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Original Contribution

History of Allergic Disease and Risk of Meningioma

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Epidemiologic studies have consistently shown inverse associations of allergic disease with risk of glioma, but it is unclear whether this association also applies to meningioma. The authors conducted a pooled analysis of meningioma risk in relation to a history of allergic disease based on data from two population-based, case-control studies with 475 cases and 1,716 controls in the United Kingdom (2001–2004). Meningioma risk was significantly reduced in relation to self-reported, physician-diagnosed allergic disease (odds ratio = 0.76, 95% confidence interval (CI): 0.61, 0.96) but was nonsignificantly reduced for individual conditions: asthma (odds ratio = 0.85, 95% CI: 0.61, 1.18), hay fever (odds ratio = 0.81, 95% CI: 0.62, 1.06), and eczema (odds ratio = 0.72, 95% CI: 0.51, 1.02). Risk reductions were greatest for asthma (odds ratio = 0.43, 95% CI: 0.21, 0.89) and hay fever (odds ratio = 0.50, 95% CI: 0.25, 1.00) with an early age at onset (<10 years) and for eczema (odds ratio = 0.46, 95% CI: 0.21, 1.07) with an onset at ages 10–19 years; they were near unity for onset in adulthood. This study suggests an inverse association between a history of allergies and meningioma risk, but with smaller risk reductions than for glioma. The reasons for this association need clarification, as well as an etiologic explanation. Consideration also needs to be given to confounding or bias.

allergy and immunology; case-control studies; meningioma

Abbreviation: CI, confidence interval.

Several epidemiologic studies have reported an inverse association between risk of glioma and a history of allergic disease (1–9). Patients with allergies have been hypothesized to be in a state of raised immunosurveillance (10), which might reduce their risk of several types of cancer (11, 12). Four studies have also reported on allergy associations for meningioma (2, 5, 7, 8) but with much smaller numbers and with less consistent results than for glioma. There is a lack of large studies on meningioma with enough detail on allergic disease to establish whether the association with allergies is specific to glioma or also extends to meningioma. Three of the previous studies were of case-control design and generally reported nonsignificant inverse associations with individual allergic conditions but no association with any allergy overall (2, 5, 7). The fourth study reported on two cohorts of subjects with self-reported allergies, with inconsistent results (8).

We conducted two population-based, case-control studies of potential risk factors for brain tumors in several areas of the United Kingdom, according to similar protocol. We previously reported on the association of allergic disease with glioma (13). In this report, we present results of a pooled

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analysis of risk of meningioma in relation to a history of allergies, with 475 cases and 1,716 controls. In this study, tumor risk is explored in detail in relation to type of allergy and the number of allergies reported, with age and time since onset of the condition and in relation to use of antiallergenic medication.

MATERIALS AND METHODS

Two population-based, case-control studies of potential risk factors for brain tumors were conducted in the United Kingdom. One study, referred to as the ''Southeast England Study,'' was carried out in the Thames regions of southeast England, and the other, referred to as the ''Northern UK Study,'' was carried out in the Trent area, the West Midlands, West Yorkshire, and central Scotland. Both studies followed the core protocol of the Interphone Study, a 13-country collaboration on brain tumors and mobile phone use (14), but with several extensions including a wider age range of patients and a much extended questionnaire.

All patients with meningioma first diagnosed during the study period at ages 18–59 years in the Southeast and at ages 18–69 years in the northern areas of the United Kingdom and resident in the study regions were eligible for the study. The study period was from December 1, 2000, to June 30, 2003, for the Northern UK Study and to February 29, 2004, for the Southeast. Cases were ascertained from neurosurgery, neurooncology, neuropathology, neuroradiology, and neurology units in hospitals in the study regions and, for the Southeast, also from the regional cancer registry. Meningioma was defined as topography code C70.0 or D32.0 by the *International Statistical Classification of Diseases and Related Health Problems* (15) and as morphology codes 9530–9539 by the *International Classification of Diseases for Oncology*, Third Edition (16). Ethical approval was obtained from the Multicenter Research Ethics committees for the Southeast and Scotland and all appropriate Local Research Ethics committees. We did not obtain ethics permission to approach proxies for deceased or ill cases, although it was permitted to interview them if they responded to the invitation letter addressed to the patient. We carried out two such case proxy interviews.

Control subjects were randomly selected from general practitioner lists of patients in the study regions by a preset algorithm. This is considered to be a representative source of population-based controls, as approximately 98 percent of the population in the United Kingdom is registered with a general practitioner (17). Potential control subjects had to be resident in the same study region and within the same age range as the cases in the study region. In the northern regions of the United Kingdom, controls were individually matched to cases on age (within 1 year), sex, and physician practice, and in the Southeast they were frequency matched to the age (5-year groups), sex, and geographic distribution of the cases.

Ascertained cases and controls were invited by letter to participate in the study. This letter included a reply slip and a stamped envelope to return to the research team. If no reply was received after several weeks, the subject was contacted by telephone or, if that was not possible, was sent a repeat letter.

Written, informed consent was obtained from all subjects at interview. Interviews were conducted in person by trained research nurses or experienced research interviewers by use of a highly structured, computer-assisted interview, with answers being entered directly into the questionnaire program on a laptop computer. Interviews were conducted at a place that was preferred by the participant, which was most frequently the subject's home and occasionally the subject's workplace or in a hospital. During the interview, subjects were asked about several medical conditions including allergies. They were asked whether they had ever been diagnosed with asthma, hay fever, and eczema and about the age at which they had the first episode of each condition. For eczema, subjects were asked whether they still suffered from eczema and, if not, at what age it stopped, the proportion of the year they were affected by eczema, and the types of exposures that triggered it. Extra details were collected in the Southeast England Study, including the ages at which subjects stopped having asthma and hay fever (if applicable) and diagnosis with seasonal or nonseasonal allergic rhinitis and conjunctivitis, as well as food or contact allergy. In addition, in the Southeast England Study, subjects who reported asthma or other allergy were asked about the frequency with which they had used antiasthmatic medication or antiallergenic drugs, respectively, and about the types of such drugs they had ever used. As a check on the quality of the collected information, the interviewer rated after completion of the interview how well he/she felt that the participant had remembered his/her own history of disease.

Regarding statistical analysis, the study was conducted as part of a larger case-control study of several types of intracranial tumor. We used all interviewed controls recruited for the entire set of cases for this analysis to increase statistical power. Meningioma risk in relation to allergies was evaluated for allergies diagnosed at least 1 year prior to first diagnosis with meningioma. For controls, we derived a censoring date comparable with the 1-year prediagnostic censoring date for cases to calculate indices of allergic disease, based on interview year and how far back the subject was asked to recall exposures, as described previously (13).

As the set of controls used in this analysis was not individually matched to cases, an (unconditional) logistic regression model was used to obtain odds ratios for risk of meningioma in relation to allergic conditions and antiallergenic medication use. All odds ratios were adjusted for sex, 5-year age groups at the reference date, region (four northern regions and the Southeast), interview year, and Townsend deprivation category (a measure of deprivation based on the subject's residential ZIP code (18)). Tumor risk in relation to allergic disease was analyzed by study center, age at the reference date in 10-year categories, and sex. Heterogeneity in results among these groups was assessed with a log-likelihood ratio test (19). STATA statistical software (20) was used for all analyses. All p values are two sided.

Analyses were repeated, with additional adjustment in the model for past diagnostic radiographic examinations of the head or cigarette smoking and after restricting analyses to

subjects who were rated by interviewers to have had good or very good recall. We also repeated the analyses without adjustment for the Townsend deprivation category to explore residual confounding and after adjustment for the subject's highest education level attained as an alternative to the Townsend score. The Northern UK Study data were also analyzed separately by use of individually matched case-control pairs, to evaluate the impact of our decision to conduct an unmatched analysis with all recruited controls.

RESULTS

A total of 718 cases and 3,774 controls were ascertained and were eligible, and 475 cases and 1,716 controls were interviewed for the study (table 1). The main reasons for nonparticipation were death or being too ill (cases: 4 percent, controls: 0.1 percent), patient's refusal (cases: 13 percent, controls: 29 percent), no response (cases: 12 percent, controls: 21 percent), and no medical permission to approach the patient (cases: 2 percent, controls: 5 percent). The overall participation rate was 66 percent among cases and 45 percent among controls and was 75 and 57 percent, respectively, based on subjects from whom we could obtain a response. Participation rates were higher in the Northern UK Study than in the Southeast England Study for cases (81 percent vs. 55 percent) but were comparable for controls.

Participants were more likely to be female than were nonparticipants among both the cases (74.5 percent vs. 67.6 percent, chi-square test $p = 0.05$) and controls (51.7 percent vs. 39.1 percent, chi-square test $p < 0.001$). Participants were also, on average, older than nonparticipants for cases (mean age: 49.7 years vs. 47.2 years, t-test $p = 0.02$) and controls (mean age: 47.4 years vs. 44.6 years, t-test $p < 0.001$) and more affluent for cases (mean Townsend score: 2.7 vs. 3.3, t-test $p < 0.001$) and controls (mean Townsend score: 2.6 vs. 3.1, t-test $p < 0.001$). When comparing interviewed cases with interviewed controls, we found that cases were more likely to be female (74.5 percent vs. 51.7 percent, chi-square test $p < 0.001$), because of the use of the entire intranial tumor control set, as described in Materials and Methods, and were somewhat older (mean age: 49.8 years vs. 48.8 years, t-test $p = 0.08$) and less affluent (mean Townsend score: 2.7 vs. 2.6, t-test $p = 0.02$).

The odds ratio for risk of meningioma was 0.85 (95 percent confidence interval (CI): 0.61, 1.18) in relation to a past diagnosis of asthma, 0.81 (95 percent CI: 0.62, 1.06) for hay fever, and 0.72 (95 percent CI: 0.51, 1.02) for eczema (table 2). Tumor risk in relation to having any of these conditions was 0.76 (95 percent CI: 0.61, 0.96), with a significant trend of decreasing risk with the number of conditions reported ($p_{\text{trend}} = 0.02$), which was not significant when restricted to affected individuals ($p_{\text{trend}} = 0.7$).

The risk was most strongly reduced for childhood-onset asthma (odds ratio = 0.43, 95 percent CI: 0.21, 0.89) and hay fever (odds ratio = 0.50, 95 percent CI: 0.25, 1.00), as well as for eczema with an onset in adolescence (odds ratio = 0.46, 95 percent CI: 0.21, 1.07). For allergies with onset at older ages, the risk was less strongly reduced or even raised. Correspondingly, there was some suggestion that risk was most strongly reduced for the period 10 or more years since onset of these conditions. There was a trend of decreasing risk of meningioma with increasing duration of having eczema ($p_{\text{trend}} = 0.04$), which was not significant when only affected individuals were included ($p_{\text{trend}} = 0.3$) (table 2). Based on the Southeast England Study only, the odds ratio was 0.86 (95 percent CI: 0.52, 1.42) for ever asthma and 0.80 (95 percent CI: 0.55, 1.16) for ever hay fever. There was a suggestive trend of risk with duration of either of these conditions (asthma: $p_{\text{trend}} = 0.07$, hay fever: $p_{\text{trend}} = 0.10$), with a significant trend for asthma but not hay fever, when considering only affected individuals (asthma: $p_{\text{trend}} = 0.02$, hay fever: $p_{\text{trend}} = 0.2$) (results not shown).

Risk was more strongly reduced in subjects who still had eczema 1 year prior to the reference date than in those who reported their eczema had stopped prior to this time (table 2). Based on data from the Southeast England Study only, this was observed to be more pronounced for asthma and hay fever, where risk was not reduced among subjects who said they had stopped having the condition. The odds ratio was 0.75 (95 percent CI: 0.40, 1.40) for current and 1.02 (95 percent CI: 0.46, 2.26) for past sufferers of asthma and 0.76 (95 CI: 0.51, 1.13) for current and 1.01 (95 percent CI: 0.46, 2.22) for past sufferers of hay fever.

TABLE 1. Demographic characteristics of meningioma cases and controls in a case-control study, United Kingdom, 2001–2004

Characteristic	Cases ($n = 475$)		Controls ($n = 1,716$)	
	No.	%	No.	%
Sex				
Male	121	25.5	829	48.3
Female	354	74.5	887	51.7
Age at reference date (years)				
18–29	15	3.2	113	6.6
30–39	69	14.5	280	16.3
40–49	138	29.1	432	25.2
50–59	191	40.2	642	37.4
60–69	62	13.1	249	14.5
Townsend deprivation score*				
1 (most affluent)	123	25.9	513	29.9
2	112	23.6	386	22.5
3	79	16.6	334	19.5
4	87	18.3	292	17.0
5 (least affluent)	74	15.6	191	11.1
Region				
Thames regions	225	47.4	630	36.7
Southern Scotland	66	13.9	277	16.1
Trent	96	20.2	372	21.7
West Midlands	26	5.5	207	12.1
West Yorkshire	62	13.1	230	13.4

* Townsend score (18), a ZIP code-based measure of deprivation categorized into quintiles, based on 2001 census data (40).

TABLE 2. Risk of meningioma in relation to past diagnosis with asthma, hay fever, and eczema in a case-control study, United Kingdom, 2001–2004

Factor	Cases		Controls		Odds ratio†	95% confidence interval	p_{trend}
	No.	%	No.	%			
Asthma							
Ever							
No	420	88.4	1,488	86.7	1.00		
Yes	55	11.6	228	13.3	0.85	0.61, 1.18	
Age at onset (years)							
<10	9	1.9	78	4.6	0.43	0.21, 0.89*	
10–19	8	1.7	46	2.7	0.66	0.30, 1.47	
≥20	38	8.0	104	6.1	1.19	0.79, 1.80	
							0.02‡
Time since onset (years)							
<10	14	3.0	51	3.0	0.89	0.47, 1.68	
10–19	17	3.6	58	3.4	1.22	0.68, 2.18	
≥20	24	5.1	119	6.9	0.68	0.42, 1.09	
							0.07§
							0.03‡
Hay fever							
Ever							
No	378	79.6	1,322	77.0	1.00		
Yes	97	20.4	394	23.0	0.81	0.62, 1.06	
Age at onset (years)							
<10	10	2.1	83	4.8	0.50	0.25, 1.00	
10–19	33	7.0	153	8.9	0.79	0.52, 1.19	
≥20	54	11.4	158	9.2	0.94	0.67, 1.34	
							0.05¶
Time since onset (years)							
<10	27	5.7	55	3.2	1.49	0.90, 2.47	
10–19	13	2.7	88	5.1	0.50	0.27, 0.93*	
≥20	57	12.0	251	14.6	0.76	0.55, 1.05	
							0.05§
							0.06¶
Eczema							
Ever#							
No	426	89.7	1,492	87.0	1.00		
Yes	48	10.1	224	13.1	0.72	0.51, 1.02	
Status							
Current eczema	28	5.9	142	8.3	0.64	0.41, 0.99*	
Past eczema	20	4.2	82	4.8	0.87	0.52, 1.48	

Table continues

The risk of meningioma was not appreciably related to the proportion of the year the subject reported that he/she was affected by eczema. Risk was similar between subjects who reported that their eczema was triggered by contact with particular exposures (odds ratio = 0.75, 95 percent CI: 0.43, 1.29) and those who said it was not (odds ratio = 0.69, 95 percent CI: 0.44, 1.07).

Based on Southeast England Study data only, odds ratios were 0.25 (95 percent CI: 0.08, 0.73) for seasonal allergic rhinitis and conjunctivitis and 0.65 (95 percent CI: 0.29,

TABLE 2. Continued

Factor	Cases		Controls		Odds ratio†	95% confidence interval	p_{trend}
	No.	%	No.	%			
Age at onset (years)							
<10	16	3.4	93	5.4	0.61	0.35, 1.07	
10–19	7	1.5	48	2.8	0.46	0.21, 1.07	
≥20	25	5.3	83	4.8	0.98	0.61, 1.60	
							0.2††
Time since onset (years)							
<10	13	2.7	38	2.2	1.17	0.60, 2.29	
10–19	4	0.8	42	2.5	0.37	0.12, 1.07	
≥20	31	6.5	144	8.4	0.70	0.46, 1.06	
							0.03§
							0.2††
Duration (years)							
<10	21	4.4	80	4.7	0.96	0.57, 1.61	
10–19	11	2.3	57	3.3	0.70	0.36, 1.38	
≥20	16	3.4	84	4.9	0.56	0.32, 1.00	
Not known			3	0.2			
							0.04§
							0.3††
Any of the above							
Ever							
No	319	67.2	1,069	62.3	1.00		
Yes	156	32.8	647	37.7	0.76	0.61, 0.96*	
No. of conditions							
1	116	24.4	484	28.2	0.76	0.59, 0.98*	
2	34	7.2	127	7.4	0.81	0.53, 1.25	
3	5	1.1	36	2.1	0.47	0.18, 1.26	
Not known	1	0.2					
							0.02§
							0.7‡‡

* $p < 0.05$ (two sided).
† Odds ratios from an unconditional logistic regression model adjusted for sex, age category, region, interview year, and Townsend deprivation category.
‡ Trend: ever asthma only.
§ Trend: all subjects.
¶ Trend: ever hay fever only.
# Status not known for one case.
†† Trend: ever eczema only.
‡‡ Trend: ever diagnosed only.

1.47) for nonseasonal allergic rhinitis and conjunctivitis. There was no appreciable relation of risk with reported food allergy (odds ratio = 1.00, 95 percent CI: 0.54, 1.83) or contact allergy (odds ratio = 1.20, 95 percent CI: 0.73, 1.99).

Based on Southeast England Study data only, the risk of meningioma was not appreciably related to the frequency of use of antiasthmatic drugs among people reporting asthma. The odds ratio was 0.84 (95 percent CI: 0.42, 1.69) among subjects reporting never use or use less than half the year of such medication and 0.82 (95 percent CI: 0.38, 1.77) among subjects who reported use almost every day, compared with subjects who did not report asthma (results not shown). There was no clear association of risk among 64 cases and 214 controls reporting hay fever and/or allergic rhinitis and conjunctivitis with ever use of antihistamines (odds ratio = 0.77, 95 percent CI: 0.38, 1.59), eye drops (odds ratio = 0.50, 95 percent CI: 0.22, 1.16), nasal sprays (odds ratio = 1.19,

95 percent CI: 0.61, 2.29) or desensitizers (zero cases, 11 controls), or any of these medications (odds ratio = 1.75, 95 percent CI: 0.62, 4.91), although the latter were based on only seven cases not taking any medication (results not shown).

Allergy associations were similar after adjustment for previous diagnostic medical radiation exposure to the head or cigarette smoking, between the sexes or age groups or by study center. Risk reductions were somewhat stronger among ever smokers than among never smokers, but with no statistically significant heterogeneity in risks (e.g., for any allergy: ever smokers' odds ratio = 0.64, 95 percent CI: 0.45, 0.89; never smokers' odds ratio = 0.88, 95 percent CI: 0.64, 1.22; $p_{\text{heterogeneity}} = 0.17$). Odds ratios after adjustment for the Townsend deprivation category were nearly identical to those without such adjustment, and neither did adjustment for the subject's highest educational level attained instead of Townsend score affect the results. Exclusion of the 10 cases and six controls who reported cranial radiotherapy 10 or more years prior to the reference date did not affect the results. For 85 percent of cases and 93 percent of controls, the interviewers rated the subject's recall as good or very good; associations were similar when restricting the analyses to these subjects only. Results of separate analyses of the Northern UK Study data using individually matched analyses did not materially affect the results for this center.

DISCUSSION

In our study, the risk of meningioma was nonsignificantly reduced in subjects with a self-reported history of physician-diagnosed asthma, hay fever, or eczema, and it was statistically significantly reduced for having any of these conditions. Tumor risk was most strongly reduced for asthma and hay fever diagnosed before age 10 years and for eczema diagnosed between ages 10–19 years, but was not substantially reduced for conditions diagnosed in adulthood. The risk was most strongly reduced in subjects reporting all three conditions, but there was no trend of risk among affected subjects only. Our study is larger than any previously published case-control studies of meningioma in relation to allergies (60–331 cases) (2, 5, 7).

Our study showed a stronger inverse association of meningioma with allergic disease overall than was previously reported (table 3), but the definition of ''allergy'' is heterogeneous between studies. The results from our study were, however, generally consistent with those from previous studies in relation to asthma and eczema and, to a lesser extent, hay fever (2, 5, 7, 8). The risk estimates in relation to individual allergic conditions are not statistically significant in our study or in previous studies, however. Larger studies with greater statistical power are needed to be more certain of these associations.

We previously reported on the association of glioma with allergic disease, based on 966 cases and the same set of controls as used for meningioma in this report (13). Risk reductions in relation to allergic conditions were stronger for glioma than those reported here for meningioma (e.g., for any allergy, for glioma: odds ratio = 0.63, 95 percent

TABLE 3. Results from past studies and the present study on the association of meningioma with self-reported allergic conditions

First author, year (reference no.)	Study design	Country	No. of cases	No. of controls	Asthma		Hay fever		Eczema		Any allergy*	
					Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval
Ryan, 1992 (2)	Case-control	Australia	60	417	1.09	0.43, 2.75			0.57	0.19, 1.69	1.14	0.64, 2.05
Schlehofer, 1999 (5)	Case-control	Six countries	331	1,123	0.82	0.46, 1.44			0.68	0.42, 1.08	0.89	0.65, 1.22
Brenner, 2002 (7)	Case-control	United States	197	799	0.86	0.53, 1.40	0.93	0.58, 1.50	0.80	0.42, 1.53	0.98	0.70, 1.38
Schwartzbaum, 2003 (8)†	Cohort	Sweden										
Cohort 1			41				0.85	0.33, 2.17	0.72‡	0.30, 1.70	0.84	0.42, 1.68
Cohort 2			26								2.44	1.08, 5.51
The present study	Case-control	United Kingdom	475	1,716	0.85	0.61, 0.18	0.81	0.62, 1.06	0.72	0.51, 1.02	0.76	0.61, 0.96

* Defined by Ryan et al. (2) and Schlehofer et al. (5) as at least one of asthma, eczema, or other allergy; by Brenner et al. (7) as ''any allergy''; by Schwartzbaum et al. (8) as asthma, hay fever, or eczema for cohort 1 and as ever having had asthma, croup, hay fever, or eczema in cohort 2; and in the present study as any of asthma, hay fever, or eczema.
† Schwartzbaum et al. (8) report results from two cohorts with self-reported allergic conditions.
‡ Eczema occurring after infancy.

CI: 0.53, 0.76; for meningioma: odds ratio = 0.76, 95 percent CI: 0.61, 0.96). This stronger association for glioma than for meningioma is in accordance with previous studies that reported on the risk of both tumors separately (2, 5, 7, 8) and has been argued to be due to the use of fewer proxy interviews for meningioma cases, because proxies tend to underreport allergic disease (6, 8). This cannot explain the findings in our study, however, because we had very few proxy interviews.

There are several possible reasons for the observed inverse association. Reduced risks of cancer have been observed in subjects with allergies for several other cancers, including pancreatic cancer and leukemia, although results have not always been consistent (11, 12, 21, 22). Burnet (10) hypothesized several decades ago that the immune system is able to recognize and destroy nascent transformed cells, and therefore it is possible that patients with allergies have lower cancer risks because of an increased state of immunosurveillance. Biologic mechanisms for tumor immunology are subject to much debate (23–25), but current understanding of antitumor immune response in the brain is limited. Although the brain has long been considered as ''immune privileged'' (26), immune reactions do occur in the brain, but they are distinctive from those at other sites (27). The mechanism by which an immune response associated with allergies could protect against brain tumors would need to be elucidated.

Another possible explanation is that the observed association could be due to a third factor that is related to development of both allergies and meningioma. Because of the lack of knowledge of brain tumor etiology, it is difficult to speculate what this factor could be, but one possibility is a genetic factor. Alternatively, as atopy may be related to early life exposures such as infections and social circumstances including family size and socioeconomic status (28), it is possible that shared early life determinants for allergy and meningioma risk confound the observed associations.

Selection bias is a concern in case-control studies. Our control participation rate was between 45 and 57 percent, depending on what proportion of nonrespondents actually received the invitation letter. The low participation rate reflects the difficulty in recruiting general population participants for medical studies in Western countries in recent years (29), as well as prevailing legislation on consent that makes the recruitment procedure labor intensive and restrictions imposed by ethics committees. To minimize selection bias toward more allergy-prone individuals, the study documentation to study participants did not mention allergies. The prevalence of reported allergy among controls (38 percent) was within the range of that in comparable studies (17–40 percent) (2, 3, 5, 7–9) and was relatively high for specific allergic conditions, but the prevalence of allergy in the United Kingdom is among the highest internationally (30–32). Interviewed controls were somewhat more affluent than cases, and atopy, as well as meningioma risk, is associated with socioeconomic status (28, 33). To control for potential confounding by socioeconomic related variables, we adjusted the analyses for the Townsend deprivation score, although the results were nearly identical to those without such adjustment.

Our case participation rate is lower than that in previous studies and reflects the lengthy process in obtaining permission to approach patients and the lack of ethics permission to contact close relatives as proxies for patients who were too ill or deceased. The main reasons for nonparticipation among cases were refusal and nonresponse, but there is no obvious reason why such nonparticipation should be related to allergy status. Although case or control selection bias cannot be ruled out, it is unlikely to be the explanation for the inverse association, because allergy associations were very similar between the two centers, despite the fact that the case participation rate in the Northern UK Study was higher. Furthermore, the strength of the associations for asthma and eczema with meningioma is consistent with those from previous studies (table 3) (2, 5, 7, 8), most of which had higher participation rates.

Interviewers could not be blinded for case-control status in this study, although they were trained to treat both groups equally to minimize interviewer bias. Despite this, it is possible that interviewers asked questions about minor disease, such as allergies, in a different way to cases than controls, because cases can be very ill and controls were relatively well. Patients may also have had worse recall of past allergic conditions than controls did, or they may have viewed such conditions as unimportant because they had a meningioma. Allergy associations were similar to those presented when analyses were restricted to subjects whom the interviewers rated to have good or very good recall of their medical history, but it is unclear how well interviewers are able to judge quality of recall. The potential presence of interviewer or recall bias could possibly explain the more strongly reduced risks of glioma than meningioma in relation to allergic disease, as it is likely that both types of bias would be more pronounced in glioma cases because they are generally more ill than meningioma cases.

In our study, risk reductions were strongest for asthma and hay fever, and to a lesser extent eczema, with early age onset, and there was no appreciable reduction of risk for allergies with an onset in adulthood. The risk was lowest in subjects reporting all three of these conditions, although based on small numbers. There was no clear association with other factors that could be regarded as a proxy for allergy severity, such as the proportion of the year subjects were affected by eczema and the frequency of use of antiasthmatic medication or of antiallergenic medication for hay fever. Our study did not include a biomarker for allergy, and some of the reported allergies might not have been immunoglobulin E mediated. Our study did, however, collect information on allergies reported as physician diagnosed, which for asthma and hay fever have been found to have high specificity and positive predictive values when assessed against clinical physiologic examination (34, 35). Our findings provide some evidence for immunologic causes of meningioma, because early onset asthma is more likely to be immunoglobulin E related than is late-onset asthma (36) and because people with multiple allergies are more likely to be truly allergic (37). The effect of age at onset of the condition and the absence of appreciably reduced risks in relation to conditions with recent onset do not provide support for the possibility of reverse causality, that is, that the

inverse association is due to immunosuppression by the tumor itself.

Most previous studies of meningioma and our study are case-control studies, with the inherent susceptibility to the biases described above. Only one paper, to our knowledge, has reported cohort analyses of the risk of meningioma (8): The rate ratio for meningioma was 0.84 (95 percent CI: 0.42, 1.68) in one cohort of subjects with self-reported allergic disease, but it was 2.44 (95 percent CI: 1.08, 5.51) in a second cohort with self-reported allergic disease reported in the same paper (table 3). The reasons for the discrepancy between the two cohorts were unclear. Several other cohort studies have reported on brain tumor risk in relation to allergies; they did not show reduced risks but have not reported on meningioma separately (22, 38, 39).

In conclusion, this study shows an inverse association of meningioma risk with a history of allergic disease, but with smaller risk reductions than for glioma. The possible reasons for this association need further exploration and include causality, confounding, or bias.

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