



Original Contribution

Allergic Conditions and Brain Tumor Risk

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An inverse association between allergic conditions and glioma risk has been reported previously. In this large population-based case-control study, the authors identified cases diagnosed with glioma or meningioma in Denmark, Norway, Finland, Sweden, and southeast England between 2000 and 2004. Detailed information on self-reported physician-diagnosed allergic conditions was collected from 1,527 glioma cases, 1,210 meningioma cases, and 3,309 randomly selected controls. Logistic regression showed an odds ratio of 0.70 (95% confidence interval: 0.61, 0.80) for glioma associated with a diagnosis of any of asthma, hay fever, eczema, or other type of allergy. The risk estimates for glioma were around 0.65 for each allergic condition (asthma, eczema, hay fever, and food allergy), and the 95% confidence intervals were equally consistent, at around 0.55, 0.80. The reduced risks of glioma related to eczema, hay fever, and allergy overall, but not asthma, were confined to current rather than past conditions. Meningioma risk was not associated with allergic conditions, except for eczema (odds ratio = 0.74, 95% confidence interval: 0.60, 0.91). Our results show a reduced risk for glioma associated primarily with current allergic conditions. If this is etiologic, it has implications for the understanding of how allergic conditions might reduce the tumor risk.

asthma; case-control studies; eczema; glioma; hypersensitivity; meningioma; rhinitis, allergic, seasonal

Abbreviations: CI, confidence interval; ICD-10, *International Classification of Diseases*, Tenth Revision; ICD-O-2, *International Classification of Diseases for Oncology*, Second Edition; IgE, immunoglobulin IgE; UICC, International Union against Cancer.

An inverse association between allergic conditions and glioma risk has been reported in several epidemiologic studies (1–9). A complicating factor in studies of these debilitating and often highly deadly tumors is the use of proxy respondents and the potential inaccuracies associated with

that source of information. Schwartzbaum et al. (8) have shown that the inverse association in relation to allergies was strongest in past studies with the highest proportion of proxy respondents, suggesting that proxies underreport cases' allergic conditions. In most studies, no association

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TABLE 1. Details of the study by study center, Nordic-UK* Brain Tumor Study, 2000–2004

	Denmark	Finland	Norway	Sweden	United Kingdom	All countries combined
Study population	Nationwide	Excluding northern Lapland and Åland	The southern and middle regions	The regions of Stockholm, Göteborg, Umeå, and Lund	The Thames regions of southeast England	
Age range (years)	20–69	20–69	20–69	20–69	18–59	
Study period	September 2000–August 2002	November 2000–September 2002	January 2001–December 2002	September 2000–August 2002	December 2000–February 2004	
Control selection source	Population register	Population register	Population register	Population register	General practitioners' practice lists	
No. of participating glioma cases	248	267	284	364	364	1,527
Participation rate (%)	71	81	77	74	37	60
Proxy interviews (%)	11	4	38	9	4	13
No. of participating meningioma cases	173	334	206	272	225	1,210
Participation rate (%)	73	90	71	84	55	74
Proxy interviews (%)	2	1	2	3	0.4	2
No. of participating controls	819	870	358	632	630	3,309
Participation rate (%)	52	42	69	66	43	50
Proxy interviews (%)	0	0	0.6	0	0	0.1

* UK, United Kingdom.

has been found between meningioma and allergic conditions (2, 5, 6, 10).

An inverse association with allergy has also been found for cancer types other than gliomas (11, 12). The biologic mechanism behind the alleged reduced risk is not fully understood. According to immune surveillance theory, the immune system is supposed to continuously recognize tumor cells as foreign and to destroy them (13, 14). An enhanced tumor immunosurveillance in allergic individuals can be hypothesized. The idea of better surveillance owing to an active immune system is also supported by the opposite condition, with an impaired immune system leading to an increased risk of cancer (15–17).

The aim of our study was to analyze the association between a history of allergic conditions and the risk of glioma and meningioma and to explore in detail the possible influence of current versus past allergic condition, age at onset of allergy, and antiallergy treatment.

MATERIALS AND METHODS

Study setting and period

The study was conducted in five countries: Denmark nationwide; Finland excluding northern Lapland and Åland; the southern and middle regions of Norway; the geographic areas in Sweden covered by the regional cancer registries in Stockholm, Göteborg, Umeå, and Lund; and the Thames regions of southeast England, United Kingdom. Eligible cases were diagnosed with glioma or meningioma during the study period, September 2000 to February 2004, although the exact dates within this period varied by country (table 1).

The study also contributes data on a subset of participants to the previously described INTERPHONE Study (18). Several additional questions have been added to the INTERPHONE core protocol, including questions concerning allergic conditions. The southeast England participants have previously been reported as part of a smaller study from the United Kingdom on allergy and brain tumor risk (9, 19).

Case ascertainment

Eligible cases were all individuals diagnosed during the study period with intracranial glioma (*International Classification of Diseases*, Tenth Revision (ICD-10), code C71; *International Classification of Diseases for Oncology*, Second Edition (ICD-O-2), codes 9380–9384, 9390–9394, 9400–9401, 9410–9411, 9420–9424, 9430, 9440–9443, 9450–9451, 9460, 9480–9481, and 9505) or intracranial meningioma (ICD-10 codes C70 and D32; ICD-O-2 codes 9530–9539). Among the glioma cases, ICD-O-2 codes 9440–9442 were defined as glioblastoma multiforme.

The age range for inclusion differed slightly among the countries (table 1). Cases were identified continuously during the study period through collaboration with the treating clinics. The completeness of case ascertainment was verified through search in population-based cancer registries, and extra cases found during the study period were included in the study, except in Finland where the cancer registry was checked only for completeness without enrolling any patients. A reference date of diagnosis was defined as the first examination leading to diagnosis (usually the first radiologic examination). Approval was sought from the attending physician to approach each case.

TABLE 2. Characteristics of glioma, glioblastoma, and meningioma cases and controls, Nordic-UK* Brain Tumor Study, 2000–2004

Characteristic	Glioma cases (n = 1,527)		Glioblastoma cases† (n = 707)		Meningioma cases (n = 1,210)		Controls‡ (n = 3,309)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	899	58.9	435	61.5	303	25.0	1,535	46.4
Female	628	41.1	272	38.5	907	75.0	1,774	53.6
Age at reference date§ (years)								
18–29	149	9.8	14	2.0	23	1.9	246/244	7.4/7.4
30–39	265	17.4	51	7.2	129	10.7	485/490	14.7/14.8
40–49	323	21.2	137	19.4	293	24.2	761/754	23.0/22.8
50–59	485	31.8	306	43.3	481	39.8	1,097/1,100	33.2/33.2
≥60	305	20.0	199	28.2	284	23.5	720/721	21.8/21.8
Education¶								
Compulsory school	431	28.2	221	31.3	399	33.0	935	28.3
Vocational/secondary	369	24.2	153	21.6	285	23.6	791	23.9
Upper secondary	337	22.1	153	21.6	237	19.6	835	25.2
University	381	25.0	174	24.6	284	23.5	741	22.4
Unknown	9	0.6	6	0.8	5	0.4	7	0.2

* UK, United Kingdom.

† Subgroup of the glioma cases.

‡ The numbers and percentages vary for controls because of the use of different reference dates in analyses of glioma or meningioma.

§ Reference date is the date of diagnosis for cases and the corresponding date for controls.

¶ Highest level of education completed.

Control selection

Controls from the Nordic countries were randomly selected from a population register of the total population of the study area, stratified on age (in 5-year groups), sex, and geographic region. In the United Kingdom, controls were randomly selected from the general practitioners' patient lists. This is a representative source of population-based controls, as it has been estimated that 98 percent of the United Kingdom population is registered with a general practitioner (20).

The reference dates for controls were constructed from the interview date of the control, with adjustment for the mean interval between the diagnostic and interview date of cases and the difference between the mean interview date of cases and controls, to adjust for the fact that controls on average were interviewed later than cases. Adjustments were done separately for each country and separately for glioma and meningioma cases.

Data collection

All interviews and contacts with cases and controls were made by interviewers trained for this purpose. Data were collected through personal interviews by use of a computer program that guided the interview with questions read by the interviewer from a laptop computer screen. In Finland, however, answers were recorded on a paper copy of the ques-

tionnaire and later entered into the computer program. Almost half the interviews in Norway were conducted over the telephone, but only a small minority elsewhere. If a case had died, the closest relative was contacted as a proxy respondent where possible, except in the United Kingdom where ethical approval was obtained only for proxy interviews for too ill or deceased patients if a relative replied to the invitation letter on the patient's behalf.

Information about allergic conditions was ascertained through questions on whether the individuals had ever been diagnosed with asthma, eczema, hay fever, or any other allergy. The term "hay fever" might be used differently in different countries, and there might have been changes in terminology over time, so additional questions on seasonal and nonseasonal allergic rhinitis and conjunctivitis were asked and included under the term hay fever in the analyses. Affirmative answers were followed by additional questions, such as the age at which the condition had started and if and when symptoms of the condition had stopped. Individuals with hay fever were asked about the use of antiallergy treatment, and participants with eczema were asked whether their eczema was triggered by contact with certain agents.

Statistical analysis

Unconditional multivariate logistic regression models were used to compute odds ratios and 95 percent confidence intervals. There was no heterogeneity in the results among

TABLE 3. Allergic conditions and risk of glioma and meningioma, Nordic-UK* Brain Tumor Study, 2000–2004

	Glioma cases (n = 1,527)	Controls† (n = 3,309)	Odds ratio‡	95% confidence interval	Meningioma cases (n = 1,210)	Controls† (n = 3,309)	Odds ratio‡	95% confidence interval
Reference (no allergy)	848	1,637			574	1,637		
Asthma	118	325	0.65	0.51, 0.82	115	326	0.94	0.74, 1.20
Status§								
Current	78	213	0.68	0.51, 0.91	75	214	0.88	0.65, 1.17
Duration of current asthma (years)								
<10	19	80	0.46	0.28, 0.78	30	82	0.86	0.55, 1.36
10–19	23	53	0.86	0.52, 1.44	11	52	0.52	0.26, 1.02
≥20	33	77	0.75	0.49, 1.17	32	77	1.10	0.70, 1.71
Past	32	96	0.53	0.34, 0.80	34	96	1.14	0.75, 1.74
Years since asthma stopped								
1–9	10	26	0.58	0.27, 1.24	12	26	1.48	0.71, 3.05
≥10	22	70	0.51	0.31, 0.84	22	70	1.01	0.61, 1.69
Age at onset (years)								
<10	44	99	0.70	0.48, 1.02	19	99	0.62	0.37, 1.05
10–19	18	43	0.70	0.39, 1.24	15	43	1.08	0.58, 2.01
≥20	53	179	0.59	0.43, 0.82	79	180	1.04	0.78, 1.40
Eczema	196	592	0.65	0.54, 0.79	174	593	0.74	0.60, 0.91
Status§								
Current	104	393	0.52	0.41, 0.66	98	394	0.61	0.47, 0.79
Duration of current eczema (years)								
<10	20	101	0.40	0.24, 0.66	16	102	0.42	0.24, 0.73
10–19	27	84	0.63	0.40, 0.99	26	84	0.83	0.52, 1.32
≥20	51	203	0.48	0.35, 0.65	55	203	0.63	0.46, 0.87
Past	83	180	0.90	0.67, 1.19	71	180	1.05	0.78, 1.43
Years since eczema stopped								
1–9	19	47	0.73	0.42, 1.28	9	46	0.58	0.27, 1.22
≥10	64	133	0.96	0.69, 1.32	62	134	1.20	0.86, 1.67
Age at onset (years)								
<10	56	168	0.60	0.43, 0.83	53	168	0.81	0.58, 1.15
10–19	34	121	0.56	0.37, 0.83	30	121	0.67	0.44, 1.02
≥20	94	293	0.66	0.51, 0.85	86	294	0.72	0.55, 0.94
Contact eczema (from plants, cosmetics, metals, or chemicals)	31	148	0.46	0.31, 0.69	45	148	0.69	0.48, 0.99

Table continues

countries (defining heterogeneity, conservatively, $p < 0.10$). In the analyses, the reference category consisted of individuals who had reported no allergic condition or allergy at all. Adjustments for the stratification variables (sex, age, country, and region within country) and highest educational level completed (compulsory school, vocational or secondary school, upper secondary school, and university) were made in all analyses. Analyses were also made to investigate possible confounding from smoking, but this did not change the results, and smoking was therefore not included in the final models. All analyses were performed with SAS, version 9.1, statistical software (21). The study protocol was approved by appropriate local ethics committees.

RESULTS

During the study period, 2,530 glioma cases, 1,629 meningioma cases, and 6,581 controls were identified. Participation rates were 60 percent ($n = 1,527$) for glioma cases, 74 percent ($n = 1,210$) for meningioma cases, and 50 percent ($n = 3,309$) for controls (table 1). Proxy respondents were interviewed for 13 percent ($n = 196$) of participating glioma cases, 2 percent ($n = 21$) of participating meningioma cases, and 0.1 percent ($n = 2$) of participating controls. Among the participating cases, 95 percent of gliomas and 91 percent of meningiomas were confirmed by histopathologic examination. The characteristics of participating subjects

TABLE 3. Continued

	Glioma cases (n = 1,527)	Controls† (n = 3,309)	Odds ratio‡	95% confidence interval	Meningioma cases (n = 1,210)	Controls† (n = 3,309)	Odds ratio‡	95% confidence interval
Hay fever	272	739	0.66	0.56, 0.78	253	740	0.93	0.77, 1.12
Status§								
Current	199	629	0.56	0.46, 0.68	209	630	0.91	0.75, 1.11
Duration of current hay fever (years)								
<10	50	161	0.54	0.38, 0.76	49	162	0.79	0.55, 1.12
10–19	48	129	0.67	0.47, 0.96	36	127	0.87	0.58, 1.30
≥20	92	308	0.52	0.40, 0.67	115	311	1.03	0.81, 1.32
Past	57	80	1.25	0.87, 1.80	33	80	1.16	0.75, 1.79
Years since hay fever stopped								
1–9	22	33	1.17	0.66, 2.08	13	33	1.23	0.62, 2.41
≥10	35	47	1.31	0.83, 2.06	20	47	1.12	0.64, 1.95
Age at onset (years)								
<10	53	135	0.63	0.45, 0.89	46	135	1.01	0.70, 1.46
10–19	73	202	0.60	0.45, 0.81	61	202	0.90	0.65, 1.24
≥20	134	371	0.68	0.55, 0.85	136	372	0.94	0.75, 1.18
Food allergy¶	86	241	0.66	0.50, 0.86	105	241	1.06	0.82, 1.39
Any allergy#,**	574	1,523	0.70	0.61, 0.80	565	1,526	0.95	0.82, 1.10
Status§								
Current	440	1,286	0.63	0.55, 0.73	475	1,289	0.93	0.80, 1.08
Past	111	200	1.01	0.78, 1.30	78	200	1.14	0.85, 1.53
Years since allergy stopped								
1–9	35	61	0.95	0.61, 1.48	22	61	1.08	0.64, 1.82
≥10	76	139	1.03	0.76, 1.40	56	139	1.17	0.83, 1.64
No. of allergic conditions#								
1	374	918	0.76	0.65, 0.88	339	921	0.95	0.81, 1.12
2	148	419	0.65	0.53, 0.81	157	419	0.98	0.78, 1.21
≥3	52	186	0.52	0.37, 0.72	69	186	0.88	0.65, 1.20

* UK, United Kingdom.

† Different number of controls in subgroups because of the use of different reference dates in analyses of glioma or meningioma.

‡ Adjusted for age, sex, education, country, and region within country.

§ When divided into current or past, the numbers do not add up because of missing information on if or when the allergy stopped.

¶ Not divided into current and past because very few individuals belonged to past categories.

Asthma, eczema, hay fever, or other types of allergy (including food allergy).

** Numbers do not add up to the total numbers because of missing information or a “don’t know” answer on one of the included variables.

are summarized in table 2. There were more men than women among the glioma cases and a strong preponderance of women among the meningioma cases. Glioma cases had a higher representation in younger age groups than did the meningioma cases. The controls were recruited stratified on sex and age from all cases and, therefore, the sex and age distribution among controls reflects primarily the distribution among the cases.

Odds ratios did not differ between men and women and are therefore presented for the two sexes combined. An odds ratio of 0.70 (95 percent confidence interval (CI): 0.61, 0.80) was estimated for glioma risk associated with past diagnosis of any of asthma, hay fever, eczema, or other type of allergy (table 3). Country-specific odds ratios for

glioma risk were 0.79 (95 percent CI: 0.58, 1.08) for Denmark, 0.62 (95 percent CI: 0.45, 0.86) for Finland, 0.68 (95 percent CI: 0.49, 0.94) for Norway, 0.78 (95 percent CI: 0.59, 1.03) for Sweden, and 0.62 (95 percent CI: 0.48, 0.82) for the United Kingdom. The risk estimates for glioma were approximately 0.65 for each allergic condition (asthma, eczema, hay fever, and food allergy), with confidence intervals equally consistent, about 0.55, 0.80. The risks did not vary with age at onset of the allergic conditions. No noteworthy associations were found for meningioma, except for a decreased risk associated with eczema (odds ratio = 0.74, 95 percent CI: 0.60, 0.91) (table 3).

For eczema, hay fever, and any allergy, the decreased risks for glioma were confined to current allergy and did not

TABLE 4. Risk of glioma in relation to diagnosis of asthma, eczema, and hay fever, by histologic type, age at reference date, and excluding proxy answers, Nordic-UK* Brain Tumor Study, 2000–2004

	Allergic condition											
	Asthma				Eczema				Hay fever			
	No. of cases	No. of controls	Odds ratio†	95% confidence interval	No. of cases	No. of controls	Odds ratio†	95% confidence interval	No. of cases	No. of controls	Odds ratio†	95% confidence interval
Histologic type												
Glioblastoma												
No allergy	413	1,637			413	1,637			413	1,637		
Allergic condition	45	325	0.55	0.39, 0.78	84	592	0.62	0.48, 0.81	119	739	0.67	0.53, 0.84
Other glioma												
No allergy	435	1,637			435	1,637			435	1,637		
Allergic condition	73	325	0.71	0.53, 0.95	112	592	0.68	0.54, 0.87	153	739	0.65	0.52, 0.80
Age at reference date‡ (years)												
<40												
No allergy	204	326			204	326			204	326		
Allergic condition	41	79	0.73	0.47, 1.14	56	153	0.59	0.41, 0.86	84	206	0.59	0.43, 0.81
40–49												
No allergy	170	358			170	358			170	358		
Allergic condition	26	81	0.66	0.40, 1.09	45	151	0.63	0.42, 0.94	74	187	0.84	0.60, 1.20
≥50												
No allergy	474	953			474	953			474	953		
Allergic condition	51	165	0.64	0.45, 0.91	95	288	0.70	0.53, 0.91	114	346	0.64	0.49, 0.82
Excluding proxy answers												
No allergy	723	1,637			723	1,637			723	1,637		
Allergic condition	103	325	0.65	0.50, 0.83	171	592	0.66	0.54, 0.80	249	737	0.69	0.58, 0.83

* UK, United Kingdom.

† Adjusted for age, sex, education, country, and region within country.

‡ Reference date is the date of diagnosis for cases and the corresponding date for controls.

vary appreciably with duration of current allergy (table 3). For asthma, on the other hand, a reduced risk was seen for both current and past disease.

The odds ratios related to eczema were lowest for individuals who reported their eczema's being triggered by certain agents: plants, cosmetics, ointments, metals, or chemicals (odds ratio = 0.46, 95 percent CI: 0.31, 0.69).

Considering the numbers of allergic conditions reported by participants, the risk estimates for glioma ranged from an odds ratio of 0.76 (95 percent CI: 0.65, 0.88) for one condition to an odds ratio of 0.52 (95 percent CI: 0.37, 0.72) for three or more conditions ($p_{\text{trend}} < 0.0001$; among affected: $p_{\text{trend}} = 0.03$) (table 3). For meningioma, the risk estimates ranged from an odds ratio of 0.95 (95 percent CI: 0.81, 1.12) for one condition to an odds ratio of 0.88 (95 percent CI: 0.65, 1.20) for three or more conditions ($p_{\text{trend}} = 0.29$; among affected: $p_{\text{trend}} = 0.32$).

There was no appreciable difference in the association with asthma, eczema, or hay fever for glioblastoma cases compared with nonglioblastoma glioma cases. Excluding proxy answers from the analyses did not change the results. Odds ratios were not substantially influenced by age at the reference date (table 4).

In table 5, analyses are limited to participants with hay fever, and the risk of glioma is compared between ever and never use of antiallergy treatments (oral antihistamines, nasal spray, eye drops, and desensitization). The risk for glioma was significantly reduced among participants with hay fever who reported ever use of eye drops or nasal spray compared with those with hay fever who reported never use, and the risk was reduced although not significantly for use of oral antihistamines or desensitization compared with never use of that type of antiallergy treatment.

The interviewers assessed that 79 percent of glioma cases, 84 percent of meningioma cases, and 88 percent of controls recalled their medical history very well or well. Reanalyzing the data including only these participants did not change the results (not shown).

DISCUSSION

To the best of our knowledge, this is the largest study published on the relation between allergic conditions and glioma and meningioma risk. We found a decreased risk of glioma associated with allergic conditions. The risk

TABLE 5. Risk of glioma associated with ever use of antiallergy treatment in individuals with hay fever, Nordic-UK* Brain Tumor Study, 2000–2004

Type of treatment	Glioma (<i>n</i> = 272)	Controls† (<i>n</i> = 739)	Odds ratio‡	95% confidence interval
Oral antihistamines				
No	141	359	1.00	
Yes	131	379	0.88	0.65, 1.18
Nasal spray				
No	195	478	1.00	
Yes	77	260	0.64	0.46, 0.88
Eye drops				
No	225	567	1.00	
Yes	47	171	0.68	0.46, 0.98
Desensitization				
No	262	702	1.00	
Yes	10	36	0.83	0.39, 1.77
Any of above				
No	107	258	1.00	
Yes	165	480	0.80	0.59, 1.10

* UK, United Kingdom.

† One control with missing information on antiallergy treatment.

‡ Adjusted for age, sex, education, country, and region within country.

estimates did not vary substantially by age at onset of the allergic conditions, age at reference date, or between glioblastoma and nonglioblastoma glioma cases. For eczema, hay fever, and any allergy, the reduced risks were primarily confined to current disease. No noteworthy associations were found for meningioma except for a decreased risk related to eczema.

The strengths of our study include the size and the population-based study design, with rapid case ascertainment. Cases were identified continuously during the study period through collaboration with the treating clinics. The proportion of proxy interviews has been associated previously with the strength of the association between allergies and glioma (8). In our study, the proportion of proxy interviews was relatively low, 13 percent for glioma cases and 2 percent for meningioma cases, and excluding proxy answers from the analyses had no appreciable impact on the results.

Our results are consistent with those of most prior case-control studies on the association between allergic conditions and glioma and meningioma risk (1–7, 9, 10). A recent paper on meningioma, based partly on data from our study, reported an inverse association with allergy overall but non-significant associations with individual conditions (19). Prior cohort studies have shown inconsistent results but generally included very small numbers of cases. One publication based on two cohorts from the Swedish Twin Registry found a nonsignificantly reduced glioma risk associated with allergy in one of the cohorts and an increased risk of meningioma in the other cohort (8). Three cohort studies evaluat-

ing the risk for many cancer types, including brain tumors, have not found a reduced risk associated with allergic conditions (22–24). Hagströmer et al. (23) reported an elevated risk of brain tumors associated with atopic dermatitis, whereas Eriksson et al. (22) found no association between atopy and brain tumors. These studies, however, included all malignant tumors in the central and peripheral nervous system without further subclassification, and the numbers of tumor cases were small. Turner et al. (24) included all malignant cerebral tumors, the majority of which are gliomas. They reported a reduced risk for overall cancer associated with a history of both asthma and hay fever, but the relative risk for brain tumors was close to unity. Their reference category comprised persons that could have had eczema or other allergies that could possibly dilute the risk estimates. It is, however, unlikely that this could completely explain the difference between our results.

The reduced risk of glioma related to eczema, hay fever, and allergy overall was confined primarily to current conditions. If this is etiologic, it implies that the state of the immune system at the time of tumorigenesis is of importance, that is, assuming that current allergy was a marker of allergy in the early phases of tumor development. Glioma patients have been shown to suffer from an impaired immunity (25). Whether the immunosuppression is evident before the diagnosis of the tumor is not known. If the reduced risk associated with allergies was an effect of immunosuppression induced by the tumor, current allergic disease would be expected to be associated with a decreased risk, and the observed association would, at least in part, be a result of reversed causation. This would mean that the tumor had at some time made an existing allergy disappear and/or suppressed the appearance of first allergic symptoms. The former would lead to the allergy's being reported as a past (not a present) allergy and, hence, lead to a greater relative risk for past conditions than for current conditions. For asthma, the results were opposite, with the lowest risks for past disease.

The nature of glioma tumors, with an often rapid debilitating course, may cause a disturbed brain function. Our results could have been affected by cases having an impaired memory. We have tried to address the problem, as far as we could, by use of the interviewers' estimation of the quality of the interview. After completing the interviews, the interviewer evaluated how he or she experienced that the interviewee could remember his or her own medical history. When we reanalyzed the data including only those assessed as having remembered very well or well, the results did not change. The reduced risk estimates were confined to current allergy for hay fever, eczema, and any allergy. If memory disturbances in glioma cases are greater for more recent than distant events, this could explain the restriction of observed effects to current allergy. To explore this further, we estimated risk by duration of allergic condition among those who reported current allergy. The results were approximately equally reduced for both short (<10 years) and long (≥20 years) duration of hay fever and eczema, thus suggesting that the results are probably not explained by an impaired memory for recent events. Brenner et al. (6) dealt with the possible effect of a deteriorated mental status in

glioma cases by restricting analysis to cases not known to have experienced impairment of cognition or memory during the weeks prior to diagnosis. Risk estimates associated with allergies after this restriction were closer to unity but still reduced.

A possible limitation of the study includes the risk of misclassification of exposure history. We chose to define the reference category in our analyses as individuals who reported never to have suffered from any allergy. The term hay fever might be used in different ways in different countries, and there might have been changes in the terminology over time. Therefore, additional questions on seasonal and nonseasonal allergic rhinitis and conjunctivitis were included in the interview protocol to minimize misclassification. The use of self-reported allergic conditions has been validated elsewhere. The sensitivity of reported physician-diagnosed asthma validated in relation to clinical diagnosis was 68 percent in reviewed studies, and the specificity was 94 percent (26). In a validation of a questionnaire assessing the history of hay fever, the physician-diagnosed hay fever question gave the most accurate result (27). Other conditions can be mistaken for allergy, for example, food intolerances, chronic respiratory diseases, and irritant contact eczema. This could cause a nondifferential misclassification that would dilute the risk estimates. Misclassification of allergy might be a greater problem for past disease and therefore attenuate these results.

The odds ratios for glioma risk decreased with the number of allergic conditions that an individual reported; it is possible that the number of conditions can be related to the activity of the immune system or severity of allergy. A perhaps more plausible explanation might be that individuals with multiple conditions are more likely to be classified correctly as allergic. Wiemels et al. (7) reported a similar pattern for glioma risk associated with the number of allergens triggering the allergic symptoms.

We compared the glioma risk for hay fever that has been treated with oral antihistamines, nasal spray, eye drops, or desensitization with glioma risk for hay fever that has not been treated and found a reduced risk when treated. Possible explanations for the somewhat stronger risk reduction among those treated, aside from chance, could be that treatment is an indicator of a more severe form of allergy, or an indicator of being truly allergic, or that treatment imparts a protective effect.

The risk estimates did not vary among the different allergic conditions. This might indicate a bias but might equally be an effect of the allergic conditions being related to the same immunologic mechanism. Food allergies have been shown to be overestimated when reported, with most adverse food reactions not being immunoglobulin E (IgE) mediated (28). The risk estimates for food allergies would therefore be expected to be closer to unity. We did not observe this, but we note also that 73 percent of controls and 74 percent of glioma cases who reported food allergy also reported asthma, eczema, or hay fever.

In our study, we found the strongest risk reduction for individuals who reported eczema due to contact with plants, cosmetics, ointments, metals, or chemicals. Contact eczema is a T-cell-mediated allergy, different from IgE-mediated

allergic conditions (29). Apart from being a chance finding, this could indicate the immunologic mechanism of importance, be an indicator of being truly allergic, or imply that this is reversed causality, since the glioma tumor could depress the cell-mediated immunity.

Nonparticipation is a potential source of selection bias. When cases and controls were initially informed about the study, the interest in allergy was not mentioned, and the risk of selection bias therefore was diminished. Allergy has been shown to be associated with socioeconomic class (30), and participation among controls is also related to socioeconomic class (31). The adjustment for education as an indicator of socioeconomic status in every analysis should have reduced the effect of this potential bias.

Apart from adjustment for the stratification variables (sex, age, country, region within country) and for education, analyses were made to investigate possible confounding from smoking, but risk estimates were not changed. There might still be confounding from unknown risk factors, including genetic factors.

A biomarker for allergy has been studied previously. Wiemels et al. (32) found a reduced level of IgE, the antibody related to atopic allergic diseases, among glioma patients compared with controls, but the risk of reversed causality could not be excluded since the level of IgE was measured after diagnosis. A study of polymorphisms in genes associated with asthma has indicated an inverse relation of these polymorphisms with risk of glioblastoma (33); these germline polymorphisms cannot be attributed to recall bias or be due to reversed causality by the tumor affecting the immune system. Glioblastoma patients with elevated levels of IgE have also been shown to have an average of 9 months' longer survival than those with normal or borderline IgE levels (34).

The biologic mechanism explaining how an immune system prone to respond with allergy can prevent the genesis of brain tumors, if there is such an effect, is still to be identified. The brain has traditionally been considered an "immune-privileged" site (35), but that view has been modified in more recent years, and the central nervous system has been demonstrated to be capable of evoking an immune response (36). Interleukin-4, an important cytokine in allergic response, has been shown to inhibit low-grade astrocytoma cell growth *in vitro* (37).

Together with previous studies, this study finds an inverse relation between self-reported allergic conditions and the risk of glioma. For eczema, hay fever, and any allergy, the reduced glioma risks were confined primarily to current allergic conditions. If this is etiologic, it has implications for the understanding of how allergic conditions might reduce the tumor risk, but the influences of reverse causation, bias, and confounding need to be taken under consideration also as potential alternative explanations.

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