L) (odds ratio [OR] = 0.73, 95% confidence interval [CI] = 0.51 to 1.06). In

contrast, Calboli et al. (14) found no association between prediagnostic respiratory allergen-specific IgE levels and risk of glioma. However, they reported an association between borderline elevated total IgE levels (25–100 kU/L) and decreased risk of glioma compared with normal levels (<25 kU/L; OR = 0.63, 95% CI = 0.42 to 0.93), but observed no association with elevated IgE levels (>100 kU/L) compared with normal levels (14).

Glioma consists of morphologically heterogeneous tumors reflecting germline genetic variation and possibly differences in etiology (15), and the most common glioma subtype is glioblastoma. Schlehofer et al. (13) found that the association between testing positive for respiratory allergen-specific IgE and high-grade (grade 3 [anaplastic astrocytoma] and grade 4 [glioblastoma]) glioma (a category that consists of both anaplastic astrocytoma and glioblastoma) was stronger than the association between testing positive for allergen-specific IgE and all grades of glioma combined. Although Calboli et al. (14) reported that stratifying on glioblastoma did not substantially alter their results, their sample was small (n = 103 glioblastoma case subjects), making this finding difficult to interpret.

In this study, we aimed to further determine the degree to which respiratory allergen-specific or total IgE levels are associated with the risk of glioma or glioblastoma. We conducted a nested case–control study using prospectively collected stored serum samples from the Janus Serum Bank (Oslo, Norway).

Methods

Study Population

In 1972, the Norwegian Cancer Society, a voluntary nonprofit organization, established the Janus Serum Bank to conduct epidemiological studies of cancer (16–18). This biobank is now owned by the Cancer Registry of Norway and presently contains serum samples from approximately 167 000 men and 158 000 women. Age at entry was between 20 and 49 years, with most subjects enrolled between 35 and 49 years. Approximately 10% of the samples come from male and female Red Cross Blood Bank donors, who were between 20 and 65 years old at the time of blood donation. Blood samples were obtained from nonfasting participants, serum was separated following standard methods, and all samples were stored at –25°C. The samples went through one thaw–freeze cycle for preparation of aliquots for the present study.

During the Bank's first years, participants gave consent for their samples to be used for cancer research (19). Since 1972, Norwegian law regarding informed consent has changed, and samples collected after 1996 are based on the new law. However, the Norwegian Data Inspectorate has approved the use of data and biological samples collected during the period 1972–2004. Serum donors have also been informed that they may unconditionally withdraw their consent at any time. Should they wish to do so, their serum samples would be destroyed and their descriptive data deleted. The Regional Ethics Committee of Southern Norway and the Data Inspectorate of Norway approved our research plan.

Using unique personal identification numbers, participants in the Janus Serum Bank project can be linked to the Cancer Registry of Norway where virtually all newly diagnosed cancers among Norwegian residents have been recorded since 1953. Registration is based on compulsory reporting by hospital departments and histopathological laboratories and covers the entire Norwegian population (18). We initially identified 624 blood donors who were subsequently diagnosed with glioma (International Classification of Disease, Oncology, Third Edition [ICD-O-3] morphology codes 9380–9411, 9420–9480, and 9505) between January 1, 1974 and December 31, 2007. However, we subsequently excluded 11 case subjects diagnosed with medulloblastoma or primitive neuroectodermal tumor (ICD-O-3 codes 9470–9474) and pilocytic astrocytoma (ICD-O-3 code 9421) because of the small number of case subjects together with differences in age distributions for these tumors (20) compared with those of the glioma case subjects. Of the remaining 613 case subjects, 17 were excluded because their IgE levels were not ascertained. Data from two more case subjects were excluded because their allergen-specific or total IgE levels were outside the World Health Organization standard test range (allergen-specific IgE > 100 kU_A/L, total IgE > 2000 kU/L) (21), leaving 594 glioma case subjects, 374 of whom had been diagnosed with glioblastoma (ICD-O-3 code 944039).

When available, two control subjects for each case subject were randomly selected according to an incidence density sampling scheme among blood donors. Control subjects were individually matched to case subjects on 2-year age interval, sex, and date of blood collection. These matched control subjects were also required to be alive and free from any cancer except non–melanoma skin cancer on the date of glioma diagnosis of the case subject. Furthermore, to save valuable serum for use in subsequent biobank studies, potential control subjects diagnosed with rare tumors (ie, all tumors other than breast, prostate, and colorectal) after the case subject's date of glioma diagnosis were excluded from the study. Of the 1254 control subjects identified, serum IgE levels were successfully measured in 1217 subjects. Three control subjects were then excluded because their allergen-specific IgE or the total IgE levels were outside the World Health Organization standard test range (allergen-specific IgE > 100 kU_A/L, total IgE > 2000 kU/L) (21). Finally, matched case–control sets with a missing case subject or no control subjects because of exclusions listed above were removed from the dataset. After all exclusions, 1177 control subjects matched with 594 glioma case subjects remained in the dataset. Glioblastoma represented the majority of tumors (63%) in the present sample. We therefore analyzed matched sets with case subjects diagnosed with glioblastoma (n = 374 glioblastoma case subjects, n = 740 control subjects) separately from all glioma combined (n = 594 case subjects, n = 1177 control subjects).

Measurement of Allergen-Specific and Total IgE

We sent 200 μL of serum from each biobank sample (one sample per subject) to the Immunology and Transfusion Medicine Laboratory (Ulleval University Hospital, Oslo, Norway) for analysis of IgE levels. Laboratory personnel were unaware of the case–control status of these samples.

Allergen-specific IgE antibodies were measured using a standard clinical instrument designed for this purpose (ImmunoCAP 1000, Phadia AB, Uppsala, Sweden). We quantified responses to the nine most prevalent respiratory allergens in Norway (common house dust mites [d1 and d2]; silver birch tree pollen [t3]; timothy grass pollen [g6]; mugwort weed pollen [w6]; cat epithelium and

dander [e1]; dog dander [e5]; horse dander [e3]; and *Cladosporium herbarum* mold [m2]) and two additional allergens common in other countries (olive tree pollen [t9] and wall pellitory [w19]) (see (22) for description of allergen nomenclature) to see if they evoked a positive response to the test (>0.35 KU_A/L) (13,14). This test has a sensitivity of 93% and a specificity of 89% (22). Total IgE levels were also measured using the same instrument (ImmunoCAP 1000), and levels greater than 100 kU/L were considered positive (13,14). To evaluate possible dose–response associations and allow comparison with previous work, we used the same dose (ie, level) categories for allergen-specific IgE as those of Schlehofer et al. (13): negative (≤0.35 kU_A/L), borderline positive (>0.35–0.70 KU_A/L), weak positive (≥0.70–3.5 KU_A/L), strong positive (≥3.5–17.5 kU_A/L), and very strong positive (≥17.5 kU_A/L). However, we merged the two highest categories, strong positive and very strong positive, to avoid strata containing sparse data. Thus, our highest category was strong positive (≥3.5 kU_A/L). Doses of total IgE were those used in the Calboli et al. study (14): normal (<25 kU/L), borderline elevated (25–100 kU/L), and elevated (ie, positive; >100 kU/L).

Statistical Analysis

We used conditional logistic regression to estimate the association between respiratory allergen-specific and total IgE and the risk of glioma. For comparison with previous literature (13,14), both allergen-specific and total IgE were represented as categorical variables using cut points described above. The odds ratios and 95% confidence intervals for allergen-specific and total IgE were stratified on sex and the most common glioma subtype, glioblastoma. The rationale for glioblastoma stratification has been described earlier. To represent joint associations of sex and IgE, and allergen-specific and total IgE, on the risk of glioblastoma and glioma, we included cross-product terms in our regression models (23). We then used the Wald χ^2 statistic to test equality of the cross-product term regression coefficients to zero. To determine whether the association between IgE levels and risk of glioma varied by time between blood collection and tumor diagnosis, we divided this time variable into overlapping intervals. The category closest to time of diagnosis was at least 2 years before diagnosis, which we selected to allow comparison with a previous study (13), and subsequent intervals were 2-year periods based on the criterion that each interval had to contain at least five case subjects (at least 2 years, at least 5 years, at least 10 years, at least 15 years, at least 20 years, and at least 25 years). The interval of longest duration between blood collection and diagnosis was at least 25 years. Statistical tests were two-sided, and P values less than .05 were considered to be statistically significant. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Characteristics of Study Subjects

Glioblastoma case subjects (n = 374) and their matched control subjects (n = 740) and glioma case subjects (n = 594) and their matched control subjects (n = 1177) were evenly balanced with respect to age at blood collection, date of blood collection, and birth date (Table 1). For example, considering both sexes combined, glioblastoma case subjects and control subjects had the same median age (42 years) at blood collection, with overlapping interquartile ranges (40–44 years for glioblastoma case subjects and 40–43 years for glioblastoma control subjects). Median ages at blood collection for glioma case subjects and control subjects were identical (median age = 41 years, interquartile range = 40–43 years).

Associations Between Allergen-Specific IgE Levels and Glioma or Glioblastoma

We assessed the associations between prediagnostic allergen-specific IgE and risk of glioblastoma and glioma stratified by sex and for both sexes combined (Table 2). We found that among women, testing positive for elevated concentrations of allergen-specific IgE (>0.35 kU_A/L) was associated with a statistically significantly decreased risk of glioblastoma compared with testing negative (≤0.35 kU_A/L; OR = 0.46, 95% CI = 0.23 to 0.93). There was no similar association among men (>0.35 kU_A/L vs ≤0.35 kU_A/L, OR = 1.02, 95% CI = 0.72 to 1.44). When data for men and women were combined, there was a nonstatistically significant decreased risk of glioblastoma among subjects testing positive for allergen-specific IgE compared with subjects testing negative (>0.35 kU_A/L vs ≤0.35 kU_A/L, OR = 0.85, 95% CI = 0.62 to 1.16). For glioma, although the estimated odds ratios were different among men and women, neither association was statistically significant. To determine whether sampling variation accounted for the differences in associations between each of the two sexes and allergen-specific IgE for each tumor type, we tested the cross-product terms between sex and allergen-specific IgE for both tumor types. We found that associations between allergen-specific IgE and glioblastoma or glioma differed between men and women. However, both cross-product terms testing sex-specific differences among glioblastoma and glioma subjects were each only of borderline statistical significance (glioblastoma: Wald $\chi^2 = 3.94$, $P = .05$; glioma: Wald $\chi^2 = 3.39$, $P = .07$). An assessment based on refined dose categories, negative (≤0.35 kU_A/L), borderline positive (>0.35–0.70 kU_A/L), weak positive (≥ 0.70–3.5 kU_A/L), and strong positive (≥3.5 kU_A/L), for both sexes combined produced no further evidence for associations between allergen-specific IgE and glioblastoma or glioma.

Associations Between Total IgE Levels and Glioma or Glioblastoma

Next, we assessed the associations between prediagnostic total IgE and risk of glioblastoma and glioma stratified by sex and for both sexes combined (Table 3). In contrast to associations with allergen-specific IgE (Table 2), sex did not modify the association between total IgE and glioblastoma (Wald $\chi^2 = 1.13$, $P = .29$) nor did it modify that with glioma (Wald $\chi^2 = 0.60$, $P = .44$). We found that for both sexes combined, testing positive for elevated concentrations of total IgE (>100 kU/L) was associated with a borderline statistically significantly decreased risk of glioblastoma compared with testing negative (≤100 kU/L; OR = 0.74, 95% CI = 0.52 to 1.05). We also observed that for both sexes combined, testing positive for elevated concentrations of total IgE was statistically significantly associated with decreased risk of glioma compared with testing negative (>100 kU/L vs ≤100 kU/L, OR = 0.75, 95% CI = 0.56 to 0.99). There were no statistically significant sex-specific differences although associations for women were of borderline statistical significance (>100

Table 1. Demographic and time variables that characterize glioblastoma and glioma case subjects and control subjects*

Variable	Glioblastoma		Glioma	
	Case subjects	Control subjects	Case subjects	Control subjects
Women				
No.	109	216	197	391
Age at blood collection, median (IQR), y	41 (40–43)	41 (40–42)	41 (40–42)	41 (40–42)
Age at glioma diagnosis, median (IQR), y	57 (52–62)	—	56 (48–60)	—
Time from blood collection to glioma diagnosis, median (IQR), y	16 (9–21)	—	15 (9–20)	—
Date of blood collection, median (IQR), calendar years	1986 (1976–1989)	1986 (1976–1989)	1986 (1977–1989)	1986 (1977–1989)
Date of birth, median (IQR), calendar years	1945 (1936–1947)	1945 (1936–1948)	1946 (1939–1948)	1946 (1939–1948)
Men				
No.	265	524	397	786
Age at blood collection, median (IQR), y	42 (40–44)	42 (41–44)	42 (40–43)	43 (40–43)
Age at glioma diagnosis, median (IQR), y	56 (51–65)	—	55 (49– 63)	—
Time from blood collection to glioma diagnosis, median (IQR), y	15 (10–23)	—	14 (9–21)	—
Date of blood collection, median (IQR), calendar years	1983 (1974–1989)	1983 (1974–1989)	1985 (1974–1989)	1985 (1974–1989)
Date of birth, median (IQR), calendar years	1943 (1931–1948)	1943 (1931–1948)	1944 (1932–1948)	1945 (1932–1948)
Total				
No.	374	740	594	1177
Age at blood collection, median (IQR), y	42 (40–44)	42 (40–43)	41 (40–43)	41 (40–43)
Age at glioma diagnosis, median (IQR), y	57 (51–64)	—	56 (49–62)	—
Time from blood collection to glioma diagnosis, median (IQR), y	16 (10–22)	—	15 (9–21)	—
Date of blood collection, median (IQR), calendar years	1985 (1975–1989)	1985 (1975–1989)	1986 (1975–1989)	1986 (1975–1989)
Date of birth, median (IQR), calendar years	1944 (1931–1948)	1944 (1931–1948)	1945 (1934–1948)	1945 (1934–1948)

* Case subjects were blood donors (1974–2007) to Janus Serum Bank, Oslo, Norway, who were subsequently diagnosed with glioblastoma or glioma. Control subjects were individually matched to case subjects on 5-year age interval at the time of blood collection, sex, and date of blood collection. IQR = interquartile range; — = not applicable.

Table 2. Association between prediagnostic allergen-specific IgE levels and risk of glioblastoma and glioma*

	Glioblastoma			Glioma		
Allergen-specific IgE level†	**Case subjects (n = 374)**	**Control subjects (n = 740)**	**OR (95% CI)**	**Case subjects (n = 594)**	**Control subjects (n = 1177)**	**OR (95% CI)**
Women						
Negative (≤0.35 kU_A/L)	98	173	1.00 (referent)	165	313	1.00 (referent)
Positive (>0.35 kU_A/L)	11	43	0.46 (0.23 to 0.93)	32	78	0.78 (0.50 to 1.23)
Men						
Negative (≤0.35 kU_A/L)	203	403	1.00 (referent)	305	608	1.00 (referent)
Positive (>0.35 kU_A/L)	62	121	1.02 (0.72 to 1.44)	92	178	1.03 (0.78 to 1.38)
Total						
Negative (≤0.35 kU_A/L)	301	576	1.00 (referent)	470	921	1.00 (referent)
Positive (>0.35 kU_A/L)	73	164	0.85 (0.62 to 1.16)	124	256	0.95 (0.75 to 1.22)
Total refined categories						
Negative (≤0.35 kU_A/L)	301	576	1.00 (referent)	470	921	1.00 (referent)
Borderline positive (>0.35–0.70 kU_A/L)	22	38	1.11 (0.64 to 1.91)	38	58	1.28 (0.84 to 1.96)
Weak positive (≥ 0.70–3.5 kU_A/L)	24	73	0.63 (0.39 to 1.02)	41	106	0.76 (0.52 to 1.11)
Strong positive (≥3.5 kU_A/L)	27	53	0.98 (0.61 to 1.58)	45	92	0.97 (0.67 to 1.40)

* We conducted a case–control study nested in a prospective cohort to assess associations between prediagnostic allergen-specific IgE levels and risk of glioblastoma and glioma. Serum samples were obtained from the Janus Serum Bank in Oslo, Norway. We used diagnostic cut points to identify positive and negative tests in kilounits of allergen-specific IgE antibody per liter (kU_A/L). Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals separately within sex-specific strata and for the total data set. OR = odds ratio; CI = confidence interval.

† Allergen-specific IgE antibodies were measured using ImmunoCap 1000, a standard clinical instrument designed for this purpose.

Table 3. Association between prediagnostic total IgE levels and risk of glioblastoma and glioma*

	Glioblastoma			Glioma		
Total IgE level†	**Case subjects (n=374)**	**Control subjects (n=740)**	**OR (95% CI)**	**Case subjects (n=594)**	**Control subjects (n=1177)**	**OR (95% CI)**
Women						
Negative (≤100 kU/L)	100	183	1.00 (referent)	179	335	1.00 (referent)
Positive (>100 kU/L)	9	33	0.52 (0.24 to 1.11)	18	56	0.62 (0.36 to 1.08)
Men						
Negative (≤100 kU/L)	224	429	1.00 (referent)	338	644	1.00 (referent)
Positive (>100 kU/L)	41	95	0.82 (0.55 to 1.23)	59	142	0.80 (0.58 to 1.10)
Total						
Negative (≤ 100 kU/L)	324	612	1.00 (referent)	517	979	1.00 (referent)
Positive (>100 kU/L)	50	128	0.74 (0.52 to 1.05)	77	198	0.75 (0.56 to 0.99)
Total refined categories						
Normal (<25 kU/L)	194	360	1.00 (referent)	297	573	1.00 (referent)
Borderline (25–100kU/L)	130	252	0.95 (0.72 to 1.26)	220	406	1.04 (0.83 to 1.29)
Positive (≥100 kU/L)	50	128	0.73 (0.50 to 1.05)	77	198	0.76 (0.56 to 1.02)

* We analyzed prediagnostic total IgE levels in serum samples from the Janus Serum Bank in Oslo, Norway. We used diagnostic cut points to identify positive and negative tests in kilounits of total IgE antibody per liter (kU/L). Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals separately within sex-specific strata and for the total dataset. OR = odds ratio; CI = confidence interval.

† Total IgE antibodies were measured using ImmunoCap 1000, a standard clinical instrument designed for this purpose.

kU/L vs ≤100 kU/L: glioblastoma, OR = 0.52, 95% CI = 0.24 to 1.11; glioma, OR = 0.62, 95% CI = 0.36 to 1.08). An assessment based on refined dose categories: normal (<25 kU/L), borderline (25–100 kU/L), and positive (>100 kU/L), for both sexes combined, merely reflected the association between testing positive vs negative for total IgE and thus provided no additional evidence for a dose–response relation between serum IgE concentration and risk of glioblastoma or glioma.

Time Between Blood Collection and Glioma or Glioblastoma Diagnosis

To determine whether the association between elevated total IgE and risk of these tumors varied with proximity to diagnosis, we stratified the analyses by overlapping periods between blood collection and tumor diagnosis (Table 4). Each time category included all subsequent but not previous periods. We found that testing positive for elevated levels of total IgE (>100 kU/L) was associated with

Table 4. Association between prediagnostic total IgE levels and risk of glioblastoma and glioma stratified by time between blood collection and tumor diagnosis*

Time from blood collection to tumor diagnosis and total IgE level†	Glioblastoma			Glioma		
	Case subjects (n=361)	Control subjects (n=714)	OR (95% CI)	Case subjects (n=568)	Control subjects (n=1121)	OR (95% CI)
At least 25 years						
Negative (≤100 kU/L)	59	104	1.00 (referent)	80	142	1.00 (referent)
Positive (>100 kU/L)	7	25	0.46 (0.18 to 1.15)	9	32	0.48 (0.22 to 1.07)
At least 20 years						
Negative (≤100 kU/L)	102	182	1.00 (referent)	142	257	1.00 (referent)
Positive (>100 kU/L)	13	43	0.50 (0.25 to 1.02)	17	55	0.54 (0.30 to 0.99)
At least 15 years						
Negative (≤100 kU/L)	171	318	1.00 (referent)	248	470	1.00 (referent)
Positive (>100 kU/L)	25	68	0.69 (0.42 to 1.12)	36	91	0.76 (0.50 to 1.14)
At least 10 years						
Negative (≤100 kU/L)	243	446	1.00 (referent)	367	678	1.00 (referent)
Positive (>100 kU/L)	34	100	0.64 (0.42 to 0.96)	49	144	0.64 (0.46 to 0.91)
At least 5 years						
Negative (≤100 kU/L)	295	556	1.00 (referent)	456	858	1.00 (referent)
Positive (>100 kU/L)	47	120	0.74 (0.52 to 1.07)	68	179	0.73 (0.54 to 0.98)
At least 2 years						
Negative (≤100 kU/L)	312	592	1.00 (referent)	492	933	1.00 (referent)
Positive (>100 kU/L)	49	122	0.76 (0.53 to 1.09)	74	188	0.76 (0.57 to 1.00)

* We analyzed total IgE levels in serum samples from the Janus Serum Bank in Oslo, Norway. We used diagnostic cut points to identify positive and negative tests in kilounits of total IgE antibody per liter (kU/L). To determine whether the association between IgE levels and risk of glioma varied by time between blood collection and tumor diagnosis, we divided this time variable into overlapping intervals. The category closest to time of diagnosis was at least 2 years before diagnosis, and the interval of longest duration between blood collection and diagnosis was at least 25 years. Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals. OR = odds ratio; CI = confidence interval.

† Total IgE antibodies were measured using ImmunoCap 1000, a standard clinical instrument designed for this purpose.

decreased risk of glioblastoma and glioma in all time categories. These associations were either statistically significant or of borderline statistical significance. For example, among subjects whose blood was collected 20 years before tumor diagnosis, testing positive for total IgE was associated with borderline or statistically significantly decreased risk of glioblastoma and glioma compared with testing negative (>100 kU/L vs ≤100 kU/L: glioblastoma, OR = 0.50, 95% CI = 0.25 to 1.02; glioma, OR = 0.54, 95% CI = 0.30 to 0.99).

Allergen-Specific IgE and Modification of Association Between Total IgE and Glioma or Glioblastoma

We evaluated the joint association of allergen-specific IgE and total IgE with risk of glioblastoma and glioma (Table 5). We found that for both sexes combined, simultaneously testing positive for allergen-specific IgE and total IgE (>0.35 kU_A/L and >100 kU/L) was associated with decreased risk of glioblastoma (OR = 0.64, 95% CI = 0.41 to 1.00) and glioma (OR = 0.72, 95% CI = 0.51 to 1.02) compared with simultaneously testing negative for both types of IgE (≤35 kU_A/L and ≤100 kU/L). Both of these associations were of borderline statistical significance. Sex-specific analysis showed that women who simultaneously tested positive for allergen-specific IgE and total IgE were at decreased risk of glioblastoma and this decrease was statistically significant (OR = 0.26, 95% CI = 0.08 to 0.88). However, the estimated odds ratio was based on only three case subjects. Furthermore, tests of whether allergen-specific IgE modified the overall association between total IgE and glioblastoma or glioma failed to reach statistical significance (glioblastoma:Wald $\chi^2 = 1.46$, $P = .23$ and glioma:Wald $\chi^2 = 1.01$, $P = .32$).

Discussion

In this nested case–control study of the association between serum IgE and glioma, the largest study to our knowledge conducted to date in this area, we found that elevated levels of prediagnostic allergen-specific IgE and total IgE are associated with reduced risk of both glioblastoma and glioma. However, the association between testing positive for allergen-specific IgE and decreased tumor risk was restricted to women. Furthermore, we observed that the association with elevated total IgE was present at least 20 years before tumor diagnosis for both sexes combined. In addition, our findings suggest that for both sexes combined, the simultaneous presence of elevated levels of both allergen-specific IgE and total IgE may be associated with a lower risk of glioblastoma and glioma than are negative levels for both types of IgE; however, it should be noted that these associations are only of borderline significance.

In a nested case–control study, Calboli et al. (14) reported no association between allergen-specific IgE concentration and glioma risk. However, our findings are remarkably similar to those reported by Schlehofer et al. (13) for high-grade (anaplastic astrocytoma and glioblastoma) glioma. We found sex-specific differences for associations between testing positive for allergen-specific IgE and glioblastoma compared with testing negative (>0.35 kU_A/L vs ≤0.35 kU_A/L: women, OR = 0.46, 95% CI = 0.23 to 0.93; men, OR = 1.02, 95% CI = 0.72 to 1.44) (13). Schlehofer et al. (13) found approximately the same magnitude of sex-specific differences for the association between allergen-specific IgE and high-grade glioma: women—OR = 0.45, 95% CI = 0.21 to 0.96; men—OR = 0.90,

Table 5. Joint association between prediagnostic allergen-specific and total IgE levels with risk of glioblastoma and glioma*

Allergen-specific and total IgE level†	Glioblastoma			Glioma		
	Case subjects (n = 374)	Control subjects (n = 740)	OR (95% CI)	Case subjects (n = 594)	Control subjects (n = 1177)	OR (95% CI)
Women						
Low allergen-specific and low total IgE	92	161	1.00 (referent)	157	291	1.00 (referent)
High allergen-specific and low total IgE	8	22	0.64 (0.28 to 1.46)	22	44	0.93 (0.54 to 1.60)
Low allergen-specific and high total IgE	6	12	0.92 (0.34 to 2.53)	8	22	0.70 (0.31 to 1.59)
High allergen-specific and high total IgE	3	21	0.26 (0.08 to 0.88)	10	34	0.56 (0.27 to 1.16)
Men						
Low allergen-specific and low total IgE	188	373	1.00 (referent)	284	562	1.00 (referent)
High allergen-specific and low total IgE	36	56	1.31 (0.82 to 2.10)	38	96	1.34 (0.91 to 1.97)
Low allergen-specific and high total IgE	15	30	0.99 (0.53 to 1.84)	54	82	0.92 (0.54 to 1.55)
High allergen-specific and high total IgE	26	65	0.79 (0.48 to 1.28)	21	46	0.78 (0.53 to 1.17)
Total						
Low allergen-specific and low total IgE	280	534	1.00 (referent)	441	853	1.00 (referent)
High allergen-specific and low total IgE	44	78	1.09 (0.73 to 1.63)	76	126	1.18 (0.87 to 1.62)
Low allergen-specific and high total IgE	21	42	0.95 (0.56 to 1.62)	29	68	0.84 (0.54 to 1.30)
High allergen-specific and high total IgE	29	86	0.64 (0.41 to 1.00)	48	130	0.72 (0.51 to 1.02)

* We analyzed allergen-specific and total IgE levels in serum samples from the Janus Serum Bank in Oslo, Norway. We used diagnostic cut points to identify positive and negative tests in kilounits of allergen-specific antibody per liter (kU_A/L) and total IgE antibody per liter (kU/L). Categories of IgE are as follows: Low allergen-specific (≤0.35 kU_A/L), low total (≤100 kU/L), high allergen-specific (>0.35 kU_A/L), and high total (>100kU/L). Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals separately within sex-specific strata and for the total dataset. To estimate joint associations between allergen-specific and total IgE we included cross product terms in our regression models. (23). We then used the Wald χ^2 statistic to test equality of the cross-product term regression coefficients to zero. OR = odds ratio; CI = confidence interval.

† Allergen-specific and total IgE antibodies were measured using ImmunoCap 1000, a standard clinical instrument designed for this purpose.

95% CI = 0.53 to 1.51. We found a similar, if somewhat weaker, pattern for all glioma, which is also similar to the findings by Schlehofer et al. (13). The reason for sex-specific variation of the association between allergen-specific IgE and risk of glioblastoma and glioma risk is not known. Female sex hormones have a complex association with allergy-induced inflammation (24,25). For example, it has recently been determined that mast cells have estrogen receptors (26). However, Michaud et al. (27) reported results of a cohort study in which they found no evidence for an association between reproductive factors and the risk of glioma.

Total IgE levels among control subjects in the present study are consistent with those reported in the study by Calboli et al. (14). They observed a mean value of the logarithm of total IgE among control subjects of 3.34 (SD = 1.91), whereas the mean value in the present study is 3.35 (SD = 1.27). However, these authors found no association between testing positive for total IgE and risk of glioma compared with testing negative (>100 kU/L vs ≤ 100 kU/L, OR = 0.98, 95% CI = 0.61 to 1.56). Although they did report a statistically significantly decreased risk of glioma for borderline IgE concentration compared with normal concentration (25–100 kU/L vs <25 kU/L: OR = 0.63, 95% CI = 0.42 to 0.93), we were unable to confirm this.

Our most important finding is that testing positive for total IgE was associated with decreased glioblastoma and glioma risk at least 20 years before diagnosis. This observation suggests that previously reported case–control associations between allergy and glioma may not be a consequence of immune suppression resulting from the preclinical tumor. Although the most common form of glioblastoma appears to arise rapidly de novo (28), our findings indicate that the genesis of this tumor may be a long process.

Our findings also suggest a joint association between allergen-specific and total IgE, and there is evidence that indicates a biological relationship between these two IgE types. Christensen et al. (6) report that the same concentrations of allergen-specific IgE vary in their ability to produce mast cell activation, depending on the characteristics of the antigen and the relative quantity of total IgE. Consistent with this observation, Hamilton and Williams (28) report that the larger the ratio of allergen-specific IgE to total IgE, the more likely the induction of inflammatory mediators.

This study has several limitations including the fact that serum samples on which we base our analyses have been stored at –25°C for as long as 39 years (median time between blood collection and IgE analysis = 26 years, interquartile range = 22–36 years). Whether individual values for IgE are the same as they would have been at the date that blood was collected cannot be determined. However, Henderson et al. (29) tested the stability of IgE levels in obstetric sera that had been stored at –20°C for between 32 and 37 years and found that long-term storage did not diminish the ability to measure IgE levels. A study of the stability of total IgE in the Janus Serum Bank suggested nonstatistically significant ($P > .05$) mean differences in serum concentration depending on storage time (30); however, there may be secular trends in IgE concentration, making it difficult to interpret comparisons across time. Paganelli et al. (31) also confirm the relative stability of allergen-specific antibodies after 8 years of sample storage. Furthermore, even if there were some degradation of antibodies over time because samples were matched on date of blood collection, both case subjects and control subjects would be similarly affected by serum degradation and secular trends, thus potentially producing nondifferential misclassification. This form of bias usually, but not always, causes the

odds ratio to be closer to the null than it should otherwise be (32). Another potential source of misclassification is that we measured IgE concentration at only one time. The nature of the resulting bias depends on the critical time of IgE exposure that is associated with the risk of glioma, which is unknown. However, it seems reasonable to assume that IgE measurements in case and control subjects would be similarly biased, thus producing nondifferential misclassification. However, if IgE levels of case subjects are altered by proximity to diagnosis of this immune-suppressive tumor, then differential misclassification, resulting in falsely increased or decreased associations, may be present. This bias, if it exists, would be stronger among samples collected near the time of diagnosis.

Consistent with our finding that total IgE was associated with decreased risk of glioma is that total IgE maintains mast cell homeostasis (33) and mast cells have immunosuppressive functions (34). Additional evidence for a regulatory role of total IgE is based on the observation that corticosteroids that suppress chronic allergic inflammation paradoxically increase total IgE levels (35). For example, dexamethasone, a glucocorticoid used to reduce intracranial swelling in glioma patients, also elevates total IgE levels (36). Although this phenomenon has been discussed as a potentially adverse effect of steroid use for asthma treatment, elevated total IgE may be a component of the mechanism by which glucocorticoids regulate allergic inflammation.

Not necessarily in conflict with an immune regulatory role of total IgE, the reduced risk of cancer among people with allergies has been attributed to immune surveillance against potentially cancerous cells (37,38). It may be that the higher levels of circulating IgE in atopic individuals provide an enhanced capability to eradicate premalignant cells before tumors can be detected. This antitumor protection could be due to IgE specific for developing tumors, to nonspecific IgE with cross-reactivity to nascent tumor antigens, or immune mediators released by the binding of IgE to specific receptors on effector cells. Another possible scenario is that of immune prophylaxis (9), in which allergy symptoms themselves, triggered by IgE, serve to expel foreign toxins or pathogens that might be mutagenic. Regardless of the mechanism, experimental evidence indicates that circulating IgE may impede early tumor development (37,38).

The third potential narrative comes from a prospective Danish record linkage study of contact allergy (5), a type of allergy that causes delayed rather than immediate hypersensitivity and involves T cells exclusively and not IgE. In the cohort of people diagnosed with contact allergy, the authors found that women, but not men, previously treated for this allergy had a lower risk of primary brain tumors. This finding does not exclude a role for IgE, however, because T cells are also involved in the induction of IgE-induced immediate hypersensitivity.

In addition to finding associations between both allergen-specific and total IgE and glioma risk, we are first to observe the presence of this association long before tumor diagnosis. Furthermore, we found that allergen-specific and total IgE may be simultaneously related to glioblastoma and glioma risk. If our findings can be replicated, basic research is needed to identify biological mechanisms that account for the observed associations. Whether this mechanism represents a form of immune surveillance or is a correlate of serum IgE concentration remains to be determined.

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