

## HISTORY OF ALLERGIES AND AUTOIMMUNE DISEASES AND RISK OF BRAIN TUMORS IN ADULTS

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**To explore a possible influence of the immune system in the development of brain tumors, we evaluated the relationship between history of allergies and autoimmune diseases and risk of brain tumors within a large, hospital-based case-control study. Cases ( $n = 782$ ) were patients recently diagnosed with glioma ( $n = 489$ ), meningioma ( $n = 197$ ) or acoustic neuroma ( $n = 96$ ) at hospitals in Boston, Phoenix and Pittsburgh (USA). Controls ( $n = 799$ ) were patients hospitalized for a variety of nonmalignant conditions and frequency-matched to cases by hospital, age, sex, race/ethnicity and distance of residence from hospital. Research nurses collected data by personal interview of patients. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression. There was a significant inverse association between glioma and history of any allergies (OR = 0.67, 95% CI = 0.52–0.86) or autoimmune diseases (OR = 0.49, 95% CI = 0.35–0.69). No significant associations were evident for meningioma or acoustic neuroma with history of any allergies. An inverse association was observed between meningioma and history of autoimmune diseases (OR = 0.59, 95% CI = 0.38–0.92). There was a suggestion of interaction between allergies and autoimmune diseases on risk of glioma ( $p = 0.06$ ), with subjects having both conditions being at lowest risk (OR = 0.24, 95% CI = 0.14–0.42). Among the specific conditions, asthma and diabetes showed the most consistent associations (OR = 0.63, 95% CI = 0.43–0.92 and OR = 0.44, 95% CI = 0.27–0.70, respectively). Our results add to evidence that persons with allergies or autoimmune diseases are at reduced risk of glioma. The basis of the associations is not clear, but they might imply a role of immunologic factors in the development of brain tumors.**  
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**Key words:** case-control studies; brain neoplasms; glioma; meningioma; neuroma, acoustic; adult; risk factors; hypersensitivity; autoimmune diseases

Despite much study, the etiology of brain tumors remains largely unknown. Several familial cancer syndromes, such as neurofibromatosis, tuberous sclerosis and Li-Fraumeni syndrome, are associated with increased risk but these account for less than 5% of all cases.<sup>1–3</sup> Only 1 environmental risk factor, ionizing radiation, is well established.<sup>1</sup> In the continued search for clues to the etiology of brain tumors, it is important to consider factors that might protect against brain tumors as well as factors that might cause them. Recent studies raise the question of whether persons with a hyperstimulated immune system might be at reduced risk of brain cancer.

Results of case-control studies published during the past decade<sup>4–9</sup> suggest an approximately 40% lower risk of glioma, but not meningioma, associated with a history of allergic diseases, including asthma, eczema and others. Evidence from prospective studies is very limited, largely because brain cancer is an uncommon disease.<sup>10</sup> Diabetes also has been negatively associated with risk of glioma in some studies<sup>5,11</sup> but not in others.<sup>7,8,12,13</sup> Several cohort studies of patients with rheumatoid arthritis,<sup>14</sup> pernicious anemia<sup>15</sup> and multiple sclerosis<sup>16,17</sup> failed to demonstrate a decreased risk of brain tumors. The findings regarding infections and

brain tumors, while suggestive of a negative association, are mixed.<sup>5,7,8,18,19</sup> Although available data on a broad range of specific medical disorders are inconsistent, immunologically mediated conditions warrant further investigation as factors that might interfere with brain tumor development.

Here, we report the associations between history of allergies and autoimmune diseases and risk of glioma, meningioma and acoustic neuroma based on data from a large, case-control study conducted at 3 hospitals in the United States. Associations with prior infections will be addressed in a separate report.

### MATERIAL AND METHODS

#### Study population and setting

Details of our study were described previously.<sup>20</sup> Briefly, our study was conducted from June 1994 to August 1998 at Brigham Hospital and Women's Hospital (Boston, MA), St. Joseph's Hospital and Medical Center (Phoenix, AZ) and Western Pennsylvania Hospital (Pittsburgh, PA). Eligible cases were patients newly diagnosed with histologically confirmed intracranial glioma or neuroepitheliomatous tumors ( $n = 489$ ; International classification of disease [ICD]-O-2 codes 9380–9473 and 9490–9506), meningioma ( $n = 197$ ; ICD-O-2 9530–9538) or acoustic neuroma ( $n = 96$ ; 4 diagnosed radiologically; ICD-O-2 9560) at the participating hospitals. Patients had to be at least 18 years old and reside within 50 miles of the hospital (or within Arizona for the Phoenix hospital) at the time of diagnosis and understand English or Spanish. Of the potentially eligible cases invited to participate in our study, 92% ( $n = 782$ ) agreed to do so.

Controls were patients admitted for a variety of nonmalignant conditions. They were frequency-matched (1:1) to the total case series by hospital, age (in 10-year strata), sex, race or ethnicity and distance of residence from hospital. Of the potentially eligible controls contacted, 86% ( $n = 799$ ) participated. The most common reasons for hospital admission among controls were injuries and poisoning ( $n = 197$ ; ICD-9 800–999, V01–V82, E800–E999) and diseases of the circulatory ( $n = 179$ ; ICD-9 390–459), musculoskeletal ( $n = 172$ ; ICD-9 710–739), digestive ( $n = 92$ , ICD-9 520–579) and nervous systems ( $n = 58$ ; ICD-9 320–389). Analyses for particular allergic or autoimmune diseases excluded controls known to have been admitted to the hospital because of that illness.

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**TABLE 1**—SELECTED CHARACTERISTICS OF PATIENTS WITH BRAIN TUMORS AND CONTROLS<sup>1</sup> FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Characteristic	Controls (n = 799) %	Glioma (n = 489) %	Meningioma (n = 197) %	Acoustic neuroma (n = 96) %
Location of hospital				
Phoenix	51	50	50	75
Boston	28	31	40	23
Pittsburgh	22	19	10	2
Age at interview, <sup>2</sup> years				
18–39	31	27	16	18
40–59	39	36	45	53
60–90	30	37	39	29
Sex				
Female	55	43	77	63
Male	45	57	23	37
Race or ethnic group				
Non-Hispanic white	89	91	83	93
Hispanic white	7	5	7	6
Black	2	2	5	0
Other or unknown	2	2	5	1
Educational level				
<High school	13	13	12	5
High school or GED	29	25	29	29
1–3 years of college	31	27	35	22
4 years of college	13	18	12	24
Graduate or professional school	11	14	12	19
Unknown	3	3	1	1
Self-reported annual household income				
<\$15,000	16	9	8	2
\$15,000–\$24,999	14	15	16	10
\$25,000–\$34,999	13	14	15	12
\$35,000–\$49,999	17	17	16	27
\$50,000–\$74,999	18	16	16	17
≥\$75,000	16	21	20	26
Unknown	6	8	9	5

<sup>1</sup>The location of the hospital, the age at the time of the interview, the sex and the race or ethnic group were matching variables. GED denotes general equivalency diploma.<sup>2</sup>The age of patients at the time of the interview was nearly identical to the age at the time of diagnosis of the tumor (for cases) and the age at the time of hospital admission.

#### Data collection

After obtaining informed consent, information was collected about a variety of risk factors by means of a computer-assisted personal interview conducted in the hospital. Because the nurse interviewers had to verify the eligibility for cases and select eligible controls, they were not blinded to the subject's case or control status. For our present analysis, we used data from questions inquiring about history of physician-diagnosed asthma, eczema, hay fever, rheumatoid arthritis, lupus erythematosus, multiple sclerosis, diabetes and pernicious anemia as well as age or year first diagnosed with the condition of interest. In addition, subjects were asked whether they were aware of certain substances or exposures that caused them serious difficulty breathing within a few minutes of exposure and, if so, to list the substances (open question). All answers were recorded and later classified into the following categories: allergy to medication, insects, food, chemicals or other substances (grouping allergies to plants, dust or animals). No specific questions were made about dermal, digestive or other reactions toward each of the reported allergens. History of any allergies (either physician-diagnosed or self-perceived) as well as any autoimmune diseases also was considered. Information was not collected concerning treatments for these diseases. No attempt was made to differentiate between atopic and nonatopic allergies or insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM). The interview included questions about sociodemographic characteristics and other possible risk factors. Information on mental status changes at, or prior to, the time of brain tumor diagnosis was abstracted from the medical records and coded as a yes/no variable. A case subject was considered mentally or cognitively impaired if there was any mention of the following: memory problem, confusion, cognitive difficulties, decline in level of consciousness, speech problems,

forms of aphasia that include cognitive impairment, personality changes, hallucinations or strange behavior.

Proxy interviews were conducted, usually with the spouse, if the subject was very ill or had died. For the medical history part of the interview, proxies were necessary for 24% of patients with glioma, 11% with meningioma, 4% with acoustic neuroma and 4% of the controls.

#### Statistical analysis

The odds ratio (OR) was used as the measure of association between history of prior medical conditions and brain tumor risk. Both conditional and unconditional multivariate logistic regression models<sup>21</sup> were fitted to estimate ORs and compute 95% confidence intervals (95% CI) and likelihood-ratio tests (2-sided tests at  $\alpha$  level of 0.05). The results were similar and we present the findings from the unconditional analyses here. Separate analyses were conducted for the different histologic types of brain tumors. In addition to matching variables, possible confounding variables that were considered included educational level, annual household income, urbanicity, marital status, religion, number of siblings, radiotherapy to the head, cigarette smoking and body mass index (BMI). We also evaluated possible effect modification by age at diagnosis and duration of allergy or autoimmune disease, admission hospital, age at tumor diagnosis, sex and education. To assess possible reporting bias, risks were estimated including and excluding proxy respondents and cases with mention of cognitive impairment. Sensitivity of results to the composition of the control series was evaluated by alternatively excluding subgroups with different discharge diagnoses (trauma or diseases of circulatory, musculoskeletal, digestive system or all others combined) and refitting regression models.

TABLE II—HISTORY OF ANY ALLERGY<sup>1</sup> OR AUTOIMMUNE DISEASE<sup>2</sup> BY SELECTED CHARACTERISTICS AMONG CONTROLS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Characteristic	Any allergy		Any autoimmune disease	
	% <sup>3</sup>	<i>p</i> -value for trend or heterogeneity	% <sup>3</sup>	<i>p</i> -value for trend or heterogeneity
Location of hospital				
Boston	41	0.72	23	<0.01
Phoenix	38		16	
Pittsburgh	38		29	
Age at interview, years				
18–39	36	0.21	11	<0.01
40–59	39		18	
60+	41		35	
Sex				
Female	45	<0.01	24	0.04
Male	31		18	
Number of siblings				
0	44	0.52	28	0.05
1	41		16	
2	36		19	
3–4	36		18	
5–20	39		28	
Education				
<High school	30	0.02	30	0.04
High school, GED or 1–3 years of college	39		22	
4 years of college or graduate or professional school	44		17	
Usual place of residence				
Urban	37	0.34	20	0.76
Suburban	41		20	
Rural	33		24	
Diagnostic subgroups				
Trauma, injury and poisoning	34	0.24	14	0.03
Diseases of circulatory system	38		27	
Diseases of musculoskeletal system and connective tissue	40		21	
Diseases of digestive system	34		21	
All others combined	45		23	

<sup>1</sup>History of any allergy considered positive if asthma, eczema or hay fever was reported as diagnosed by a physician or there was self-perceived serious difficulty breathing associated with certain substances.—<sup>2</sup>History of any autoimmune disease considered positive if rheumatoid arthritis, lupus erythematosus, multiple sclerosis, diabetes or pernicious anemia was reported as diagnosed by a physician.—<sup>3</sup>Proportion of subjects with a positive history.

## RESULTS

### General characteristics of cases and controls

The patients with brain tumors tended to be older (mean 52.5 years vs. 49.6 years), more highly educated and from homes with higher household incomes than controls (Table I). These differences were most apparent for acoustic neuroma. The ratio of men to women was 1.3 among patients with glioma, 0.3 among those with meningioma and 0.6 among those with acoustic neuroma.

### Distribution of allergies and autoimmune diseases among controls by selected characteristics

Among controls, history of allergy (either physician-diagnosed or self-perceived) tended to be more common in older age groups, among females and subjects without siblings, increased with level of education and urbanicity and did not vary by diagnostic subgroups (Table II). The associations were significant for sex ( $p < 0.01$ ) and education ( $p = 0.02$ ). The proportion of controls with a history of autoimmune diseases was highest in Pittsburgh and lowest in Phoenix ( $p < 0.01$ ), increased with age ( $p < 0.01$ ), was more common in females ( $p = 0.04$ ), decreased with level of education ( $p = 0.04$ ), did not vary by urbanicity or sibship and was highest among controls hospitalized for circulatory diseases ( $p = 0.03$ ).

### Allergies and autoimmune diseases and risk of brain tumors

Most types of allergies that we evaluated were associated with a reduced risk of glioma (Table III). For asthma and allergy to chemicals, the associations were significant. No strong associations or consistent pattern in ORs was found for meningioma, whereas hay fever, allergy to food and allergy to other substances were associated with significantly elevated risks of acoustic neuroma. For a history of any allergy, there was a statistically signifi-

cant inverse association for glioma but not for meningioma or acoustic neuroma. When history of multiple physician-diagnosed allergies was considered, there was no apparent trend ( $p = 0.27$ ) in risk of glioma with multiple conditions (not shown).

A significant inverse association was observed for diabetes and risk of glioma (Table IV) and risks of each of the other autoimmune diseases were nonsignificantly reduced. A history of any autoimmune disease was inversely associated with risk of glioma and meningioma but not acoustic neuroma.

Limiting the data to self-responders did not materially change ORs associated with history of any allergies or autoimmune diseases and any type of brain tumor (not shown). Additional adjustment for educational level, annual household income, place of residence, marital status, religion, number of siblings, radiotherapy to the head, smoking and BMI had little effect on risk estimates (not shown).

### Age at diagnosis and duration of allergies and autoimmune diseases and risk of brain tumors

For prevalent physician-diagnosed disorders that demonstrated significant or suggestive associations with brain tumor risk, we analyzed the possible modifying effects of age at first diagnosis and duration of the condition. There was little variation in ORs for glioma associated with asthma by age at diagnosis or duration of asthma (Table V). Risk of acoustic neuroma increased with older age at diagnosis and shorter duration of hay fever, but neither trend was significant (Table V). ORs for glioma decreased with earlier age at diagnosis of diabetes and longer duration of diabetes (Table VI). Among subjects with rheumatoid arthritis, ORs for glioma varied little by age at diagnosis or duration.

**TABLE III** – ASSOCIATION BETWEEN HISTORY OF ALLERGIC DISEASES AND RISK OF GLIOMA, MENINGIOMA AND ACOUSTIC NEUROMA AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Medical condition	Controls <sup>1</sup> (n = 799)	Glioma			Meningioma			Acoustic neuroma		
		Cases <sup>1</sup> (n = 489)	OR <sup>2</sup>	95% CI <sup>3</sup>	Cases <sup>1</sup> (n = 197)	OR <sup>2</sup>	95% CI <sup>3</sup>	Cases <sup>1</sup> (n = 96)	OR <sup>2</sup>	95% CI <sup>3</sup>
Asthma <sup>5</sup>										
No	672	431	1.0 <sup>4</sup>		170	1.0 <sup>4</sup>		76	1.0 <sup>4</sup>	
Yes	111	43	0.63	0.43–0.92	26	0.86	0.53–1.40	16	1.34	0.73–2.46
Eczema <sup>5</sup>										
No	732	450	1.0 <sup>4</sup>		182	1.0 <sup>4</sup>		87	1.0 <sup>4</sup>	
Yes	52	23	0.76	0.45–1.27	14	0.80	0.42–1.53	5	0.92	0.34–2.48
Hay fever <sup>5</sup>										
No	674	409	1.0 <sup>4</sup>		166	1.0 <sup>4</sup>		67	1.0 <sup>4</sup>	
Yes	110	63	0.97	0.69–1.37	28	0.93	0.58–1.50	25	2.36	1.38–4.03
Allergy to medicine <sup>6</sup>										
No	717	443	1.0 <sup>4</sup>		181	1.0 <sup>4</sup>		87	1.0 <sup>4</sup>	
Yes	63	27	0.79	0.49–1.27	13	0.76	0.40–1.46	5	0.53	0.20–1.42
Allergy to insects <sup>6</sup>										
No	728	450	1.0 <sup>4</sup>		177	1.0 <sup>4</sup>		84	1.0 <sup>4</sup>	
Yes	52	20	0.61	0.36–1.05	17	1.32	0.72–2.43	8	1.12	0.49–2.54
Allergy to food <sup>6</sup>										
No	765	463	1.0 <sup>4</sup>		189	1.0 <sup>4</sup>		86	1.0 <sup>4</sup>	
Yes	15	6	0.66	0.25–1.74	5	1.18	0.40–3.48	6	3.01	1.06–8.53
Allergy to chemicals <sup>6</sup>										
No	757	466	1.0 <sup>4</sup>		192	1.0 <sup>4</sup>		89	1.0 <sup>4</sup>	
Yes	23	3	0.23	0.07–0.79	2	0.26	0.06–1.16	3	0.79	0.22–2.84
Allergy to other substances <sup>6</sup>										
No	764	462	1.0 <sup>4</sup>		189	1.0 <sup>4</sup>		84	1.0 <sup>4</sup>	
Yes	16	7	0.79	0.32–1.96	5	1.19	0.41–3.42	8	3.81	1.45–9.99
Any allergy <sup>7</sup>										
No	476	334	1.0 <sup>4</sup>		113	1.0 <sup>4</sup>		54	1.0 <sup>4</sup>	
Yes	301	136	0.67	0.52–0.86	80	0.98	0.70–1.38	38	1.02	0.64–1.63

<sup>1</sup>Numbers may not add up to column totals because of missing data. <sup>2</sup>OR, odds ratio. ORs adjusted for matching factors. <sup>3</sup>95% CI, 95% confidence interval. <sup>4</sup>Referent group. <sup>5</sup>These were self-reported, physician-diagnosed conditions. <sup>6</sup>These were self-reported, self-perceived conditions. Allergy to other substances includes allergies to plants, dust or animals. <sup>7</sup>This category was based on history of any allergy (physician-diagnosed or self-perceived).

**TABLE IV** – ASSOCIATION BETWEEN HISTORY OF AUTOIMMUNE DISEASES AND RISK OF GLIOMA, MENINGIOMA AND ACOUSTIC NEUROMA AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Medical condition	Controls <sup>1</sup> (n = 799)	Glioma			Meningioma			Acoustic neuroma		
		Cases <sup>1</sup> (n = 489)	OR <sup>2</sup>	95% CI <sup>3</sup>	Cases <sup>1</sup> (n = 197)	OR <sup>2</sup>	95% CI <sup>3</sup>	Cases <sup>1</sup> (n = 96)	OR <sup>2</sup>	95% CI <sup>3</sup>
Rheumatoid arthritis										
No	713	441	1.0 <sup>4</sup>		184	1.0 <sup>4</sup>		89	1.0 <sup>4</sup>	
Yes	66	26	0.67	0.41–1.09	12	0.60	0.31–1.17	2	0.28	0.07–1.21
Lupus erythematosus										
No	774	467	1.0 <sup>4</sup>		195	1.0 <sup>4</sup>		92	1.0 <sup>4</sup>	
Yes	9	3	0.71	0.19–2.71	1	0.31	0.04–2.61	0	0	0–1.38 <sup>5</sup>
Multiple sclerosis										
No	777	47	1.0 <sup>4</sup>		196	1.0 <sup>4</sup>		91	1.0 <sup>4</sup>	
Yes	8	3	0.70	0.18–2.72	0	0	0–2.56 <sup>5</sup>	1	3.60	0.36–36.21
Diabetes										
No	703	446	1.0 <sup>4</sup>		179	1.0 <sup>4</sup>		85	1.0 <sup>4</sup>	
Yes	82	27	0.44	0.27–0.70	17	0.67	0.37–1.20	7	0.76	0.33–1.77
Pernicious anemia										
No	764	467	1.0 <sup>4</sup>		183	1.0 <sup>4</sup>		90	1.0 <sup>4</sup>	
Yes	18	5	0.38	0.14–1.08	9	1.41	0.59–3.38	2	1.25	0.26–6.06
Any autoimmune disease										
No	614	407	1.0 <sup>4</sup>		161	1.0 <sup>4</sup>		79	1.0 <sup>4</sup>	
Yes	163	58	0.49	0.35–0.69	33	0.59	0.38–0.92	12	0.61	0.31–1.19

<sup>1</sup>Numbers may not add up to column totals because of missing data. <sup>2</sup>OR, odds ratio. ORs adjusted for matching factors. <sup>3</sup>95% CI, 95% confidence interval. <sup>4</sup>Referent group. <sup>5</sup>Computation of the intervals is based on the profile likelihood function.

#### Effect modification and risk of glioma

ORs associated with allergy did not vary significantly by admission hospital, age at cancer diagnosis or education, although the OR for the age 60+ -year category was lower than for other age groups (not shown). There was a suggestion of a difference in the OR for allergy by gender ( $p = 0.06$ ), with females having a lower risk (OR = 0.54, 95% CI = 0.38–0.78) compared to males (OR = 0.83, 95% CI = 0.58–1.19). ORs for autoimmune disease did not vary significantly by any characteristic considered. However, the

ORs were lowest for Boston, increased with age and were higher for females (not shown). For both allergy and autoimmune diseases, ORs did not vary by major histologic subtypes of glioma or by histologic grade (Table VII).

There was an indication of interaction between history of allergies and autoimmune diseases on risk of glioma (Table VIII). Subjects with a history of both types of diseases appeared to be at the lowest risk (OR = 0.26, 95% CI = 0.15–0.46) and the joint effects were more than multiplicative ( $p = 0.06$ ).

**TABLE V**—ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR GLIOMA AND ACOUSTIC NEUROMA BY AGE AT FIRST DIAGNOSIS AND DURATION OF ASTHMA AND HAY FEVER AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Type of tumor	Characteristic	Status	<10 years	10–30 years	30+ years	Missing	<i>p</i> -value for trend
Glioma	Age at diagnosis of asthma	Case	12	16	12	18	0.65
		Control	32	32	41	22	
		OR <sup>1,3</sup>	0.55	0.81	0.52		
	Duration of asthma	Case	12	11	17	18	0.63
		Control	33	33	39	22	
		OR <sup>1,3</sup>	0.66	0.54	0.64		
Acoustic neuroma	Age at diagnosis of hay fever	Case	4	11	8	6	0.51
		Control	20	62	23	20	
		OR <sup>2,3</sup>	1.60	1.93	4.37		
	Duration of hay fever	Case	4	9	10	6	0.16
		Control	14	39	52	20	
		OR <sup>2,3</sup>	5.43	2.93	1.58		
		95% CI	1.45–20.40	1.27–6.80	0.74–3.38		

<sup>1</sup>Referent group consisted of persons without history of asthma.—<sup>2</sup>Referent group consisted of persons without history of hay fever.—<sup>3</sup>ORs adjusted for matching factors.

**TABLE VI**—ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR GLIOMA BY AGE AT FIRST DIAGNOSIS AND DURATION OF DIABETES AND RHEUMATOID ARTHRITIS AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Characteristic	Status	<40 years	40–54 years	55+ years	Missing	<i>p</i> -value for trend
Age at diagnosis Diabetes	Case	2	9	14	18	0.05
	Control	26	33	23	14	
	OR <sup>1,3</sup>	0.13	0.38	0.67		
	95% CI	0.03–0.54	0.18–0.82	0.33–1.35		
Rheumatoid arthritis	Case	8	9	9	22	0.39
	Control	31	16	16	23	
	OR <sup>2,3</sup>	0.48	0.92	0.90		
	95% CI	0.21–1.05	0.40–2.16	0.38–2.13		
Characteristic	Status	<10 years	10–29 years	30+ years	Missing	<i>p</i> -value for trend
Duration Diabetes	Case	19	5	1	18	0.06
	Control	40	31	11	14	
	OR <sup>1,3</sup>	0.64	0.20	0.11		
	95% CI	0.36–1.15	0.08–0.54	0.01–0.88		
Rheumatoid arthritis	Case	9	13	4	22	0.97
	Control	27	26	10	23	
	OR <sup>2,3</sup>	0.60	0.81	0.68		
	95% CI	0.27–1.30	0.40–1.61	0.20–2.24		

<sup>1</sup>Referent group consisted of persons without history of diabetes.—<sup>2</sup>Referent group consisted of persons without history of rheumatoid arthritis.—<sup>3</sup>ORs adjusted for matching factors.

**TABLE VII**—ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR DIFFERENT TYPES OF GLIOMA ASSOCIATED WITH HISTORY OF ANY ALLERGIES AND AUTOIMMUNE DISEASES AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

Glioma	<i>n</i> = 489	History of any allergy			History of any autoimmune disease		
		OR <sup>1</sup>	95% CI	<i>p</i> -value <sup>2</sup>	OR <sup>1</sup>	95% CI	<i>p</i> -value <sup>2</sup>
Histologic subtype							
Glioblastoma	241	0.62	0.44–0.88	0.82	0.51	0.34–0.78	0.62
Anaplastic astrocytoma	70	0.97	0.56–1.68		0.51	0.23–1.13	
Other astrocytoma	34	0.53	0.23–1.22		0.38	0.08–1.67	
Oligodendroglioma	85	0.60	0.36–1.02		0.20	0.06–0.66	
Other glioma	59	0.77	0.42–1.42		0.66	0.27–1.64	
Histologic grade							
Low	135	0.72	0.47–1.10	0.86	0.39	0.18–0.84	0.62
High	354	0.67	0.50–0.89		0.51	0.35–0.74	

<sup>1</sup>ORs adjusted for matching factors.—<sup>2</sup>*p*-value for test of heterogeneity.

#### Evaluation of potential biases

To evaluate the possibility that the inverse associations seen for glioma and allergies or autoimmune diseases might be a result of underreporting of exposure due to impaired memory or cognition, we estimated risks for glioma including and excluding cases with

a medical record notation indicating mental impairment. The ORs associated with allergies or autoimmune diseases did not differ significantly in the 2 groups (heterogeneity *p* = 0.10 and *p* = 0.78, respectively). Risks associated with allergies were 0.76 (95% CI = 0.58–1.01) and 0.47 (95% CI = 0.30–0.72) when limited to cases

**TABLE VIII**—INTERACTION BETWEEN HISTORY OF ALLERGIES AND AUTOIMMUNE DISEASES ON RISK OF GLIOMA AMONG PATIENTS FROM HOSPITALS IN BOSTON, PHOENIX AND PITTSBURGH, USA, 1994–1998

History of any allergy	Status	History of any autoimmune disease	
		No	Yes
No	Case/control	287/395	40/76
	OR <sup>1,4</sup>	1.0 <sup>3</sup>	0.66
	95% CI <sup>2</sup>		0.43–1.02
Yes	Case/control	117/212	17/86
	OR <sup>1,4</sup>	0.78	0.26
	95% CI <sup>2</sup>	0.59–1.03	0.15–0.46

<sup>1</sup>OR, odds ratio. ORs adjusted for matching factors.—<sup>2</sup>95% CI, 95% confidence interval.—<sup>3</sup>Referent group.—<sup>4</sup>Test for interaction:  $p = 0.06$ .

with no notation of impaired mental status ( $n = 342$ ) and cases with mental impairment ( $n = 147$ ), respectively. Risks associated with autoimmune diseases were 0.51 (95% CI = 0.34–0.75) and 0.44 (95% CI = 0.26–0.76), respectively. Thus, an inverse association between risk of glioma and history of allergies or autoimmune diseases persisted after allowance for possible underreporting of exposure by some of the cases. Excluding or including different diagnostic subgroups of controls from the analysis had little effect on risk estimates for any type of these tumors for any of the allergies or autoimmune diseases considered (not shown).

#### DISCUSSION

This large, hospital-based case-control study demonstrated an inverse association between risk of glioma and history of allergy of any type, a finding that parallels those from previous population-based studies.<sup>4–6,8,9</sup> The apparent specificity of the inverse association for glioma was confirmed in our present study, as there was no overall association between history of allergy and risk of meningioma or acoustic neuroma. History of autoimmune diseases was associated with a reduced risk of both glioma and meningioma supporting some studies<sup>5,11</sup> but not others.<sup>7,8,12–16</sup> Interestingly, we found that persons with a history of allergies and autoimmune diseases were at especially low risk of developing glioma. Distinctive features of our study include its large size, high participation rates, low proportion of proxy respondents, consideration of possible underreporting by mentally impaired glioma cases and inclusion of autoimmune diseases as well as allergies.

With respect to specific medical conditions and risk of glioma, asthma and diabetes showed the most consistent associations in our study. Risk estimates associated with asthma were less than 1.0 and varied little between early and late ages at asthma diagnosis or for short and long durations of asthma prior to tumor diagnosis. These observations are in agreement with prior studies.<sup>5,6,8</sup> Findings for allergy to substances that cause serious difficulty breathing, particularly allergy to chemicals, should be interpreted with caution, since these were self-perceived and reported conditions, no information was obtained on dermal, digestive or other allergic reactions to these substances and risk estimates were based on small numbers. Risk estimates associated with diabetes were less than 1.0 but, contrary to asthma, were lower for early ages at diabetes diagnosis and for long duration of diabetes. Our findings support a population-based case-control study that found reduced risks of glioma associated with diabetes<sup>5</sup> and another 1 that demonstrated a reduced frequency of gliomas in diabetic compared to nondiabetic autopsied hospital patients.<sup>11</sup> However, several case-control and cohort studies did not find any substantial deviation in risk from unity,<sup>7,8,12</sup> and 1 study suggested an elevated risk for glioma among diabetics.<sup>13</sup> These inconsistencies might be attributable to different study designs or may reflect heterogeneity in diabetic series. We could not distinguish between IDDM and NIDDM. IDDM is known to have an early onset and autoimmune component and the age-dependency of glioma risk might imply that IDDM is more protective for glioma.

The overall history of autoimmune diseases was associated with a decreased risk of meningioma in our study. This is in agreement with another study that found a reduced risk of meningioma with diabetes.<sup>5</sup> However, the available evidence concerning this topic is sparse. Given that we did not see a clear or consistent pattern in ORs of meningioma by sex, age, duration of the prior autoimmune disease or other characteristics and that there was no association between meningioma and allergies, the etiologic relevance of this finding is not clear.

We are not aware of any previous reports concerning allergies and acoustic neuromas. The elevated risks associated with hay fever of short duration may be noteworthy in view of reports that IgE-mediated allergic rhinitis may contribute to the development of eustachian tube dysfunction and otitis media.<sup>22</sup> This might result in additional diagnostic examinations and more likely diagnosis of acoustic neuroma, a slow-growing tumor. Alternatively, hay fever or its treatment might somehow promote the development of acoustic neuroma. The small numbers require cautious interpretation, but the findings warrant further investigation.

To the best of our knowledge, earlier studies did not address the possible effect of mental status changes in glioma patients on risk estimates. We had some concern that glioma patients might underreport previous medical conditions due to tumor-related impairment of cognition or memory and that this would bias estimates of the relative risk downward. When we restricted analysis to cases not known to have experienced impairment during the weeks or days prior to tumor diagnosis and treatment, risk estimates were closer to 1.0 but still reduced. Although changes in mental status of glioma patients might contribute to the negative associations with allergies and autoimmune diseases, it does not appear that such an effect can account completely for the observed associations.

Our findings do not appear to be artifacts of enrollment of hospital controls, who were admitted for a wide variety of non-malignant diseases and conditions. The prevalence of allergic conditions among controls in this study was similar to values reported in population-based U.S. studies,<sup>23</sup> with the exception of asthma, for which we observed a higher relative frequency.<sup>24–26</sup> However, risk estimates associated with asthma were similar to those derived from other populations with lower reported prevalence.<sup>6,8</sup> Whereas the proportion of controls with rheumatoid arthritis, lupus erythematosus, multiple sclerosis or pernicious anemia was somewhat higher than that reported in other international<sup>5,7,8</sup> and U.S. population-based studies,<sup>27,28</sup> the proportion with diabetes was within the range reported in the U.S.<sup>29,30</sup> The overall pattern of autoimmune diseases among the controls was as one would expect based on the literature—higher for females than males, increased with age and decreased with level of education.<sup>27,28,30</sup> For both allergies and autoimmune diseases, risk estimates were insensitive to whether broad diagnostic groupings, such as diseases of the circulatory, musculoskeletal, digestive systems, injuries and poisoning or all other conditions combined were included or excluded from the control series.

Like other investigators, we relied on self-reported information concerning prior medical history. The sensitivity of ascertainment of physician-diagnosed allergic conditions has been estimated as about 68% and the specificity as about 94% when validated against clinical diagnosis.<sup>31</sup> For chronic autoimmune diseases, sensitivity and specificity are somewhat higher and vary from 73–90% and from 90–99%, respectively.<sup>32–34</sup> If the error in reporting is non-differential for cases and controls, it would tend to drive estimates of the OR toward unity (1.0). Allergies and autoimmune diseases are not generally perceived to be related to risk of brain tumors. Nonetheless, to minimize differential reporting, both cases and controls were interviewed by trained interviewers using a standardized interview script. The proportion of interviews that required surrogate respondents or assistance was small compared to other studies,<sup>6,7</sup> and limiting the analysis to self-responders had no material effect on the risk estimates.

We did not collect information about treatments associated with prior medical conditions. Current treatments for allergies may include antihistamines, corticosteroids and desensitization vaccinations.<sup>35</sup> Adjustment for self-reported use of antiallergenic drugs in a large international study had little effect on relative risk estimates.<sup>8</sup> Treatments for autoimmune diseases include a wide variety of medications, depending on the type and severity of the disease. Whether any of these might affect risk of brain tumors is not clear.

Given the consistency of results from case-control studies of allergies and glioma in population-based and hospital-based studies,<sup>4-6,8,9</sup> the observed association is not readily explainable in terms of selection or reporting bias. The findings regarding autoimmune diseases are intriguing, although, overall, the available data are mixed.<sup>5,7,8,11-17</sup> While questions remain whether the associations are causal, our finding of an indication of interaction between allergies and autoimmune diseases on risk of glioma, but not meningioma, as well as an interaction between allergies and infections observed in a large international study<sup>8</sup> point to a possible role of immunologic factors in the development of brain cancer.

The brain is no longer considered to be a strictly immune "privileged" site,<sup>36</sup> inaccessible to elements of the immune system. Clinical evidence suggests that occurrence of certain infections and nervous system lymphoma and, possibly, glioma in immunocompromised patients might result from an impaired immune surveillance.<sup>37-39</sup> Recent experiments confirm that activated T cells can nonspecifically cross the blood-brain barrier and that populations of brain parenchymal cells can produce a wide range of cytokines and express class I and II major histocompatibility complex (MHC) molecules necessary for antigen presentation.<sup>40,41</sup> On the other hand, an effective antitumor response is lacking in

most glioma patients and immunotherapies have not yet been shown to be consistently effective.<sup>42,43</sup> These findings may be attributable to tumor cell release of transforming growth factor beta (TGF- $\beta$ ), the latter believed to be responsible for local and systemic immunosuppression, a lack of tumor-specific antigens and failure of glioma cells to present antigens.<sup>42</sup> Although allergies and autoimmune diseases differ in underlying immune alterations, they both are a result of inappropriate response to innocuous foreign substances in 1 case and to self-antigens in the other.<sup>44,45</sup> It is not clear how a hyperstimulated immune response might be protective against glioma, but the mechanism could include activated T and B cells<sup>46-50</sup> or cytokine-mediated mechanisms.<sup>42,51-53</sup> Alternatively, there might be a common, yet unknown factor not immunologic in nature that both predisposes to allergies or autoimmune diseases and protects against development of brain cancer.

In summary, this large, hospital-based case-control study indicates that persons with allergies or autoimmune diseases are at reduced risk of glioma. It is not yet clear whether these associations are causal, but several lines of evidence point to a possible mediating role of immunologic factors. Confirmation of the finding in a large prospective study, with direct ascertainment of immunologic markers or susceptibility markers predisposing to certain immunologic conditions, would add to the credibility of the hypothesis.

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#### REFERENCES

- Preston-Martin S, Mack WJ. Neoplasms of the nervous system. In: Schottenfeld D, Fraumeni JF Jr., eds. *Cancer epidemiology and prevention*, 2nd ed. New York: Oxford University Press, 1996. 1231-81.
- Louis DN, von Deimling A. Hereditary tumor syndromes of the nervous system: overview and rare syndromes. *Brain Pathol* 1995;5:145-51.
- Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. *Epidemiol Rev* 1995;17:382-414.
- Hochberg F, Toniolo P, Cole P, et al. Nonoccupational risk indicators of glioblastoma in adults. *J Neurooncol* 1990;8:55-60.
- Schlehofer B, Blettner M, Becker N, et al. Medical risk factors and the development of brain tumors. *Cancer* 1992;69:2541-7.
- Ryan P, Lee MW, North B, et al. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer* 1992;51:20-7.
- Cicuttini FM, Hurley SF, Forbes A, et al. 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, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. *Int J Cancer* 1999;82:155-60.
- Wrensch M, Wiemels J, Sison J, et al. Do common allergies prevent brain tumors? [abstract] *Neuro-oncology* 2001;3 (Suppl 1):S48.
- Eriksson NE, Holmen A, Hogstedt B, et al. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995;50:718-22.
- Aronson SM, Aronson BE. Central nervous system in diabetes mellitus. Lowered frequency of certain intracranial neoplasms. *Arch Neurol* 1965;12:390-8.
- Wideroff L, Gridley G, Mellekjær L, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997;89:1360-5.
- Mills PK, Preston-Martin S, Annegers JF, et al. Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. *Neuroepidemiology* 1989;8:266-75.
- Gridley G, McLaughlin JK, Ekblom A, et al. Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993;85:307-11.
- Mellekjær L, Gridley G, Moller H, et al. Pernicious anaemia and cancer risk in Denmark. *Br J Cancer* 1996;73:998-1000.
- Midgard R, Glatte E, Gronning M, et al. Multiple sclerosis and cancer in Norway. A retrospective cohort study. *Acta Neurol Scand* 1996;93:411-5.
- Moller H, Kneller RW, Boice JD Jr, et al. Cancer incidence following hospitalization for multiple sclerosis in Denmark. *Acta Neurol Scand* 1991;84:214-20.
- Wrensch M, Weinberg A, Wiencke J, et al. Prevalence of antibodies to four herpesviruses among adults with glioma and controls. *Am J Epidemiol* 2001;154:161-5.
- Ryan P, Hurley SF, Johnson AM, et al. Tumours of the brain and presence of antibodies to *Toxoplasma gondii*. *Int J Epidemiol* 1993;22:412-9.
- Inskip PD, Tarone RE, Hatch EE, et al. Cellular-telephone use and brain tumors. *N Engl J Med* 2001;344:79-86.
- SAS/STAT User's Guide, ver. 8. Cary, NC: SAS Institute, 1999.
- Bernstein JM. The role of IgE-mediated hypersensitivity in the development of otitis media with effusion: a review. *Otolaryngol Head Neck Surg* 1993;109:611-20.
- Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2000;21:1-6.
- Holly EA, Lele C, Bracci PM, et al. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* 1999;150:375-89.
- Mills PK, Beeson WL, Fraser GE, et al. Allergy and cancer: organ site-specific results from the Adventist Health Study. *Am J Epidemiol* 1992;136:287-95.
- McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI followup data. *Cancer* 1988;62:451-5.
- Jacobson DL, Gange SJ, Rose NR, et al. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84:223-43.
- Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778-99.
- Strickler HD, Wylie-Rosett J, Rohan T, et al. The relation of type 2 diabetes and cancer. *Diabetes Technol Ther* 2001;3:263-74.
- Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000;133:592-9.
- Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;104:600-8.

32. Martin LM, Leff M, Calonge N, et al. Validation of self-reported chronic conditions and health services in a managed care population. *Am J Prev Med* 2000;18:215–8.
33. Ling SM, Fried LP, Garrett E, et al. The accuracy of self-report of physician diagnosed rheumatoid arthritis in moderately to severely disabled older women. *Women's Health and Aging Collaborative Research Group. J Rheumatol* 2000;27:1390–4.
34. Rasooly I, Papageorgiou AC, Badley EM. Comparison of clinical and self reported diagnosis for rheumatology outpatients. *Ann Rheum Dis* 1995;54:850–2.
35. Kay AB. Allergy and allergic diseases. Second of two parts. *N Engl J Med* 2001;344:109–13.
36. Medawar PB. Immunity to homologous grafted skin. III. The fate of skin homografts transplanted to the brain, to subcutaneous tissue and to the anterior chamber of the eye. *Br J Exp Pathol* 1948;29:58–69.
37. Frisch M, Biggar RJ, Engels EA, et al. Association of cancer with AIDS-related immunosuppression in adults. *J Am Med Assoc* 2001;285:1736–45.
38. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998;351:1833–9.
39. Smith TW, De Girolami U, Hickey WF. Neuropathology of immunosuppression. *Brain Pathol* 1992;2:183–94.
40. Sedgwick JD. Immune surveillance and autoantigen recognition in the central nervous system. *Aust N Z J Med* 1995;25:784–92.
41. Van Meir EG. Cytokines and tumors of the central nervous system. *Glia* 1995;15:264–88.
42. Weller M, Fontana A. The failure of current immunotherapy for malignant glioma. Tumor-derived TGF-beta, T-cell apoptosis and the immune privilege of the brain. *Brain Res Brain Res Rev* 1995;21:128–51.
43. Tada M, de Tribolet N. Recent advances in immunobiology of brain tumors. *J Neurooncol* 1993;17:261–71.
44. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med* 2001;344:30–7.
45. Ermann J, Fathman CG. Autoimmune diseases: genes, bugs and failed regulation. *Nat Immunol* 2001;2:759–61.
46. Jarvinen KM, Aro A, Juntunen-Backman K, et al. Large number of CD19+/CD23+ B cells and small number of CD8+ T cells as early markers for cow's milk allergy (CMA). *Pediatr Allergy Immunol* 1998;9:139–42.
47. Virchow JC Jr, Oehling A, Boer L, et al. Pulmonary function, activated T cells, peripheral blood eosinophilia and serum activity for eosinophil survival in vitro: a longitudinal study in bronchial asthma. *J Allergy Clin Immunol* 1994;94:240–9.
48. Timonen T, Stenius-Aarniala B. Natural killer cell activity in asthma. *Clin Exp Immunol* 1985;59:85–90.
49. De Miguel S, Galocha B, Jover JA, et al. Mechanisms of CD23 hyperexpression on B cells from patients with rheumatoid arthritis. *J Rheumatol* 2001;28:1222–8.
50. Ilonen J, Surcel HM, Kaar ML. Abnormalities within CD4 and CD8 T lymphocytes subsets in type 1 (insulin-dependent) diabetes. *Clin Exp Immunol* 1991;85:278–81.
51. Robinson DS. Th-2 cytokines in allergic disease. *Br Med Bull* 2000;56:956–68.
52. Halminen M, Simell O, Knip M, et al. Cytokine expression in unstimulated PBMC of children with type 1 diabetes and subjects positive for diabetes-associated autoantibodies. *Scand J Immunol* 2001;53:510–3.
53. Schuerwegh AJ, van Offel JF, Bridts CH, et al. Influence of longterm therapy with methotrexate and low dose corticosteroids on type 1 and type 2 cytokine production in CD4+ and CD8+ T lymphocytes of patients with rheumatoid arthritis. *J Rheumatol* 2001;28:1793–9.