

COHORT STUDIES OF ASSOCIATION BETWEEN SELF-REPORTED ALLERGIC CONDITIONS, IMMUNE-RELATED DIAGNOSES AND GLIOMA AND MENINGIOMA RISK

Judith SCHWARTZBAUM^{1,2*}, Fredrik JONSSON¹, Anders AHLBOM¹, Susan PRESTON-MARTIN³, Stefan LÖNN¹, Karin C. SÖDERBERG¹ and Maria FEYCHTING¹

¹Division of Epidemiology, Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

²Division of Epidemiology and Biometrics, School of Public Health, Ohio State University, Columbus, OH, USA

³University of Southern California School of Medicine, Los Angeles, CA, USA

An inverse association between self-reported allergies and glioma and meningioma risk, has been previously observed in case-control studies. Approximately 27% (median) of the information on both glioma and meningioma in these studies, however, is collected from proxy respondents. In fact, the odds ratios (OR) among previous brain tumor studies are inversely related to the proportion of proxy respondents (Pearson correlation coefficient = -0.94 ; 95% CI = -1.00 to -0.65); this correlation suggests bias. We therefore constructed 3 cohorts based on the Swedish Twin, Hospital Discharge, and Cancer Registries. In Cohort I (14,535 people developed 37 gliomas and 41 meningiomas) and II (29,573 people developed 42 gliomas and 26 meningiomas) median time from self-report of allergies to brain tumor diagnosis was 15.4 years. Cohort III, which overlaps with Cohorts I and II (52,067 people developed 68 gliomas and 63 meningiomas), was linked to the Swedish Hospital Discharge Registry where pre-brain tumor immune-related discharge diagnoses were recorded. Allergies are inversely associated with glioma risk in Cohort I (Hazard ratio [HR] = 0.45 ; 95% CI = 0.19 – 1.07) and among high grade (III and IV, HR = 0.45 ; 95% CI = 0.11 – 1.92) but not low grade (I and II, HR = 2.60 ; 95% CI = 0.86 – 7.81) gliomas in Cohort II. In Cohort III, immune-related discharge diagnoses are also inversely associated with glioma (HR = 0.46 ; 95% CI = 0.14 – 1.49). There is no strong evidence against (and some for) the hypothesis that allergies reduce glioma risk.

© 2003 Wiley-Liss, Inc.

Key words: cohort studies; brain neoplasms; glioma; meningioma; hypersensitivity; autoimmune diseases

A consistent inverse association between self-reported allergic conditions and glioma risk is shown in case-control studies conducted since 1990 in Table I.^{1–7} The two most recent manuscripts^{1,2} contain detailed information on allergens, allergic symptoms, age at diagnosis, and duration of allergic conditions and most of this evidence points to a strong inverse relationship between allergic conditions and glioma risk. In 1999, Schlehofer *et al.*⁴ conducted a less detailed but larger (1,178 glioma cases) international study that included data from the Cicuttini *et al.*,³ Ryan *et al.*⁷ and Schlehofer *et al.*⁵ studies (Table I) and 5 additional study centers (not shown). Schlehofer *et al.*⁴ report that 7 of 8 study centers found that self-reported allergic conditions are inversely related to glioma risk. They also argue that further evidence for the validity of the allergic conditions–glioma association comes from the apparent absence of such a relationship between allergic conditions and meningioma indicating that the association between allergic conditions and glioma is not attributable to systematic underreporting by case patients.⁴

We undertook the present study to determine whether previous case-control findings of an inverse association between allergic conditions and other immune-related diseases and brain tumors would be replicated using a cohort design. We restricted our studies to glioma and meningioma because these tumors had been previously studied and there were sufficient numbers of them in our data sets to conduct meaningful statistical analyses.

MATERIAL AND METHODS

Cohort I consists of a sample of individuals from the Swedish Twin Registry birth cohort of same gender twins born between 1886–1925. This sample includes individuals who gave complete answers to questions concerning whether they ever had allergic conditions in response to a questionnaire mailed in 1967. Of 20,810 individuals in this cohort who were alive in 1968 and who had not been previously diagnosed with meningioma or glioma, 14,535 answered all 4 questions relating to allergic conditions (69.85% response rate). These participants were followed from January 1, 1968 until death, loss to follow-up (*e.g.*, moving to another country), diagnosis of first glioma or meningioma, or January 1, 2000, whichever occurred first. Vital status and glioma and meningioma diagnoses were determined from the Swedish Mortality and Cancer Registries using the unique number assigned to each Swedish citizen and resident.

Measurement of allergic conditions was based on 4 questions concerning whether the respondent ever had asthma (1st question), hay fever or allergic rhinitis (2nd question), and eczema as an infant (3rd question) or after infancy (4th question). An affirmative response to any of the 4 questions concerning these conditions was considered evidence of an allergic condition and a negative response to all 4 questions was considered absence of an allergic condition.

Cohort II consists of a sample from the Swedish Twin Registry birth cohort of same gender twins born between 1926–1958. This sample includes individuals who answered a question concerning the presence of allergic conditions in response to a questionnaire mailed in 1973. Of 36,536 individuals in this cohort who were alive in 1974, were not previously diagnosed with meningioma or glioma, and received the questionnaire, 29,573 answered the question concerning allergic conditions (80.94% response rate). These participants were followed from January 1, 1974 until death, loss to follow-up (*e.g.*, moving to another country), diagnosis of first glioma or meningioma, or January 1, 2000, whichever occurred first. Vital status and glioma and meningioma diagnoses were determined from the Swedish Mortality and Cancer Registries

Grant sponsor: Swedish Council for Working Life and Social Research; Grant number: 2001-2906.

*Correspondence to: Ohio State University, School of Public Health, Division of Epidemiology and Biometrics, Starling-Loving Hall, 320 W. Tenth Ave, Columbus, Ohio, 43210. Fax: +01-614-293-3937. E-mail: schwartzbaum.1@osu.edu

Received 30 September 2002; Revised 18 February 2003; Accepted 28 March 2003

DOI 10.1002/ijc.11230

TABLE I—CASE-CONTROL STUDIES OF ASSOCIATION BETWEEN ALLERGIES AND ADULT PRIMARY BRAIN TUMORS¹

Investigators (reference)	Cases	% proxy interviews	Allergy	Asthma
Brenner et al., 2002, (1)	489 gliomas	24.0	0.67 (0.52–0.86)	0.63 (0.43–0.92)
	197 meningiomas	11.0	0.98 (0.70–1.38)	0.86 (0.53–1.40)
	96 acoustic neuroma	4.0	1.02 (0.64–1.63)	1.34 (0.73–2.46)
Wiemels et al., 2002 (2)	407 gliomas	33.5	0.47 (0.33–0.67)	0.57 ¹ (0.38–0.86)
Schlehofer et al., 1999 (4)	1178 gliomas	26.7	0.59 (0.49–0.71)	0.75 (0.55–1.03)
	331 meningiomas	3.0	0.89 (0.65–1.22)	0.82 (0.46–1.44)
Cicuttini et al., 1997 (3) ²	416 gliomas	43.7	Not given	0.80 (0.50–1.20)
Schlehofer et al., 1992 (5) ²	115 gliomas	All types combined = 4.0	0.71 (0.5–1.0) ³	Not given
	81 meningiomas			
	30 acoustic neuromas			
Ryan et al., 1992 (7) ²	110 gliomas	Both types combined = 24.7	0.54 (0.33–0.89)	0.40 (0.14–1.15)
	60 meningiomas		1.14 (0.64–2.05)	1.09 (0.43–2.75)
Hochberg et al., 1990 (6)	160 astrocytomas	20.0	0.60 (0.40–1.00)	Not given

¹Odds ratios for those reporting symptoms of wheezing vs. those reporting no wheezing and no allergy.—²Included in Schlehofer et al., 1999 (4).—³Allergy includes asthma and eczema.

respectively using the unique number assigned to each Swedish citizen and resident.

Measurement of allergic conditions was based on a response to a single question concerning whether the respondent ever had asthma, croup (acute laryngotracheobronchitis of viral origin in child associated with “barking cough”), hay fever or eczema. Evidence for an allergic condition was based on a positive and evidence for absence of an allergic condition was based on a negative response to this question.

Cohort III includes all individuals (52,067 individuals) from both Cohorts I and II above who were alive in 1980 and who had not been previously diagnosed with glioma or meningioma, whether or not they received or answered an allergy questionnaire in 1967 or 1973 (this cohort contained 16,306 individuals from Cohort I and 35,761 individuals from Cohort II). In-patient discharge diagnoses from the Swedish Hospital Registry from 1980–1996 were recorded if they were classified as immune-related diseases. All discharge codes for all immune-related were identified for each patient whether these codes were primary discharge diagnoses or not. Identifying all such codes increased the sensitivity with which immune-related discharge diagnoses were measured.

Our category immune-related diseases included asthma, eczema, psoriasis and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, lupus erythematosus and pernicious anemia. Although Type I diabetes is considered to have autoimmune components, we were unable to identify the type of diabetes from the discharge code. We therefore included all discharge diagnoses of diabetes. This decision was justified by the Brenner *et al.* finding of an inverse association between a history of self-reported diabetes and glioma risk.¹ Thus, the primary independent variable was defined as a discharge diagnosis of an immune-related disease or diabetes or the absence of such a discharge diagnosis.

Participants were followed from January 1, 1980 until death, loss to follow-up (*e.g.*, moving to another country), diagnosis of first glioma or meningioma or January 1, 2000, whichever occurred first. As they were for Cohorts I and II, the Swedish Mortality and Cancer Registries were used to determine vital status and to identify individuals who had been diagnosed with glioma or meningioma.

Statistical Analysis

We used the Cox Proportional Hazards Regression Model to estimate age and gender adjusted hazard ratios (HRs). In addition, we adjusted HRs for body mass index (BMI) and smoking history but in no case did these 2 latter potentially confounding variables meaningfully alter the HRs. Therefore, all HRs shown in the present paper are adjusted for age and gender only. There was only 1 concordant glioma twin pair in Cohort I and 0 in Cohorts II and III. There were no concordant meningioma pairs. Reanalysis of

TABLE II—SELF-REPORTED OR DIAGNOSED ALLERGIC OR IMMUNE-RELATED CONDITIONS¹

Condition	Respondents (n)	% report condition ²
Cohort I (self-reported 1967)		
Asthma	14,535	3.38
Hay fever or allergic rhinitis	14,535	14.41
Eczema (infant)	14,535	1.89
Eczema (after infancy)	14,535	18.70
Allergic conditions ³	14,535	30.56
Rheumatoid arthritis	12,977	11.74
Cohort II (self-reported 1973)		
At least 3 colds/year	28,779	14.26
Allergic Conditions ⁴	29,573	16.87
Cohort III (discharge diagnoses 1980–1996)		
Asthma	52,067	1.30
Diabetes	52,067	4.25
Rheumatoid arthritis	52,067	0.58
Other immune-related diagnoses ⁵	52,067	2.89
Total immune-related discharge diagnoses	52,067	8.33

¹Cohort I born 1886–1925. Cohort II born 1926–1958. Immune-related discharge diagnoses in Cohort III born 1886–1958.—²Total % does not equal sum of individual conditions because some participants had at least 2 allergic conditions or discharge diagnoses.—³Asthma, hayfever, or infant or post-infancy eczema. Based on 4 questions that asked whether respondent “ever had” these conditions.—⁴Single question asked whether respondent “ever had” asthma, croup, hayfever, or eczema.—⁵All immune-related discharge diagnoses except asthma, diabetes, or rheumatoid arthritis.

data from Cohort I excluding the concordant glioma pair produced results that are identical to those shown.

Although we analyzed data on an individual level and ignored twin pairs, we corrected HR CIs for correlations within twin pairs.^{8–11} Corrected CIs were similar to uncorrected values, therefore, our results are shown without this dependency correction.

RESULTS

The 2 salient differences between Cohorts I and II are differences in the prevalence of allergic conditions, Cohort I has almost twice the prevalence of allergic conditions (Table II), and differences in their age distributions (Table III). Most individuals in Cohort II (99.03%) are found in the youngest quartile of age at the beginning of observation in Cohort I. Differences in the prevalence of allergic conditions between the 2 cohorts, however, cannot be attributed to differences in their age distributions because the percentage reporting allergic conditions in the youngest quartile of age in Cohort I is similar to the percentage reporting allergic conditions in the cohort as a whole (reporting allergies in youngest quartile of age = 31.72%, reporting allergies in all 4 quartiles =

TABLE III – COMPARISON OF DEMOGRAPHIC CHARACTERISTICS, BODY MASS INDEX, AND SMOKING HISTORY¹

Variable	Cohort I (Self-reported 1967)		Cohort II (Self-reported 1973)		Cohort III (Discharge diagnoses 1980-1996)	
	Allergic conditions ²	No allergic conditions	Allergic conditions ³	No allergic conditions	Immune-related disease	No immune-related disease
Total respondents (n)	4,442	10,093	4,989	24,584	4,337	47,730
Female (%)	55.67	55.52	57.49	51.25	54.81	53.16
Age start (median)	54.30	54.97	29.40	30.16	58.81	40.35
Age end (median)	79.22	79.40	55.03	55.71	74.35	60.11
Follow-up (median)	26.12	26.02	26.02	26.03	19.07	20.01
Smoking respondents (n)	4,144	9,402	4,943	24,383	3,339	41,621
Non-smoker (%)	52.94	57.96	42.93	44.38	48.70	47.67
Smoker (%)	33.37	30.93	43.35	43.40	39.20	40.01
Former smoker (%)	13.68	11.11	13.72	12.23	12.10	12.32
Body mass index respondents (n)	4,418	10,026	4,919	24,218	3,847	40,939
Body mass index (median) ⁴	26.11	24.34	21.19	21.60	24.49	22.31

¹Cohort I born 1886–1925. Cohort II born 1926–1958. Immune-related discharge diagnoses in Cohort III born 1886–1958.—²Four questions asked whether respondent “ever had” asthma, hay fever, or infant or post-infancy eczema.—³Single question asked whether respondent “ever had” asthma, croup, hay fever, or eczema.—⁴Body mass index is defined as weight in kilograms divided by the square of height in meters.

TABLE IV – AGE- AND GENDER-ADJUSTED HAZARD RATIOS AND 95% CI FOR ASSOCIATIONS BETWEEN SELF-REPORTED ALLERGIC CONDITIONS, RHEUMATOID ARTHRITIS, AND FREQUENT COLDS (COHORTS I AND II) OR DISCHARGE DIAGNOSIS OF IMMUNE-RELATED DISEASES (COHORT III) AND GLIOMA OR MENINGIOMA

	Glioma	No glioma ¹	Hazard ratio	Meningioma	No meningioma ¹	Hazard ratio
Cohort I ²						
Self-reported hay fever or allergic rhinitis						
No	33	12,407	1.00	36	12,404	1.00
Yes	4	2,091	0.74	5	2,089	0.85
95% CI			0.26–2.08			0.33–2.17
Self-reported eczema after infancy						
No	33	11,784	1.00	35	11,782	1.00
Yes	4	2,714	0.52	6	2,711	0.72
95% CI			0.19–1.48			0.30–1.70
Self-reported allergic conditions ³						
No	31	10,062	1.00	30	10,063	1.00
Yes	6	4,436	0.45	11	4,430	0.84
95% CI			0.19–1.07			0.42–1.68
Self-reported rheumatoid arthritis						
No	27	11,426	1.00	36	11,416	1.00
Yes	3	1,521	0.85	3	1,521	0.63
95% CI			0.25–2.84			0.25–1.63
Cohort II						
Self-reported allergic conditions ⁴						
No	35	24,549	1.00	17	24,573	1.00
Yes	7	4,982	1.09 ⁵	9	4,982	2.44 ⁵
95% CI			0.48–2.48			1.08–5.51
Self-reported at least 3 colds/year						
No	31	24,644	1.00	19	24,664	1.00
Yes	8	4,096	2.05 ⁶	7	4,097	2.50 ⁶
95% CI			0.92–4.60			1.01–6.15
Cohort III						
Diagnosis of immune-related condition						
No	65	47,665	1.00	58	47,675	1.00
Yes	3	4,334	0.46	5	4,332	0.69
95% CI			0.14–1.48			0.27–1.73

¹Totals for non-cases differ slightly between glioma and meningioma because dates of tumor diagnosis determine whether person is included in cohort.—²Questions asked whether respondent “ever had” allergic condition.—³Reporting at least one of the following: asthma, hay fever, infant or post-infancy eczema.—⁴Single question asked whether respondent “ever had” asthma, croup, hayfever or eczema.—⁵Adjusted for colds.—⁶Adjusted for allergic conditions.

30.56%). Further, the percentage reporting allergic conditions in Cohort I decreases rather than increases with age so that Cohort II allergic condition percentages would not necessarily increase as this cohort ages.

Table III further reflects disparities between Cohorts I and II by showing that median follow-up times for these cohorts are similar although Cohort I was observed from 1968–2000 (32 years) whereas Cohort II was only observed from 1974–2000 (26 years). The similarity of median follow-up times again reflects differences in the age distributions of these two cohorts. In 2000, at the end of observation for Cohort I, only 35.34 % of the cohort members

were still alive and had not been diagnosed with a brain tumor. The percentage in this category for Cohort II is 93.61%. That is, members of Cohort II were more likely to be alive during the observation period.

Results for glioma and meningioma in Cohorts I and III (Table IV) are similar to those found in the previous literature (Table I). In Cohort I, HRs for self-reported allergic conditions (asthma, hay fever and eczema in infancy and after infancy) are <1 for both glioma and meningioma as they are for allergic rhinitis, adult eczema and rheumatoid arthritis (the number of glioma and meningioma patients reporting asthma and infant eczema was too

small to allow estimation of a separate HR for these conditions). In Cohort III diagnoses of immune-related or allergy-related conditions are inversely associated with glioma and meningioma risk. Findings for allergic conditions in Cohort II differ from both those in Cohort I and for glioma and meningioma. Hazard ratios for the variable having at least 3 colds/year are similar for glioma and meningioma.

Median dates of diagnosis for cases shown in Table IV in Cohorts I and II differ by 9 years (1980 and 1989) and span the introduction and use in 1984 of X-ray computed tomography (CT scan) in Sweden. Therefore, we would expect Cohort II to have a greater proportion of low grade gliomas (Grades I and II) than Cohort I. This is, in fact, true with 33.3% of gliomas in Cohort II being low grade whereas only 18.9% of tumors in Cohort I are low grade. The percentage of low grade gliomas in Cohort III is 20.5.

Although there are not sufficient numbers of observations to conduct a formal test for statistical interaction between histologic grade and allergic conditions, we stratified the glioma analyses in Table IV on low and high grade (Table V). When the analysis is limited to gliomas diagnosed after the introduction of CT scans (1984), results are more extreme (Cohort I, high grade, HR = 0.24; 95% CI = 0.30, 1.89 [there was only 1 low grade glioma case diagnosed in Cohort I after 1984]; Cohort II, low grade, HR = 3.68; 95% CI = 0.98, 13.7, Cohort II, high grade, of 21 cases diagnosed, none reported allergies, although 17.1 % of controls reported allergies [Fisher's exact test, $p = 0.04$]). Also shown in Table V are results of analyses stratified on median age at diagnosis of Cohort II.

When results for Cohorts I and II are restricted to individuals who reported allergic conditions 5 years before diagnosis of brain tumors, HRs are similar to those reported in Table IV (Cohort I: glioma, HR equals; 0.41; 95% CI = 0.16, 1.07; meningioma, HR = 0.85; 95% CI = 0.40, 1.84; Cohort II glioma, HR = 1.00; 95% CI = 0.42, 2.41; meningioma, HR = 2.39; 95% CI = 1.14, 7.25). Although the number of brain tumor cases with immune-related discharge diagnoses is small, a reanalysis of these data using only those immune-related discharge diagnoses made 5 years before brain tumor diagnosis, results are similar (HR glioma = 0.62 [95% CI = 0.19, 1.99] HR meningioma = 0.37 [95% CI = 0.09, 1.54]).

DISCUSSION

These are the first cohort studies to focus on the association between allergic and immune-related conditions and glioma and meningioma risk and our results are mixed. Findings in Cohorts I and III for both glioma and meningioma are consistent with previous case-control observations (Table I). These findings, however, are based on a small number of exposed cases (especially for Cohort III where there are only 3 exposed glioma and 5 exposed meningioma cases) and may therefore be unstable. Not consistent with previous research are overall observations in Cohort II of no association between allergic conditions and glioma risk and a relatively strong positive association between allergic conditions and meningioma risk.¹⁻⁷

We found an inverse association between allergic and immune-related conditions and meningioma in both Cohorts I and III (Table

IV). This result is consistent with the findings of Schlehofer *et al.*⁴ who reported a pooled OR (pooled over 8 study centers) for meningioma of 0.89 (95% CI = 0.65, 1.22) (Table I). In Figure 1 of their study they show that when OR for both meningioma and glioma are reported, the allergy-meningioma ORs are similar to the allergy-glioma ORs but slightly closer to the null value (except for the study conducted in Stockholm where the allergy OR is 1.0 for glioma and >1.0 for meningioma).⁴ It should be noted that although Brenner *et al.*, also observed ORs for the associations between asthma, eczema, hayfever and meningioma of <1.0, their summary OR for all allergic conditions combined shows no association with meningioma (OR = 0.98; 95% CI = 0.70, 1.38).¹ Ryan *et al.*, however, did not observe an inverse association between allergies and meningioma risk (Table I, OR equals; 1.14; 95% CI = 0.64, 2.05).⁷

Differences in the consistency and strength of the inverse associations between allergies and glioma and allergies and meningioma may be explained by the use of fewer proxy interviews for meningioma cases (Table I). In addition, Schlehofer *et al.* evaluated 1,178 glioma but only 331 meningioma cases.⁴ Their results for meningioma may have been stronger (or at least statistically significant) had they observed larger numbers of such cases. Brenner *et al.*¹ and Ryan *et al.*⁷ also examined fewer meningioma than glioma cases (Brenner *et al.* evaluated 489 glioma and 197 meningioma cases; Ryan *et al.* 110 glioma and 60 meningioma cases).

We cannot offer a definitive explanation for conflicting findings for overall associations between allergic conditions and brain tumors in Cohorts I and II (Table IV). We speculate, however, that differences may reflect both changes in diagnostic technology and ways that individuals are selected into the population of brain tumor patients. Berkson¹² observed that admission to the hospital is more probable for individuals who have 2 diseases than it is for individuals who have only 1. Presumably people with more than 1 disease are similarly selected for diagnosis. Because more members of Cohort II were diagnosed after the introduction of CT scans than were members of Cohort I (see Results), we speculate that allergic conditions themselves increased the probability of having a CT scan and therefore of being diagnosed with meningioma or low grade glioma in Cohort II (Table V). This selection bias would not be expected to work to the same extent for high grade glioma because most individuals with high grade glioma are eventually diagnosed.¹³⁻¹⁵

Another possible source of the difference between findings for Cohorts I and II may be underreporting of allergic conditions in Cohort II (16.87 %, Table II). The prevalence of allergic conditions that we observe in Cohort I (30.56%, Table II) is similar to that reported by Brenner *et al.* and to the prevalence of allergic conditions found in population-based studies in the United States.^{1,16} In addition, the percentage reporting hay fever or allergic rhinitis in Cohort I [14.41%] is also close to that observed by Brenner *et al.*¹ [14.03%]. That the reported prevalence of hayfever is similar to that observed in Cohort II for all allergic conditions (16.87 %, Table II), suggests that eczema may have been underreported in Cohort II. Adult eczema accounts for 18.70% (Table II) of the allergic conditions in Cohort I and this figure is consistent with a recent Swedish survey that found a self-reported prevalence

TABLE V - AGE AND GENDER-ADJUSTED ASSOCIATION BETWEEN ALLERGIC CONDITIONS AND GLIOMA AND MENINGIOMA¹

	Cohort I		Cohort II	
	Glioma	Meningioma	Glioma	Meningioma
Low grade (I and II)	0.38 (0.05-3.13)	—	2.60 (0.86-7.81)	—
High grade (III and IV)	0.46 (0.18-1.21)	— ²	0.45 (0.11-1.92)	—
Below median age	— ²	—	0.63 (0.18-2.21)	1.81 (0.39-8.43)
Median age or older	0.45 (0.18-1.07)	0.84 (0.42-1.68)	1.51 (0.50-4.60)	2.18 (0.67-7.06)

¹Hazard ratio and 95% CI. Median age at diagnosis of glioma cases is 49.5 years and meningioma cases is 48.8 years.—²Number of cases insufficient to produce estimate of hazard ratio.

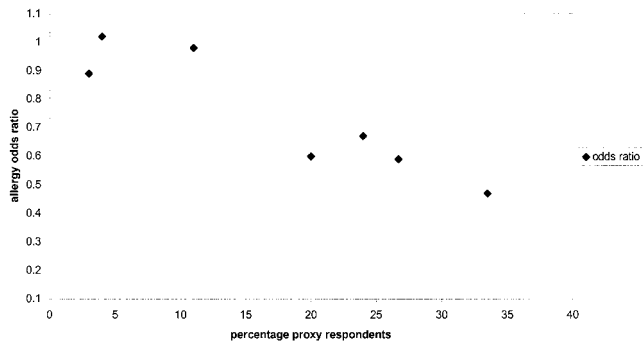


FIGURE 1 – Association between percentage of proxy respondents and allergy ORs.

of hand eczema alone of 19% among Swedish women.¹⁷ The underreporting of eczema may be attributed to the fact that information on 4 specific allergic conditions in Cohort II was collected in response to a single question on 3 respiratory conditions (asthma, croup and hayfever) and eczema. Even if eczema is underreported in Cohort II, however, neither our results (Table IV) nor those of others suggest a subset of allergic conditions that increases rather than decreases glioma or meningioma risk.^{1,2}

If differences in findings between Cohorts I and II are attributable to age, then one would expect younger cases (that characterize Cohort II) to be positively- and older cases to be negatively-associated with glioma or meningioma risk. Results of age stratification (Table V) do not follow this pattern, however, further age stratification (well beyond the sample size limits of the present data set) would be required to be certain that age or other demographic variables do not modify the allergic condition-brain tumor association.

Results from Cohorts I and II are based on self-reported allergic conditions. Validity of self-reported asthma is relatively high when the gold standard is clinical diagnosis. Toren *et al.*¹⁸ reviewed the literature on the sensitivity and specificity of self-reported asthma questions and found average sensitivity of 68% (range 48–100%) and average specificity of 94% (78–100%). There is one known study validating allergic rhinitis self-reports. Annesi-Maesano *et al.*¹⁹ developed and assessed a questionnaire to measure allergic rhinitis. Using a specialist's diagnosis of allergic rhinitis together with a positive skin prick test as the gold standard, they found 74% sensitivity and 83% specificity for their 8 questions. Our allergic condition variables are based on fewer questions and may therefore be subject to more error, however, we have no reason to believe that this error depended on case status as it might in a case-control study. We therefore assume that non-differential error biased the allergic condition HRs toward the null.

To determine the validity of Swedish Hospital Registry discharge diagnoses, Nilsson *et al.*²⁰ organized a committee of physicians trained in disease classification. This committee evaluated medical records and all other relevant documentation (radiation reports, operation reports, pathology reports, *etc.*) of hospital stays of 995 patients whose discharge diagnoses were reported in the Swedish Hospital Registry. The evaluators found that 0.7% of the primary diagnoses were incorrect due to data entry errors, 5.9% had been incorrectly coded (*i.e.*, the primary diagnosis in the medical records was correct but the diagnostic code used was wrong), and 10.7% of the primary diagnoses found in the medical records and subsequently in the Swedish Hospital Registry were wrong. In the last category, the evaluators decided that 3% could, with liberal judgment, be regarded as correct, whereas 3% had a primary diagnosis that should have been reported as a secondary diagnosis. Overall, 17.3% of the discharge diagnoses in the Hospital Registry had an error in the primary diagnosis. These percentages, however, are based on coding on a 5-digit level. Dis-

charge diagnoses that we used in the present study would have somewhat less error because we used a 4-digit level code (with broader diagnostic categories than the 5-digit code) and included all discharge diagnoses whether they were the primary diagnosis or not.

Nilsson *et al.*²⁰ also report results for asthma, one of the diseases that we designated as immune-related. Fourteen cases received a main diagnosis of asthma. The evaluators identified 1 case of the 14 that should not have had asthma as a primary diagnosis. The authors provide no information as to whether asthma was an appropriate secondary diagnosis. In addition, they found no false negative asthma patients (patients who should have had asthma as a main diagnosis, but did not).

Individuals with a discharge diagnosis of immune-related disease may differ from individuals who have immune-related disease but are not hospitalized. For example, those hospitalized may have more severe illness, or in the case of diabetes, may fail to control their diabetes. By including all discharge codes (not just the primary discharge diagnosis [Material and Methods]), however, our discharge diagnosis groups may be somewhat more representative of non-hospitalized patients than they would have been had we studied primary discharge diagnoses only. Nonetheless, those discharged with immune-related disease clearly do not represent all patients with immune-related disease. Those hospitalized, however, may be thought of as being in the highest dose “exposure” group to the extent that hospitalization is an indicator of severity of disease. In this sense, it is appropriate to compare the proportion of brain tumor patients among hospitalized immune-related disorder patients to the proportion with and without immune-related disorders but not hospitalized for immune-related disorders. This comparison, however, can only lead to inferences about the association between severe immune-related disease and brain tumor risk. In addition, if severity of immune-related disease does not matter (that is, if there is no dose-response relationship), then the brain tumor HRs will be biased toward the null.

Berksonian selection bias could have produced HRs >1.0 in Cohort III especially for meningioma (as perhaps it did in Cohort II). This bias could have occurred had individuals hospitalized for immune-related conditions been more likely to be diagnosed with meningioma. We do not, however, observe this result (Table V). Were the sample size larger, we would have adjusted for time of diagnosis and may have seen HRs closer to the null for meningioma patients diagnosed after the introduction of the CT scan.

Another potential source of bias is that the Swedish Hospital Registry monitored only 80% of Cohort III for discharge diagnoses until 1987 but we included discharge diagnoses beginning in 1980. Surveillance, however, was based on geographic region and those regions monitored had brain tumor incidence rates that were similar to those regions that were not monitored.²¹ We consider this figure analogous to an 80% response rate that is not unusual and if independent of outcome status would be expected to pull HRs toward their null values.²²

Results of our present study are mixed so it is important that they be interpreted in the context of previous work. Findings concerning allergic conditions and glioma form part of a larger body of epidemiological evidence that suggests that glioma development is influenced by the immune system. For example, in their hospital-based case-control study, Brenner *et al.*¹ found that autoimmune diseases, like allergies, are negatively related to glioma risk. Additional evidence for protection against glioma afforded by the immune system is provided by Wrench *et al.*²³ who observed that glioma patients have lower antibody titers to varicella zoster virus and also report fewer chicken pox infections than do controls. Further evidence for an association between immune-related conditions and glioma is provided by epidemiologic studies showing that allergic conditions may play a protective role in tumors at sites other than the brain (*e.g.*, Negri *et al.*).²⁴ Finally, there are experimental observations that support a risk-reducing effect of allergies on glioma. For example, interleukin-4 (IL-4), one of the most

important cytokines in the allergic response, inhibits glioma cell growth *in vitro*, possibly because of its anti-angiogenic properties.²⁵

The most obvious potential problem with previous evidence is the use of a relatively large proportion of proxy-reported cases (in Table I, median percentage of cases interviewed by proxy = 26.7% [weighted by number of cases]). As shown in Figure 1 there is an inverse association between the percentage of proxy-reported cases and the allergy ORs for studies in Table I for which there is histology-specific information on the percentage of proxy-reported cases^{1,2,4,6} (Pearson correlation coefficient [ρ] = -0.94 ; 95% CI equals; -1.00 , -0.65). The implications of Figure 1 are that a large percentage of the variation among the allergy ORs is attributable to proxy reports. Also, differences among ORs for glioma and the benign tumors, meningioma and acoustic neuroma, may be partly attributable to the fact that the ORs for these benign tumors are based on fewer proxy responses.

Note, however, that Figure 1 is based on aggregate data in which the units are studies rather than individuals. Therefore conclusions founded on these data may be subject to the ecologic fallacy. That is, the association between proxy-reported cases and allergy ORs may be present between but not within studies. In their case-control study of 405 incident glioma cases, however, Wiemals *et al.*² found that the allergy OR for proxy-reported cases was only 0.31 (95% CI = 0.20, 0.49) whereas the ORs for self-reported cases was 0.65 (95% CI = 0.43, 0.97) indicating that the relationship between reporting mode and allergy ORs is also present within at least 1 study.

Berkson's selection bias may have distorted ORs in the Brenner *et al.*¹ hospital-based case-control study where an inverse association between reported history of autoimmune disease and glioma risk was observed (OR = 0.49; 95% CI = 0.35, 0.69). The control group selected in the hospital might have had more autoimmune disease than the glioma group because most individuals with glioma are eventually hospitalized whereas those with autoimmune disease would have been preferentially selected into the control group.¹³ Thus, a spurious inverse association between autoimmune disease and glioma might have been observed. In addition, meningiomas and acoustic neuromas are more likely to be discovered on autopsy than is glioma^{13-15,26} thus this hypothetical selection bias may work in the reverse direction for these benign tumors.

In summary, previous research together with the present work is not definitive and further research needs to be conducted to determine the validity of the association between allergic conditions, immune-related diseases and brain tumor risk. At the same time, research on allergic conditions and immune-related disease seeks to develop interventions or treatments that will eradicate these diseases. Ironically, the hygiene hypothesis suggests that the present asthma epidemic results from eradication of infectious diseases that previously functioned to lower asthma risk.²⁷ If the present study becomes part of a body of research that shows that immune-related conditions decrease brain tumor risk then treatments for such conditions should be developed that do not interfere with the mechanisms by which these conditions lower brain tumor risk.

REFERENCES

- Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG, Black PM, Inskip PD. History of allergies and autoimmune diseases and risk of brain tumors in adults. *Int J Cancer* 2002;99:252-9.
- Wiemals JL, Wiencke JK, Sison JD, Miike R, McMillan A, Wrensch M. History of allergies among adults with glioma and controls. *Int J Cancer* 2002;98:609-15.
- Cicuttini FM, Hurley SF, Forbes A, Donnan GA, Salzberg M, Giles GG, McNeil JJ. Association of adult glioma with medical conditions, family and reproductive history. *Int J Cancer* 1997;71:203-7.
- Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, Ahlbom A, Choi WN, Giles GG, Howe GR, Little J, Menegoz F, Ryan P. Role of medical history in brain tumour development. Results from the international adult brain tumour study. *Int J Cancer* 1999;82:155-60.
- Schlehofer B, Blettner M, Becker N, Martinsohn C, Wahrendorf J. Medical risk factors and the development of brain tumors. *Cancer* 1992;69:2541-7.
- Hochberg F, Toniolo P, Cole P, Salzman M. Non occupational risk indicators of glioblastoma in adults. *J Neurooncol* 1990;8:55-60.
- Ryan P, Lee MW, North B, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer* 1992;51:20-7.
- Wei D, Lin D, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *JASA* 1989;84:1065-73.
- Iwasaki K, Rogers LR, Estes ML, Barna BP. Modulation of proliferation and antigen expression of a cloned human glioblastoma by interleukin-4 alone and in combination with tumor necrosis factor- α and/or interferon- γ . *Neurosurgery* 1993;33:489-94.
- Aldape K, Simmons ML, Davis RL, Miike R, Wiencke J, Barger G, Lee M, Chen P, Wrensch M. Discrepancies in diagnoses of neuroepithelial neoplasms: the San Francisco Bay Area Adult Glioma Study. *Cancer* 2000;88:2342-9.
- White H. Maximum likelihood estimate of misspecified models. *Econometrica* 1982;50:1-25.
- Schieve L. Berkson's fallacy. In: Gail M, ed. *Encyclopedia of epidemiologic methods*. Chichester: John Wiley and Sons, Ltd., 2000.
- Annegers JF, Schoenberg BS, Okazaki H, Kurland LT. Epidemiologic study of primary intracranial neoplasms. *Arch Neurol* 1981;38:217-9.
- Helseth A. Incidence and survival of intracranial meningioma patients in Norway 1963-1992. *Neuroepidemiology* 1997;16:53-9.
- Stanczek W, Janisch W. Epidemiologic data on meningiomas in East Germany 1961-1986: incidence, localization, age and sex distribution. *Clin Neuropathol* 1992;11:135-41.
- Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2000;21:1-6.
- Socialstyrelsen, Miljöhälsorapport 2001. Karolinska Institutet: Institute of Environmental Medicine, 2001.
- Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993; 104:600-8.
- Annesi-Maesano I, Didier A, Klossek M, Chanal I, Moreau D, Bousquet J. The score for allergic rhinitis (SFAR): a simple and valid assessment method in population studies. *Allergy* 2002;57:107-14.
- Nilsson AC, Spetz CL, Carsjö K, Nightingale R, Smedby B. [Reliability of the hospital registry. The diagnostic data are better than their reputation]. *Lakartidningen* 1994;91:598, 603-5.
- Swedish Oncological Centres. Atlas of cancer incidence in Sweden: a collaboration between six oncological centres in Sweden. Stockholm: 1995.
- Rothman K, Greenland S. *Modern epidemiology*. Philadelphia: Lippincott-Raven, 1998.
- Wrensch M, Weinberg A, Wiencke J, Masters H, Miike R, Barger G, Lee M. Does prior infection with varicella-zoster virus influence risk of adult glioma? *Am J Epidemiol* 1997;145:594-7.
- Negri E, Bosetti C, La Vecchia C, Levi F, Tomei F, Franceschi S. Allergy and other selected diseases and risk of colorectal cancer. *Eur J Cancer* 1999;35:1838-41.
- Saleh M, Wiegman A, Malone Q, Styli SS, Kaye AH. Effect of in situ retroviral interleukin-4 transfer on established intracranial tumors. *J Natl Cancer Inst* 1999;91:438-45.
- Anderson TD, Loevner LA, Bigelow DC, Mirza N. Prevalence of unsuspected acoustic neuroma found by magnetic resonance imaging. *Otolaryngol Head Neck Surg* 2000;122:643-6.
- Maticardi PM, Ronchetti R. Are infections protecting from atopy? *Curr Opin Allergy Clin Immunol* 2001;1:413-9.