Primary brain tumours and specific serum immunoglobulin E: a case–control study nested in the European Prospective Investigation into Cancer and Nutrition cohort

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Abstract

Background: Case–control studies suggest that patients with allergic diseases have a lower risk of developing glioma but not meningioma or schwannoma. However, those data can be differentially biased. Prospective studies with objective measurements of immunologic biomarkers, like immunoglobulin E (IgE), in blood obtained before cancer diagnosis could help to clarify whether an aetiological association exists.

Methods: The present case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) measured specific serum IgE as a biomarker for the most common inhalant allergens in 275 glioma, 175 meningioma and 49 schwannoma cases and 963 matched controls using the ImmunoCAP specific

IgE test. Subjects with an IgE level ≥0.35 kUA/l (kilo antibody units per litre) were classified as sensitized by allergens. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by adjusted conditional logistic regression models for each tumour subtype. The effect of dose–response relationship was assessed in five increasing IgE level categories to estimate *P*-values for trend.

Results: The risk of glioma was inversely related to allergic sensitization (OR = 0.73; 95% CI 0.51–1.06), especially pronounced in women (OR = 0.53; 95% CI 0.30–0.95). In dose–response analyses, for high-grade glioma, the lowest OR was observed in sera with the highest IgE levels (*P* for trend = 0.04). No association was seen for meningioma and schwannoma.

Conclusion: The results, based on serum samples prospectively collected in a cohort study, provide some support for the hypothesis that individuals with allergic sensitization are at reduced risk of glioma and confirm results from previous case–control studies.

Only high dose ionizing radiation and genetic predisposition are established risk factors for primary brain tumours (1–4). To date, the results from case–control studies have shown an inverse association between glioma and allergies; however, the results have been less consistent for meningioma (5–9). Cohort studies have also provided conflicting results. A Swedish register-based cohort study, which included younger and older participants (median age of 30 and 54 years, respectively), found that glioma and meningioma increased risks of the younger and decreased risks of the older age group (10). A further register-based retrospective cohort study reported a positive association between atopic dermatitis and all brain tumours (11), whereas other cohort studies showed no association with allergies (12, 13).

At present, no conclusive biological mechanism is known for the suggested link between allergy and brain tumour development (14). According to one hypothesis, the immune system continuously recognizes and destroys tumour cells (15). Thus, a hyper-active immune system of allergic persons would lead to an enhanced tumour immune surveillance. Whether this applies to brain tumours is currently not known.

Most studies of allergies and brain tumours used questionnaire data; hence, allergies were self-reported (5, 7, 16–18) and could therefore be influenced by recall biases or differential misclassification. Only one case–control and one cohort study defined the atopic status of the study participants by measuring total serum IgE levels in glioma cases and controls in addition to the questionnaire data (10, 19) and another cohort study used a skin prick test (12). However, it is known that not all persons with atopic conditions actually express allergic symptoms. Using a biomarker, like IgE, instead has the advantage of detecting atopic predisposition independently of clinical symptoms. Specific serum IgE are indicative of allergic sensitization to specific (environmental) allergens but might also be influenced by the immunological situation during cancer development. Therefore, the measurement of biomarkers like IgE at the time of tumour diagnosis might be affected by the cancer disease.

The aim of the present nested case–control study was to investigate for the first time in a large prospective study setting the association between IgE levels and primary brain tumours (glioma, meningioma and schwannoma). Because of the lack of sufficient data for nutritional allergies from this study, we focus here on the most common inhalant allergens for which a valid test is available. Serum samples were prospectively collected in the framework of a large international, multi-centric prospective cohort study – the European Prospective Investigation into Cancer and Nutrition (EPIC).

Abbreviations

95% CI, 95% confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HGG, high-grade glioma; ICD-O, International classification of diseases for oncology; IgE, immunoglobulin E; kUA/l, kilo antibody units per litre; LGG, low-grade glioma; OR, odds ratio.

Materials and methods

The EPIC cohort

The EPIC cohort study investigates associations between cancer, or other chronic diseases and nutritional habits, lifestyle and environmental factors; 521 457 men and women mainly aged 35–70 years are included, from 23 study centres in ten European countries: Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Greece, Italy (Florence, Naples, Ragusa, Turin, Varese), the Netherlands (Bilthoven, Utrecht), Norway, Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmö, Umea) and the United Kingdom (Cambridge, Oxford).

A detailed description of the design of the EPIC study, its study population, baseline data collection and follow-up procedures for cancer incidence and vital status has been given elsewhere (20). Briefly, recruitment took place between 1992 and 1998. Besides the collection of questionnaire data, also personal interviews about medical, occupational and lifestyle factors were conducted. In addition, about 386 000 participants provided a blood sample at or near recruitment.

The present study measured serum-specific IgE antibodies as a biomarker for allergic sensitization and investigated the relationship to the incidence of primary brain tumours. Data and serum samples of cases and controls from all but France

and Norway EPIC centre were used. Incident cases were identified by cancer registries through record linkage (Spain, Italy, the Netherlands, UK, Denmark and Sweden) or by active follow-up (Germany and Greece). Data on vital status were collected by linkage with mortality registries or by letter contact during follow-up. Participants of the cohort were censored between December 2002 and December 2005. For Germany and Greece, the end of follow-up was considered to be the last known contact, date of diagnosis, or date of death, whichever came first.

From all participants who gave written consent, a 30 ml blood sample was collected according to a standardized protocol (detailed description see elsewhere) (20). All centres, but Sweden and Denmark, sent blood fractions (serum, plasma, red cells and buffy coat for DNA extraction) to the EPIC Biobank at IARC Lyon, where they are stored. Danish and Swedish samples were stored locally. The median time between blood sampling and diagnosis was 3010 days (8.24 years); with a range of 29–4981 days.

The study was approved by the local ethics committees in all participating countries and the Internal Review Board of the IARC, Lyon, France (20). All information allowing the identification of the participants was removed from the study data base used for data analyses. Serum used in laboratory analyses was labelled using anonymous codes.

Selection of cases and controls

Brain tumour cases of the EPIC cohort were defined as those diagnosed with a primary brain tumour as the first cancer after recruitment date and before censoring date. Of 696 tumour cases with histological confirmed diagnosis 372 were glioma cases [International classification of diseases for oncology (WHO, 2000); ICD-O codes M9380–M9473], 253 were meningioma cases (ICD-O M9530-M9539), and 71 schwannoma cases (ICD-O M9540 (21). In addition, glioma cases were divided into high-grade glioma (HGG), (ICD-O codes: M9440/3, M9441/3, M9442/3, M9401/3, M9380/3, M9451/3) and low-grade glioma (LGG), (ICD-O codes: M9382/3, M9383/1, M9384/1, M9390/0, M9394/1, M9400/3, M9411/3, M9420/3, M9421/3, M9450/3, M9505/1, M9391/3).

Overall, 1188 control subjects free of cancer and with available blood samples were identified. Two control subjects, selected randomly from the EPIC cohort, were matched to each case according to study centre, gender, data of birth (± 1 year), age at blood collection (± 6 months), date of blood collection (± 1 month), time of blood collection (± 1 h) and length of follow-up.

Laboratory method

The immediate (atopic or anaphylactic) type of allergy is a function of serum antibodies belonging to the IgE class of immunoglobulins (22, 23). Specific IgE antibodies were measured by the ImmunoCAP specific IgE test (Phadia AB, Uppsala, Sweden), a well-established *in vitro* quantitative measurement used for the determination of IgE in serum or plasma; however, the test focus on the detection of inhalant allergens. According to Vidal et al. (24), the test has a sensitivity of 70.8% (95% CI 61.7–78.6%) and a specificity of 90.7% (95% CI 87.0–93.5%) tested in an unselected adult sample, and tested in symptomatic patients 79.2% (95% CI 68.2–87.3%) and a specificity of 91.6% (95% CI 85.6–95.4%) and allows detection of very low concentrations of IgE antibodies (23, 25, 26). It allows quantitative measurements [in kilo antibody units per litre (kUA/l)] of specific antibodies against a mixture of the eight most common respiratory allergens, including those with the international allergen codes: g6-timothy grass, g12-cultivated rye, t3-common silver birch, w6-mugwort, d1-Dermatophagoides pteronyssinus, e1-cats epithelium and dander, e5-dog dander, m2-Cladosporium herbarum.

Using the UniCap 100 apparatus (Phadia AB, Uppsala, Sweden), each standardized test needed 40 µl serum or plasma from the respective participant. The concentration of specific IgE was determined automatically according to the instructions of the ImmunoCap™ (Phadia AB, Uppsala, Sweden) using ≥0.35 kUA/l as the cut-off for a positive value.

Finally, because of missing of blood samples for testing and invalid IgE measurements ($n = 46$), specific IgE serum levels could be determined in 1462 blood samples. Thus, statistical analyses included 275 glioma cases and 528 controls, 175 meningioma cases and 343 controls, and 49 schwannoma cases and 92 controls.

Statistical analyses

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for all brain tumour subtypes, using conditional logistic regression models (27) (LOGISTIC procedure of the SAS software package, Version 9.1; SAS Institute, Inc., Cary, NC, USA). Separate analyses have been performed for men and women because of considerable gender differences in brain tumour subtypes.

Adjustments were made in all analyses for educational level (primary school or less, technical/secondary school, university degree and not specified or none educational degree) and for smoking status (never, former, current, unknown). Alcohol consumption (never, former, only at recruitment, lifetime, unknown), physical activity (inactive, moderately inactive, moderately active, active, unknown) and hormone replacement therapy (HRT) for women had only marginal influence on the risk estimates ($< 10\%$) and were therefore not retained in final models.

According to the cut-point of ≥0.35 kUA/l, specific IgE levels were divided into a 'positive' group and a 'negative' group. Dose–response relationships were estimated using sub-categories within the positive group as follows: 'borderline positive' (≥0.35–0.7), 'weak positive' (≥0.7–3.5), 'strong positive' (≥3.5–17.5), and 'very strong positive' (≥17.5 kUA/l). In addition, the *P*-value for trend across these categories was estimated by assigning each category its median level of specific IgE.

Before pooling the data of the different centres, a chi-square-test for heterogeneity was performed, a *P*-value of < 0.05 was considered as evidence for heterogeneity between centres.

Sensitivity analyses were performed for the specific IgE level measurements by excluding cases that were diagnosed with their brain tumour within 2 years and their matched controls to exclude the possibility of reverse causation. Furthermore, analyses for glioma and meningioma were conducted with respect to the location of the tumour in the brain cavity or in the spinal cord (glioma – ICD-O topography code C71.0–C71.9 or C72.0; respectively meningioma ICD-O topography code C70.0 or C70.1 or C70.9) without seeing major differences, and location therefore was ignored in the analyses.

Results

Baseline characteristics of the study participants are shown in Table 1. Marginal differences were found for education and smoking habits among glioma or meningioma cases and controls, whereas schwannoma cases had attained more education compared with their controls.

An inverse association was found between all glioma and allergic sensitization (OR = 0.73; 95% CI 0.51–1.06) (Table 2). ORs were significant only for women (OR = 0.53; 95% CI 0.30–0.95), especially for those with HGG (OR = 0.45; 95% CI 0.21–0.96). For men, the effects were weaker; however, the CI is widely overlapping with those for women. When positive specific IgE levels were stratified by concentrations of IgE, the lowest OR for glioma was seen in the highest ('very strong positive') category. For HGG in men and women combined, but not for LGG, the higher the intensity of the specific IgE the lower the OR (trend analyses: $P = 0.04$).

Excluding those cases, and their matched controls, with a follow-up time between IgE measurement and tumour diagnosis of <2 years, weakened the effect for glioma; however, the trend for the intensity of the IgE levels and HGG was marginally significant (P-value 0.06).

For meningioma no associations were found, including intensity of specific IgE levels. No association between specific IgE levels and schwannoma risk were observed (Table 3).

Discussion

This is the first study using data collected in participants of a prospective cohort study to investigate the atopic status (determined by measured IgE levels) in a large sample of cases with primary brain tumours. An inverse association between allergic sensitization and glioma occurrence was found for pre-diagnostic specific serum IgE categories, whereas no association was observed for meningioma. HGG showed an inverse trend of decreasing risk with increasing IgE concentrations.

Characteristics of cases in all brain tumour subtypes in this cohort were similar as expected based upon previous studies

Table 1 Description of glioma, meningioma and schwannoma cases and controls in respect to age, specific IgE categories, gender, education and smoking status. Case–control study nested into the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)

	Glioma		Meningioma		Schwannoma	
	Cases	Controls*	Cases	Controls†	Cases	Controls‡
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Total numbers	275 (100)	528 (100)	175 (100)	343 (100)	49 (100)	92 (100)
Age (years, mean)	55.35	55.34	54.92	54.89	55.53	55.54
Serum specific IgE level§						
≥0.35 kUA/l	59 (21.5)	141 (26.7)	38 (21.7)	78 (22.7)	10 (20.4)	21 (22.8)
<0.35 kUA/l	216 (78.5)	387 (73.3)	137 (78.3)	265 (77.3)	39 (79.6)	71 (77.2)
Gender						
Male	136 (49.5)	261 (49.4)	43 (33.3)	132 (33.9)	17 (34.7)	31 (33.7)
Female	139 (50.5)	267 (50.6)	86 (66.7)	257 (66.1)	32 (65.3)	61 (66.3)
Highest education level						
Primary school	98 (35.6)	174 (33.0)	72 (41.1)	113 (32.9)	12 (24.5)	32 (34.8)
Tech/secondary school	111 (40.4)	220 (41.7)	71 (40.6)	163 (47.5)	25 (51.0)	37 (40.2)
University	55 (20.0)	112 (21.1)	26 (14.9)	54 (15.8)	9 (18.4)	17 (18.5)
Unknown	11 (4.0)	22 (4.2)	6 (3.4)	13 (3.8)	3 (6.1)	6 (6.5)
Smoking status						
Never	125 (45.5)	245 (46.4)	87 (49.7)	182 (53.1)	27 (55.0)	43 (46.7)
Former	87 (31.6)	156 (29.6)	46 (26.3)	79 (23.0)	11 (22.5)	24 (26.1)
Current	61 (22.2)	118 (22.3)	40 (22.9)	77 (22.4)	11 (22.5)	25 (27.2)
Unknown	2 (0.7)	9 (1.7)	2 (1.1)	5 (1.5)	0	0

*22 controls are missing.

†Seven controls are missing.

‡Six controls are missing.

§Cut points: specific IgE level ≥0.35 kUA/l = positive; specific IgE level <0.35 kUA/l = negative.

Table 2 Adjusted* odds ratios (OR) and 95% confidence intervals (95% CI) for all glioma, high-grade glioma (HGG) and low-grade glioma (LGG), meningioma and atopic sensitization, overall and by gender. Case–control study nested into the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)

	Glioma				HGG				LGG				Meningioma			
	Cases	Controls			Cases	Controls			Cases	Controls			Cases	Controls		
Specific IgE	*N*	*N*	OR*†	95% CI	*N*	*N*	OR*	95% CI	*N*	*N*	OR*	95% CI	*N*	*N*	OR*†	95% CI
All																
Negative‡	216	387	1.00	–	161	286	1.00	–	55	101	1.00	–	137	265	1.00	–
Positive	59	141	0.73	0.51–1.06	44	107	0.73	0.48–1.11	15	34	0.85	0.38–1.90	38	78	0.96	0.61–1.51
Men																
Negative‡	98	183	1.00	–	81	151	1.00	–	17	32	1.00	–	32	56	1.00	–
Positive	38	78	0.89	0.55–1.45	31	64	0.90	0.53–1.51	7	14	0.92	0.22–3.79	11	30	0.64	0.26–1.54
Women																
Negative‡	118	204	1.00	–	80	135	1.00	–	38	69	1.00	–	105	209	1.00	–
Positive	21	63	0.53	0.30–0.95	13	43	0.45	0.21–0.96	8	20	0.76	0.28–2.02	27	48	1.15	0.65–2.02
All																
Negative§	216	387	1.00	–	161	286	1.00		55	101	1.00		137	265	1.00	
Borderline	16	32	0.81	0.42–1.57	13	23	0.95	0.44–2.03	3	9	0.57	0.14–2.36	9	21	0.79	0.34–1.84
Weak positive	17	45	0.67	0.38–1.19	15	31	0.88	0.47–1.64	2	14	0.29	0.06–1.36	9	22	0.75	0.33–1.70
Strong positive	18	40	0.87	0.48–1.57	13	35	0.68	0.35–1.34	5	5	3.62	0.74–17.7	11	20	1.21	0.55–2.68
Very strong positive	8	24	0.54	0.23–1.26	3	18	0.29	0.08–1.02	5	6	1.57	0.37–6.65	9	15	1.19	0.49–2.92
P for categorical trend				0.18				0.04				0.33				0.62
P for log-linear trend				0.11				0.04				0.55				0.83
Excluding recent cases¶																
Negative‡	169	313	1.00		129	241	1.00		40	72	1.00		108	210	1.00	
Positive	50	108	0.84	0.56–1.27	40	84	0.90	0.57–1.42	10	24	0.69	0.25–1.92	31	62	1.03	0.61–1.71

*OR are adjusted for highest education level and smoking status.

†Chi-square test for heterogeneity: Glioma: $P = 0.74$; Meningioma $P = 0.84$.

‡Categories: <0.35 kUA/l = negative; ≥0.35 kUA/l = positive.

§Categories are negative (<0.35), borderline positive (≥0.35–0.7), weak positive (≥0.7–3.5), strong positive (≥3.5–17.5), very strong positive (≥17.5 kUA/l).

¶Excluding cases (and their matched controls) with a follow-up time between IgE measurement and diagnosis of the brain tumour of <2 years.

Table 3 Adjusted* odds ratios (OR) and 95% confidence intervals (95% CI) for schwannoma and specific IgE categories. Case–control study nested into the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)

	Schwannoma			
	Cases	Controls		
Specific IgE	*N*	*N*	OR*†	95% CI
All				
Negative (<0.35 kUA/l)	39	71	1.00	–
Positive (≥0.35 kUA/l)	10	21	0.80	0.32–1.99

*OR are adjusted for highest education level and smoking status.
†Chi-square test for heterogeneity: $P = 0.89$.

(5, 6, 16). The slightly higher number of glioma in women reflects the larger proportion of women in the overall EPIC cohort population. The study design of the case–control study nested in the EPIC cohort allowed for investigating specific IgE values in pre-diagnostic blood samples for the specific IgE values which were only collected at the time of enrolment into the cohort; thus, we could not analyse longitudinal changes. Our results support those from case–control studies based on self-reported allergic diseases (5–7, 16, 17, 28–32) and especially those of one case–control study using IgE measurement at the time of tumour diagnosis (19).

In two case–control studies, associations between age at onset or duration of allergies (in years) and glioma risk were investigated using questionnaire data, but with conflicting results (16, 18). In one cohort study (10), a reanalysis of data from individuals who reported allergies 5 years before a diagnosis of brain tumours were similar to results of the whole cohort. Berg-Beckhoff et al. (18) show that asthma, eczema and hay fever together ('allergic condition') were inversely associated with glioma or meningioma diagnosis when the duration was < 10 years prior the brain tumour diagnosis.

Overall, we found no significant association between allergic sensitization and meningioma or schwannoma, which is in agreement with the results of most case–control studies (5–7, 16, 28, 30). Gender-specific analyses showed inconsistent results for all tumour types. We assume that these results might be because of chance, probably small sample sizes have led to low precision of some of the estimates. Additional adjustments, e.g., for HRT or education did not alter the risks.

For brain tumours, only high doses of ionizing radiation and some hereditary conditions are confirmed risk factors, but results from most case–control studies have also quite consistently shown an inverse association between allergic diseases and glioma. Our results support observations of case–control studies insofar that specific IgE levels overall show a negative association with glioma risk (17); however, taking into account a 2-year latency, this association was somewhat weakened. One explanation for the inverse associations between a history of atopic disease and cancer risk is the immuno-surveillance hypothesis, proposed first in 1970 by Burnet (15). This hypothesis states that the immune system protects the host against the development of cancer. Another explanation might be reverse causality, which means that the observed association might be due to the suppression of the immune system by the tumour itself. For brain tumours, it is accepted that some of them have a long pre-diagnostic period (e.g. meningioma, LGG), but HGG seems to have a relatively short progression period. In addition, glioma patients are known to have immunological defects such as abnormal delayed hypersensitivity responses, low number of circulating T-cells, decreased antibody response and impaired T-cell cytotoxicity (33, 34). Our results based on prospectively collected data cannot give a conclusive answer which hypothesis might be favoured, but for HGG our data provide some support for the immune surveillance hypothesis. Whether this is because of a stronger reaction of the immune system of HGG patients on environmental influences (compared with LGG patients) or vice-versa is at this stage only speculative. However, our result supports the observation of Sherman et al. (35) who noted that an inverse association with allergies were more often found for cancer of different tissues, including brain tissue, and organ systems that interface with external environment than in those tissue that do not so. The site specificity of the association between allergies and cancer is also described in a review by Merill et al. (2007) (36).

The timing between the onset of alteration of atopic sensitization (e.g. measured by specific serum IgE) and tumour development might be an important issue. However, studies where biomarkers were determined in biological specimens obtained at the time of tumour diagnosis cannot ascertain whether the tumour itself influenced the immune system. Because of the uncertainty of tumour latency, even the present study which used prospectively collected blood samples many years before brain tumour diagnosis is not conclusive, because only the date of diagnosis and the date of recruitment into the cohort as reference dates could be used to estimate how long the atopic status was present prior to cancer diagnosis.

One of the main strengths of this study is the use of an allergy biomarker for allergic sensitization (specific IgE) instead of self-reported data on allergy from questionnaires. The ImmunoCap test (Pharmacia AB, Uppsala Sweden) is one of the standardized tests for atopy in medical diagnostics (25, 26), covering about 70–80% of the most common eight inhalant allergens in Europe. In addition, there is no evidence that the specific IgE concentration is influenced by gender and also the lower OR observed by Berg-Beckhoff et al. (18) in children with a history of allergy compared with adults have not been confirmed until now. The IgE categories are known to be very stable in blood samples over 17 years (23) without any apparent degradation of IgE-defined allergies. All participants of our study are adults; their blood donation took place less than 14 years ago, so that we do not expected that our results were influenced by blood sample storage and stability.

Atopic disposition does not necessarily lead to a clinically relevant allergic disease. Studies on allergies using question-

naires will misclassify subjects without symptoms. Also, recall bias might occur because of lack of diagnostic accuracy of allergic diseases and differential recall bias because of mental modifications, especially for glioma patients. Biomarker-based studies using blood samples collected before tumours diagnoses, like ours, may overcome some of these limitations. The study was focused on inhalant allergies as there was limited information on nutritional allergies from the participants. In addition, although adjustment was made for potential confounders, because of the observational nature of this study, we cannot rule out the possibility of residual confounding.

In conclusion, to our knowledge, this is the first study based on specific IgE levels measured in pre-diagnostic serum samples of brain tumour patients. This study support results from previous observational studies showing an inverse association between glioma risk and allergies, although there was a lack of statistical power to detect associations with rarer subtypes of glioma. These results suggest that individuals with biochemical evidence of allergic sensitization, especially for inhalant allergens, may be at reduced risk of glioma. No association was observed between IgE levels and meningioma or schwannoma. Further studies based on multiple measurements of immunological biomarkers including specific IgE and, perhaps in combination with other biomarkers, will be required to confirm these results suggesting a relation between immune system reaction and brain tumour development.

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Conflicts of interest

No potential conflicts of interest were disclosed.

Contributions

Each of the named authors has contributed scientific work to this manuscript.

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