

History of allergies and risk of glioma in adults

Minouk J. Schoemaker^{1*}, Anthony J. Swerdlow¹, Sarah J. Hepworth², Patricia A. McKinney², Martie van Tongeren³ and Kenneth R. Muir⁴

¹Section of Epidemiology, Institute of Cancer Research, Sutton SM2 5NG, United Kingdom

²Centre for Epidemiology and Biostatistics, University of Leeds, 30 Hyde Terrace, Leeds LS2 9LN, United Kingdom

³Centre for Occupational and Environmental Health, Division of Epidemiology and Health Sciences,

University of Manchester M13 9PL, United Kingdom

⁴Division of Epidemiology and Public Health, University of Nottingham, Nottingham NG7 2UH, United Kingdom

Epidemiological studies have consistently reported an inverse association between a history of allergic disease and risk of glioma. The reason for this association is unclear, and there is a lack of studies with the detail and size to explore the association in depth. We conducted a UK population-based case-control study with 965 glioma cases and 1,716 controls to investigate glioma risk in relation to allergic disease. Risk was reduced in subjects reporting a history of asthma (odds ratio (OR) = 0.71, 95% confidence interval (CI): 0.54–0.92), hay fever (OR = 0.73, 95% CI: 0.59–0.90), eczema (OR = 0.74, 95% CI: 0.56–0.97) and other allergies (OR = 0.65, 95% CI: 0.47–0.90). Risk was reduced for all the main histological groups. There was no significant trend of risk with age, at the onset of each condition, or the number of conditions reported. Risk reductions were strongest for asthma or hay fever with recent onset. Risk in asthmatic subjects was not related to frequency of use of antiasthmatic drugs, but was significantly reduced for use of antiallergenic medication among subjects with hay fever. The study showed an inverse association of glioma risk with allergic disease. Possible reasons for the association, as well as potential immunological aetiology, include confounding, bias and reverse causality.

© 2006 Wiley-Liss, Inc.

Key words: glioma; allergy; case-control; aetiology

Epidemiological studies consistently show an inverse association between a history of allergic conditions and risk of glioma.^{1–9} The reason for this finding is unclear. Reduced risks in allergic subjects have also been reported for several other types of cancer,¹⁰ which have been hypothesised to be due to a state of raised immunosurveillance.¹¹ Possible other reasons, however, for the inverse association with glioma risk include reverse causality, confounding or bias. There is a lack of large studies with enough detail to explore the association between allergies and glioma risk in depth, particularly in relation to age at onset or time since onset, duration and severity, and few studies have investigated the relationship of risk and use of antiallergy medication or have been large enough to investigate risk by histological tumour type.

We conducted a large population-based case-control study of risk factors for glioma in several areas in the UK, with 965 cases and 1,716 controls. This study collected information on a range of potential risk factors, including allergies, and on mobile phone use as part of the Interphone study,¹² on which we recently reported.¹³ We report here on the risk of glioma in relation to allergic conditions and use of antiallergenic medication.

Methods

Study design and recruitment

Two population-based case-control studies were conducted in the UK according to a similar protocol. One was in the Thames regions of Southeast England and the other in the Trent area, the West Midlands, West Yorkshire and Central Scotland (referred to as Northern UK). The study area, for the 2 studies combined, comprised a population of 28.4 million people, representing 48% of the UK population. Both studies followed the core protocol of the Interphone Study,¹² to which all subjects aged 30–59 interviewed in our study will contribute, but with several extensions including a wider age range of patients and a much extended questionnaire.

Cases were ascertained from neurosurgery, neuro-oncology, neuropathology, neuroradiology and neurology units in hospitals in the study regions, and for SE England, also from the regional cancer registry. Eligible cases were individuals diagnosed with glioma during the study period (from December 1, 2000 to June 30, 2003 for the Northern UK and to February 29, 2004 for the Southeast) at ages 18–59 in the Southeast and 18–69 in the Northern UK areas and resident in the study areas. Glioma was defined according to the International Classification for Disease as topography C71¹⁴ and morphology (ICD-O-3) 9380–9411, 9420–9451, 9480 and 9505.¹⁵ The date of diagnosis was defined as the date of the first scan that revealed a space-occupying lesion in the brain or, if not available, date of biopsy or surgery. 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.

Control subjects were defined as people who had not been diagnosed with a brain tumour, resident in the same study region and within the same age range as the cases in the study region. Controls were randomly selected from general practitioner patient lists by a preset algorithm. In the Southeast the controls were frequency matched to reflect the age, sex and geographical distribution of brain tumour cases. In the northern centres, 1 control per case was individually matched on age, sex and GP practice. Approximately 98% of the UK population was registered with a general practitioner in 1992.¹⁶

Subjects were invited by letter to participate in the study. If no reply was received, a repeat letter was sent or the subject was contacted by telephone. The study was introduced to participants as a study of risk factors for brain tumours (Northern UK) or as a study of modern lifestyle factors and health (SE England), with no emphasis on any particular risk factor. Ethical approval for this study was obtained from the multicentre research ethics committees for the Southeast and Scotland and all appropriate local research ethics committees. Informed consent was obtained from all subjects at interview.

Consenting subjects were personally interviewed by trained research nurses or experienced research interviewers using a computer-assisted interview, with the answers being directly entered into the questionnaire program on a laptop computer. Interviews were conducted in the subject's home, workplace or in hospital, as

Grant sponsor: European Commission Fifth Framework Program; Grant number: QLK4-CT-1999-01563; Grant sponsor: the Mobile Manufacturers' Forum and the GSM Association, through the International Union against Cancer (UICC); Grant number: RCA/01/08; Grant sponsor: Mobile Telecommunications and Health (MTHR) Programme; Grant sponsors: Mobile Manufacturers' Forum, GSM Association, Health and Safety Executive, Department of Health, Scottish Executive, UK Network Operators (O2, Orange, T-Mobile, Vodafone, '3').

*Correspondence to: Section of Epidemiology, Institute of Cancer Research, 15, Cotswold Road, Sutton SM2 5NG, UK. Fax: +44-(0)208-7224019. E-mail: Minouk@icr.ac.uk

Received 25 January 2006; Accepted after revision 21 April 2006

DOI 10.1002/ijc.22091

Published online 5 July 2006 in Wiley InterScience (www.interscience.wiley.com).

was most convenient to the participant. During the interview, subjects were asked whether they had ever been diagnosed with asthma, eczema and hay fever and the age at onset of this 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 SE England study, including the ages at which subjects stopped having asthma and hay fever (if applicable), and diagnosis with seasonal or non-seasonal allergic rhinitis and conjunctivitis, or food or contact allergy. In addition in SE England, subjects who reported asthma or other allergy were asked about the frequency with which they had used antiasthmatic medication or antiallergenic drugs, respectively (almost every day, not every day but more than half the year, less than half the year, never). Subjects were asked to specify the types of antiallergenic drugs they had ever used (antihistamines, nasal spray, eye drops, desensitisers and other (specified by the participant)).

Statistical analysis

The study was conducted as part of a larger case-control study on several types of intracranial tumour, with controls recruited for the entire set of cases. To increase statistical power, we used all controls for this analysis.

In the calculation of all exposure indices, allergic conditions diagnosed within 1 year of diagnosis of glioma were ignored in this analysis, because they are unlikely to be aetiologically relevant. As not all controls were individually matched to cases, we derived a comparable censoring date to truncate exposure for controls, which would take into account how far back the subject was asked to recall exposures. The reference date for controls was obtained by constructing case-strata by interview year (2001, 2002, 2003 and ≥ 2004) and single year interval between diagnosis and interview ('interview lag time'). Controls interviewed in each interview year were randomly allocated to strata of interview lag time, proportionally to the distribution of the cases interviewed in the same period, to obtain a similar distribution of lag time as in the cases. The reference dates for controls were then calculated by subtracting the mean interview lag time in cases in that stratum from the interview dates of the controls.

Risk of glioma was analysed in relation to a history of asthma, eczema and hay fever in the pooled data set and in relation to other allergies and use of antiallergenic medication in the SE England study. Odds ratios for the condition or exposure of interest were calculated as estimates of the relative risk, using a logistic regression model adjusting for sex, 5-year categories of age at reference date, region (4 northern regions and 1 Southeast), interview year and Townsend deprivation category (a measure of deprivation based on the subject's residential postcode).¹⁷ Adjustment for Townsend category was made because atopy as well as glioma risk is associated with socioeconomic status^{18,19} and for age and sex, because all recruited controls were used for this analysis, rather than only controls matched to glioma cases, which led to some unequal distributions of demographic characteristics between cases and controls. Tests for trend were done on the original values rather than on categorised variables and were carried out with and without the baseline group, *i.e.*, subjects not affected by the condition, except for age at onset, as no value could be assigned to the baseline group. The Northern UK data were also analysed using individually matched case-control pairs as a background check; this did not materially alter the results.

Tumour risk in relation to these conditions was analysed by study centre, and for males and females separately. Heterogeneity in results between these groups was assessed with a log likelihood ratio test.²⁰ Tumour histology or tumour grade-specific (grade I/II vs. III/IV) odds ratios in relation to allergy were obtained with a polytomous logistic regression model. Heterogeneity between type-specific odds ratios was assessed with a log likelihood ratio test, comparing an unconstrained model with a model where expo-

TABLE 1 – CHARACTERISTICS OF GLIOMA CASES AND CONTROLS, UK

Characteristic	Cases (n = 965)		Controls (n = 1,716)	
	N	%	N	%
Sex				
Male	603	62.5	829	48.3
Female	362	37.5	887	51.7
		$p \chi^2 < 0.001$		
Age at reference date (years)				
18–29	100	10.4	112	6.5
30–39	199	20.6	281	16.4
40–49	216	22.4	429	25.0
50–59	327	33.9	645	37.6
60–69	123	12.7	249	14.5
		$p \chi^2 < 0.001$		
Townsend deprivation category*				
1 (most affluent)	257	26.6	513	29.9
2	229	23.7	386	22.5
3	178	18.5	334	19.5
4	180	18.7	292	17.0
5 (least affluent)	121	12.5	191	11.1
		$p \chi^2 = 0.3$		
Marital status				
Single	122	12.6	207	12.1
Married/cohabiting	758	78.6	1,318	76.8
Separated/divorced	61	6.3	145	8.5
Widowed	23	2.4	44	2.6
Not known	1	0.1	2	0.1
		$p \chi^2 = 0.2$		
Region				
Thames regions	367	38.0	630	36.7
Southern Scotland	151	15.7	277	16.1
Trent	199	20.6	372	21.7
West Midlands	115	11.9	207	12.1
West Yorkshire	133	13.8	230	13.4
		$p \chi^2 = 0.9$		

*Townsend score (17), a postcode-based measure of deprivation, categorised into quintiles based on 2001 census data (49).

sure coefficients were constrained to be equal. The statistical package STATA was used for all analyses.²¹

Analyses were repeated to investigate whether additional adjustment for interview lag time or cigarette smoking status affected the results; the latter because cigarette smoking has been found to be associated with atopy.²² We also repeated the analysis after adjusting for having had diagnostic radiographic examinations involving the head prior to the reference date as a background check on the results. Finally, as glioma patients might have problems with recall of past exposures due to the tumour or brain surgery, we explored risk in relation to allergies by the quality of recall by the patient as recorded by the interviewer.

Results

A total of 966 cases and 1,716 controls were interviewed for the study. The reasons for nonparticipation were death or being too ill (cases 30%, controls 0.1%), patient's refusal (cases 10%, controls 29%), no response (cases 2%, controls 21%), no medical permission to approach the patient (cases 5%, controls 5%) and other reasons (cases 2%, controls 0.2%). The participation rate among all cases was 51%, and was 61% among low and 47% among high-grade tumours. The overall control participation rate was 45% and was 57% based on subjects who had definitely received the invitation letter. One case was excluded because allergy data were not collected, leaving 965 cases in the analysis. Twenty three close relatives offered to participate as case-proxies because of the patient's poor health or death; their interviews are included in the analysis.

Interviewed cases were similar to noninterviewed cases with regard to sex (37.5% vs. 38.2% female, $p = 0.8$) but were younger at diagnosis (mean age 46.8 vs. 49.5 years, $p < 0.001$) and more affluent (Townsend score 2.7 vs. 3.0, $p < 0.001$). Interviewed con-

TABLE II – RISK OF GLIOMA IN RELATION TO PAST DIAGNOSIS WITH ASTHMA, HAY FEVER OR ECZEMA, UK

Factor	Cases (n = 965)		Controls (n = 1,716)		OR (95% CI)*
	N	%	N	%	
<i>Asthma</i>					
<i>Ever^a</i>					
No	866	89.8	1,488	86.7	1.00
Yes	98	10.2	228	13.3	0.71 (0.54–0.92) ^c
<i>Age at onset (years)</i>					
<10	44	4.6	78	4.6	0.81 (0.54–1.22)
10–19	17	1.8	46	2.7	0.54 (0.30–0.97) ^c
≥20	37	3.8	104	6.1	0.70 (0.47–1.04)
<i>Time since onset (years)</i>					
<10	17	1.8	51	3.0	Trend (ever asthma only) $p=0.4$
10–19	20	2.1	59	3.4	0.53 (0.30–0.95) ^c
≥20	61	6.3	118	6.9	0.58 (0.34–0.99) ^c
					0.84 (0.60–1.18)
					p trend=0.15 Trend (ever asthma only) $p=0.5$
<i>Hay fever</i>					
<i>Ever^b</i>					
No	787	81.7	1,321	77.0	1.00
Yes	176	18.3	395	23.0	0.73 (0.59–0.90) ^d
<i>Age at onset (years)</i>					
<10	37	3.8	83	4.8	0.63 (0.41–0.96) ^c
10–19	72	7.5	153	8.9	0.79 (0.58–1.07)
≥20	67	7.0	159	9.3	0.73 (0.53–0.99) ^c
<i>Time since onset (years)</i>					
<10	29	3.0	56	3.3	Trend (ever hay fever only) $p=1.0$
10–19	38	4.0	87	5.1	0.84 (0.51–1.36)
≥20	109	11.3	252	14.7	0.58 (0.38–0.89) ^c
					0.76 (0.59–0.99) ^c
					p trend=0.03 Trend (ever hay fever only) $p=0.9$
<i>Eczema</i>					
<i>Ever</i>					
No	872	90.4	1,492	87.0	1.00
Yes	93	9.6	224	13.0	0.74 (0.56–0.97) ^c
<i>Status</i>					
Current eczema	48	5.0	142	8.3	0.61 (0.43–0.88) ^d
Past eczema	45	4.7	82	4.8	0.94 (0.63–1.39)
<i>Age at onset (years)</i>					
<10	49	5.1	93	5.4	0.89 (0.61–1.30)
10–19	20	2.1	48	2.8	0.67 (0.39–1.17)
≥20	24	2.5	83	4.8	0.58 (0.36–0.94) ^c
<i>Time since onset (years)</i>					
<10	12	1.2	38	2.2	Trend (ever eczema only) $p=0.7$
10–19	18	1.9	42	2.5	0.57 (0.29–1.13)
≥20	63	6.5	144	8.4	0.74 (0.41–1.34)
					0.78 (0.56–1.07)
<i>Duration (years)</i>					
<10	41	4.3	80	4.7	p trend=0.10 Trend (ever eczema only) $p=0.8$
10–19	19	2.0	56	3.3	0.85 (0.56–1.27)
≥20	33	3.4	85	5.0	0.62 (0.36–1.08)
					0.72 (0.47–1.11)
Not known			3	0.2	p trend=0.07 Trend (ever eczema only) $p=0.7$
<i>Any of the above</i>					
<i>Ever</i>					
No	687	71.2	1,069	62.3	1.00
Yes	276	28.6	647	37.7	0.63 (0.53–0.76) ^c
Not known	2	0.2			
<i>Number of conditions</i>					
1	201	20.8	483	28.2	0.61 (0.50–0.75) ^c
2	58	6.0	128	7.5	0.67 (0.48–0.94) ^c
3	16	1.7	36	2.1	0.79 (0.42–1.50)
Not known	1	0.1			p trend<0.001 Trend (ever affected only) $p=0.4$

*Odds ratios adjusted for sex, age category, region, interview year and Townsend deprivation category—^aAsthma status not known for 1 case.—^bHay fever status not known for 2 cases.—^c $p < 0.05$.—^d $p < 0.01$.—^e $p < 0.001$.

trols were more likely to be female (51.7% vs. 39.1%, $p < 0.001$) and were older (47.4 vs. 44.6 years, $p < 0.001$) and more affluent (Townsend score 2.6 vs. 3.1, $p < 0.001$) compared with noninterviewed controls. Among interviewed subjects, cases were more often male and younger than controls but were similar with regard to Townsend deprivation score and marital status (Table I).

The relative risk of glioma was significantly reduced in subjects reporting ever having been diagnosed with asthma (OR = 0.71, 95% CI: 0.54–0.92), hay fever (OR = 0.73, 95% CI: 0.59–0.90), eczema (OR = 0.74, 95% CI: 0.56–0.97) or any of these conditions (OR = 0.63, 95% CI: 0.53–0.76) (Table II). Risk was also reduced for subjects reporting other types of allergy (OR = 0.65,

95% CI: 0.47–0.90, SE England only; not indicated in the table). There was no appreciable difference in risk between allergic subjects who reported a family history of allergic disease compared with those who did not. There was no heterogeneity in results between the 2 study centres (defining heterogeneity, conservatively, as $p < 0.10$), therefore pooled results are presented for brevity.

There were no statistically significant trends of risk with age at onset of each condition or with the number of conditions reported when restricting analysis to affected subjects only (Table II). Glioma risks in relation to eczema and asthma were somewhat lower for subjects diagnosed within 10 years before the reference date

than for subjects diagnosed a longer time ago, but this was not the case for hay fever, and there were no statistically significant trends of risk among affected subjects. There was no trend of decreasing risk with the duration of having the condition among subjects diagnosed with eczema (p -trend = 0.7) or, based on SE England data only, among subjects diagnosed with asthma (p -trend = 0.8; not indicated in the table). For hay fever, risk was reduced for longer durations of having the condition; the trend was not significant among those diagnosed with hay fever only (p -trend = 0.6), but was significant when including subjects never diagnosed with this condition as the baseline category (p -trend = 0.007; not indicated in the table).

The relative risk of glioma was 0.61 (95% CI: 0.43–0.88) in subjects who reported having eczema 1 year prior to the reference date, but was not materially reduced in those who reported that their eczema had stopped prior to this time (OR = 0.94, 95% CI: 0.63–1.39) (Table II). On the basis of SE England data only, this was similarly observed for hay fever with a relative risk of 0.48 (95% CI: 0.33–0.69) for current hay fever sufferers *versus* 1.50 (95% CI: 0.83–2.72) for past sufferers, but not for asthma (OR = 0.75 (95% CI: 0.44–1.30) for current asthma *vs.* 0.48 (95% CI: 0.24–0.96) for past asthma (not indicated in the table).

Glioma risk was not appreciably related to the proportion of the year the subject was affected by eczema: the relative risk was 0.61 (95% CI: 0.38–0.99) for those affected for 8 months or more and was 0.66 (95% CI: 0.42–1.03) for those who said they were occasionally affected compared to subject not affected by eczema. The risk reduction was strongest in subjects who reported that their eczema was triggered as a result of contact with particular substances (OR = 0.41, 95% CI: 0.23–0.70 not indicated in the table).

Risk of all the main histological types of glioma was reduced in subjects reporting asthma, eczema or hay fever, and there was no statistically significant heterogeneity in risk by histology (Table III). Allergy associations were not appreciably stronger or weaker in glioblastoma than in non-glioblastoma tumours, or in grade I/II compared with grade III/IV tumours.

Study participants in the SE England study were asked about other allergies they had ever been diagnosed with. Risk was reduced for all defined types of allergy; the relative risk was 0.35 (95% CI: 0.15–0.81) for seasonal allergic rhinitis and conjunctivitis and 0.39 (95% CI: 0.15–0.99) for nonseasonal allergic rhinitis and conjunctivitis, respectively, 0.74 (95% CI: 0.40–1.36) for food allergy and 0.54 (95% CI: 0.30–0.97) for contact allergy (not indicated in the table).

Risk of glioma in the SE England study was significantly reduced among subjects with hay fever or allergic rhinitis and conjunctivitis who reported ever using nasal sprays (OR = 0.43, 95% CI: 0.24–0.79) compared with those who did not, but not for use of antihistamines, eye drops or desensitisers, based on very small numbers (Table IV). Risk was significantly reduced for use of any of these medications (OR = 0.48, 95% CI: 0.24–0.96) but was similar for subjects reporting use for less than half the year compared with use for more than half the year to almost every day. Risk in asthma sufferers who reported using antiasthmatic drugs almost every day was 0.62 (95% CI: 0.31–1.24) compared with nonasthma sufferers, similar to those reporting never-use or use less than half the year (OR = 0.65, 95% CI: 0.36–1.19; not indicated in the table).

For 93% of controls and 83% of cases interviewers rated that the participant remembered their medical history well or very well. Repeating the analyses including only these subjects did not materially affect the results. The results for allergic conditions were not altered by additional adjustment for smoking status, interview lag time, or for past diagnostic radiographic examinations involving the head. Five cases and 3 controls had had radiotherapy to the head 10 or more years prior to the reference date; results were similar after excluding these subjects from the analyses. Associations with allergic conditions were somewhat stronger for females than males, but not consistently or significantly so.

TABLE III – RISK OF GLIOMA IN RELATION TO PAST DIAGNOSIS WITH ASTHMA, HAY FEVER OR ECZEMA, BY HISTOLOGICAL TUMOUR TYPE AND GRADE, UK

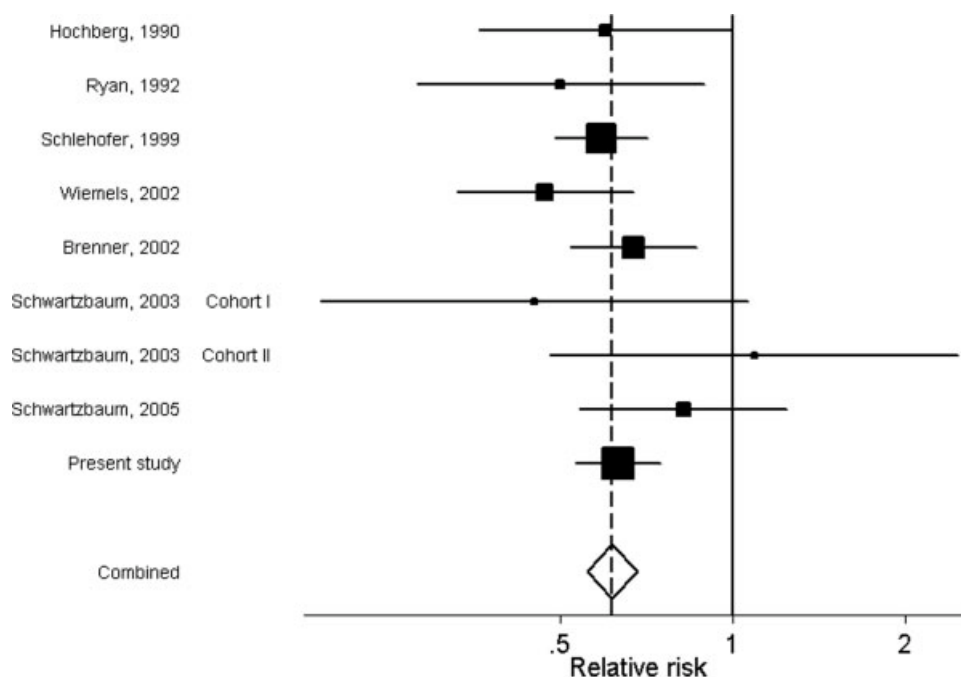
Histological tumour type	Allergic condition							
	Asthma		Hay fever		Eczema		Any of these conditions	
	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*
<i>Histological group^a</i>								
Glioblastoma (<i>n</i> = 447)	40	0.71 (0.49–1.03)	77	0.79 (0.59–1.05)	36	0.69 (0.47–1.02)	119	0.67 (0.52–0.85) ^e
Non-glioblastoma, total (<i>n</i> = 490)	56	0.74 (0.53–1.03)	94	0.69 (0.53–0.91) ^e	55	0.79 (0.56–1.10)	149	0.62 (0.49–0.78) ^f
		<i>p</i> heterogeneity = 0.9		<i>p</i> heterogeneity = 0.5		<i>p</i> heterogeneity = 0.6		<i>p</i> heterogeneity = 0.6
Astrocytoma (<i>n</i> = 314)	38	0.78 (0.53–1.14)	58	0.66 (0.48–0.92) ^e	37	0.83 (0.56–1.22)	93	0.59 (0.45–0.79) ^f
Oligodendroglioma (<i>n</i> = 98)	13	0.96 (0.52–1.79)	19	0.70 (0.41–1.18)	9	0.69 (0.34–1.41)	30	0.64 (0.41–1.01)
Other glioma (<i>n</i> = 78) ^b	5	0.41 (0.16–1.03)	17	0.79 (0.45–1.39)	9	0.79 (0.39–1.63)	26	0.69 (0.42–1.13)
		<i>p</i> heterogeneity = 0.4 ^c		<i>p</i> heterogeneity = 0.8 ^c		<i>p</i> heterogeneity = 0.9 ^c		<i>p</i> heterogeneity = 0.9 ^c
<i>Tumour grade</i>								
Grade I/II (<i>n</i> = 293)	30	0.61 (0.40–0.94) ^d	54	0.60 (0.43–0.84)	33	0.74 (0.49–1.12)	95	0.63 (0.47–0.83) ^e
Grade III/IV (<i>n</i> = 644)	66	0.78 (0.57–1.05)	117	0.81 (0.64–1.03)	58	0.74 (0.54–1.02)	173	0.64 (0.52–0.79) ^f
		<i>p</i> heterogeneity = 0.3		<i>p</i> heterogeneity = 0.13		<i>p</i> heterogeneity = 1.0		<i>p</i> heterogeneity = 0.9

TABLE IV – RISK OF GLIOMA IN RELATION TO EVER USE OF ANTI-ALLERGENIC MEDICATION IN SUBJECTS WITH PAST DIAGNOSIS WITH HAY FEVER OR ALLERGIC RHINITIS AND CONJUNCTIVITIS, SE ENGLAND

Factor	Cases (n = 84)		Controls (n = 215)		OR (95% CI)*
	N	%	N	%	
<i>Antihistamines</i>					
No	37	44.1	82	38.1	1.00
Yes	47	55.9	133	61.9	0.83 (0.47–1.48)
<i>Nasal spray</i>					
No	56	66.7	114	53.0	1.00
Yes	28	33.3	101	47.0	0.43 (0.24–0.79) ^b
<i>Eye drops</i>					
No	66	78.6	159	74.0	1.00
Yes	18	21.4	56	26.0	0.82 (0.42–1.57)
<i>Desensitisers</i>					
No	82	97.6	204	94.9	1.00
Yes	2	2.4	11	5.1	0.61 (0.12–3.05)
<i>Any of above</i>					
No	21	25.0	40	18.6	1.00
Yes	63	75.0	175	81.4	0.48 (0.24–0.96) ^a
<i>Frequency of use</i>					
Less than half the year	48	57.1	144	67.0	0.49 (0.24–0.98) ^a
More than half the year but not every day/almost every day	15	17.9	31	14.4	0.48 (0.19–1.21)

*Odds ratios adjusted for sex, age category, region, interview year and Townsend deprivation category. ^a $p < 0.01$. ^b $p < 0.05$.

FIGURE 1 – Relative risk of glioma in relation to self-reported history of allergy, previous studies and the present study. The definition of 'allergy' varies by study, but usually includes asthma, hay fever and eczema. Wiemels et al. (2002) defined it as being allergic to specified allergens and Schwartzbaum et al. (2005) as having a history of asthma or hay fever. All studies are case-control studies except for the study by Schwartzbaum et al. (2003), who reported results of 2 cohorts of subjects with self-reported allergic conditions. The combined estimate was 0.62 (95% CI: 0.56–0.68, p -heterogeneity = 0.5), obtained using the 'meta' command in STATA.²¹



Discussion

We conducted a large population-based case-control study of risk of glioma in relation to history of allergic conditions. Risk of glioma was significantly reduced in people who reported a past diagnosis of asthma, eczema, hay fever or other types of allergy. Risk was reduced for all the main histological groups of glioma and there was no significant heterogeneity in risk between groups. Among affected subjects, there was no significant evidence for a gradient of risk with age at onset or time since onset or with the number of conditions reported. Our study did not suggest that use of antiasthmatic drugs was related to risk in asthmatic subjects, but use of antiallergenic medication was related to a significantly reduced risk of glioma in subjects with hay fever or allergic rhinitis and conjunctivitis. To our knowledge, only 1 published case-control study on allergies was larger than the present one, includ-

ing 1,178 glioma cases, but that study reported relatively little detailed information on allergies.⁵

The overall results of this study are comparable to those from most previous studies on glioma, which have consistently reported reduced risks in relation to allergic disease^{1–9} (Fig. 1) or with elevated total IgE levels.²⁴ Reduced risks of glioma have also been reported for autoimmune disease^{7,8} and for IgG-positivity to varicella-zoster, but not to several other viruses^{25–27} or *Toxoplasma gondii*.²⁸ It is interesting to note that overt immunodeficiency such as in AIDS-related immunosuppression has been associated with moderately increased risks of glioma.^{29–31} Studies of meningioma^{2,3,5,7,8} have generally reported nonsignificantly reduced risks in relation to allergies, although often less strongly reduced than for glioma, leaving it uncertain to what extent the association with allergies is specific to glioma, or general to intracranial tumours.

Reduced risks of malignancy in subjects with allergies have been observed for several other cancers, including pancreatic cancer and leukaemia, but results have often not been consistent, and for some cancers, such as lung cancer, the evidence points to an increased risk.^{10,32–34} It has been hypothesised that reduced risks of cancer in individuals with allergies are due to an increased state of tumour immunosurveillance¹¹; this hypothesis has recently been refined.³⁵

There are, however, potential alternative explanations. There was a notable lack of specificity of glioma risk in our data across allergic conditions and histological groups or in relation to number of allergies or age at onset. This could point to confounding or bias as the explanation. Confounding cannot be evaluated because of the paucity of knowledge on causes of glioma. Development of atopy, however, is related to early life exposures, such as infections and social circumstances including family size and socio-economic status,¹⁸ and it is possible that shared early life determinants for allergy and glioma confound the observed associations. Genetic factors could also confound the relationship.

Interviewer bias could have occurred if interviewers asked questions about minor conditions such as allergies in a different way to glioma cases, who are often very ill, than to controls, who are relatively well. As in many previous studies, our interviewers could not be blinded to the participants' case-control status, although they were trained to treat both groups equally. Recall bias could have occurred if cases had worse recall of their medical history than controls, or if they saw as unimportant minor conditions such as allergies, because they have a tumour. Our results did not alter, however, if restricted to subjects whom the interviewer felt, rightly or wrongly, had good recall.

Selection bias is possible given the relatively low participation rate of controls—a problem in many Western countries in recent years.³⁶ We did not mention allergies in the invitation to take part in the study, however, and selective participation of allergic subjects among controls would need to have been large to explain the results. Also, as the results of this study are consistent with those from previous case-control studies with higher participation rates, it seems unlikely that selection bias could explain the results. In our study, the 51% case participation rate reflects the lengthy process in obtaining permission to approach patients, the poor prognosis of the tumour and the lack of ethics permission to actively approach proxies of ill or deceased patients for interview. This seems unlikely to have given bias, since there is no obvious reason why such nonparticipation should be related to allergy status and because allergies were not associated with histology or tumour grade, *i.e.*, with proxies of tumour prognosis. To control for potential confounding by socio-economic related variables, we adjusted the analyses for Townsend deprivation score, but this cannot rule out the presence of residual confounding.

Reverse causality is possible, *i.e.*, the inverse association between allergies and glioma risk might be due to suppression of the immune system by the tumour itself. Glioma patients are known to have immunological defects such as abnormal delayed hypersensitivity responses, low number of circulating T cells, decreased antibody response and impaired T-cell cytotoxicity.^{37,38} It is not clear, however, for what length of time the tumour would be able to exert immunological effects in its preclinical phase, which is thought to be long for low-grade but brief for high-grade gliomas.³⁹ Most previous studies on brain tumour risk in relation to allergy or IgE levels were case-control studies, and so exposure was assessed when the tumour was already present. Supporting reverse causation in our study, glioma risk was only reduced in subjects reporting eczema or hay fever present 1 year before the reference date, but not for those whose condition had ceased before then. In addition, risk reductions were strongest in subjects reporting asthma or eczema with recent onset, although this did not apply to hay fever. We did not, however, find convincing evidence that risk reductions were strongest for low-grade tumours, which might be reasonably expected because of their longer pre-

clinical phase. A recent study reported significant inverse associations of risk of glioblastoma with several single nucleotide polymorphisms in genes positively related to asthma or inflammation.⁹ If confirmed in future studies, this would imply an underlying constitutional effect related to allergies, rather than reverse causation or bias.

If the inverse association of glioma risk with allergies is due to bias or reverse causality, cohort studies, if they incorporate long enough lag periods, should not show reduced risk. The only cohort study reporting on glioma risks⁸ showed a nonsignificantly reduced risk of glioma in 1 group of subjects, but not in a second group, with self-reported allergic disease (Fig. 1). Three other cohorts have reported risk of brain tumours or CNS tumours; 2 (including 1 very large) did not report significantly reduced risks^{33,40} and 1 reported a significantly increased risk.⁴¹ These studies did not report on risks of glioma separately, although gliomas represent the majority of brain tumours.⁴²

In our study, and in others,^{5–7} there is no clear trend of decreasing risk with younger age at onset of the allergic condition. Furthermore, risk in our study was not more strongly reduced in subjects with several allergic conditions than in subjects reporting only 1 condition. This argues somewhat against immunological causes of glioma, because early-onset asthma, for example, is more likely to be IgE-related than late-onset asthma,⁴³ and because people with multiple allergies are more likely to be truly allergic.⁴⁴ Results related to severity of allergy were ambiguous. Glioma risk among people with hay fever was halved for use of antiallergenic medication, but this could reflect an effect of medication as well as disease severity. In contrast, risk was unrelated to medication use among asthma sufferers or to the proportion of the year subjects were affected by eczema, which might be proxies of severity of these allergies. Data on allergies reported as physician-diagnosed were collected in this study, which for asthma and hay fever have high specificity and positive predictive values when assessed against clinical physiological examination.^{45,46} The prevalence of reported allergy among controls was relatively high in this study compared with previous studies, but the prevalence of allergies in the UK have been reported to be among the highest in international surveys.^{47–49} Our study did not have a concrete biomarker for allergy and some of the conditions reported by participants might not have been atopic (IgE-mediated). A previous study, however, found strong inverse associations of glioma risk both with IgE levels and self-reported allergy, although concordance between the latter two was low, suggesting that an IgE-mediated response might not directly be the mechanistic process driving the observed reduced risk.²⁴

In conclusion, this study showed reduced risks of glioma in subjects with a history of allergies, consistent with previous studies. There was, however, a lack of specificity of effect across conditions and histological groups, and an absence of a clear relationship of risk with age at onset, latency, duration and severity of allergy. Reasons for the association need clarification, as well as aetiology, confounding, bias and reverse causality need to be considered.

Acknowledgements

The funders had no involvement in the study design, data collection, statistical analysis or interpretation of the data, report writing or decision to submit this paper. The views expressed in the publication are those of the authors and not necessarily those of the funders. We would like to thank Dr. Elisabeth Cardis, the coordinator of the Interphone study along with her colleagues for support. We would also like to thank Dr. Adrian Mander for help with the metagraph command for STATA.

The Northern UK study would like to thank all study interviewers, administrators and computer programmers involved in the study. They wish to acknowledge the support of the membership of the study Steering Group chaired by Prof. David Coggon.

We acknowledge the support of the following neuropathologists, neuroradiologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, specialist nurses and administrators based in hospitals located in Scotland (Mr Barlow, Professor I Bone, Ms J Brown, Mr J Crowther, Miss R Dolan, Mr Dunn, Mr MO Fitzpatrick, Mrs M Fraser, Dr R Grant, Dr A Gregor, Professor J Ironside, Mr Johnstone, Mr Lyndsay, Mrs S Macnamara, Miss J Mair, Mr R Mills, Miss Myles, Mr B O'Reilly, Mr V Papanastassiou, Professor R Rampling, Mr Russell, Mr D Sim, Mr P Statham, Mr Steers, Mr Taylor, Professor Teasdale, Professor I Whittle), West Midlands (Dr JM Anderson, Dr Barbour, Dr CR Barraclough, Dr P Bennett, Dr HG Boddie, Mr Brind, Dr Carey, Mr M Choksey, Mr M Christie, Dr RN Corston, Professor GS Cruickshank, Dr A Detta, Mr P Dias, Dr SJ Ellis, Mr G Flint, Dr DA Francis, Mr AH Grubneac, Mr SP Harland, Dr C Hawkins, Dr T Heafield, Dr RC Hughes, Dr DG Jamieson, Dr A Logan, Mr CHA Meyer, Mrs R Mitchell, Professor K Morrison, Dr P Newman, Dr D Nicholl, Dr S Nightingale, Dr HS Pall, Mr JR Ponsford, Dr A Shehu, Mr Singh, Dr JA Spillane, Mr P Stanworth, Dr B Summers, Mr AR Walsh, Mr J Wasserberg, Professor AC Williams, Dr J Winer, Mr S Zygmunt), Trent (Dr RJ Abbott, Ms S Adams, Mr RD Ashpole, Mr RDE Battersby, Professor L Blumhardt, Mr P Byrne, Miss M Cartmill, Dr SC Coley, Dr P Critchley, Dr BB Faraj, Dr A Gibson, Dr P Griffiths, Dr R Grunwald, Dr TJ Hodgson, Mr DT Hope, Dr S Howell, Dr D Jefferson, Mr D Jelinek, Dr N Jordan, Mr A Kemeny, Dr MC Lawden, Professor J Lowe, Dr N Messios, Ms Kirsty Pardoe, Dr S Price, Dr IF Pye, Mr M Radatz, Mr I Robertson, Dr K Robson, Dr C Romanowski, Dr G Sawle, Dr B Sharrock, Prof P Shaw, Dr C Smith, Dr W Temperley, Dr G Venables, Mr B White, Mr AM Whiteley, Dr Wills) and West Yorkshire (Dr Al-Din, Dr D Ash, Dr J Bamford, Dr M Bond, Dr G Bonsor, Dr L Bridges, Dr B Carey, Dr Chakrabarty, Mr P Chumas, Dr D Dafalla, Dr H Ford, Dr Gerrard, Dr Goulding, Dr J Howe, Dr S Jamieson, Dr Johnson, Dr Louizou, Mr P Marks, Dr M Nelson, Dr S Omer, Mr N Phillips, Mr S Ross, Dr I Rothwell, Dr H Spokes, Dr J Straiton, Mr G Towns, Mr A Tyagi, Mr P Vanhille, Dr M Busby).

The Southeast England study would like to thank Mrs D Hogen for study administration and their research nurses, Mrs A Butlin, Mrs J Owens, Mrs A Hart, Mrs R Knight, Mrs C Parsley, Mrs M Pelerin, Mrs K Sampson and Mrs M Swanwick, for data collection. They thank Professor H Møller, Mr B Plewa and Mr S Richards from the Thames Cancer Registry and the following neuropathologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, administrators and secretaries for the help they provided: Mr DG Hardy, Mr PJ Kilpatrick, Mr R Macfarlane (Addenbrooke's Hospital); Ms M Cronin, Ms T Foster, Ms S Furey, Dr M G Glaser, Ms F Jones, Mr ND Mendoza, Prof ES Newlands, Mr KS O'Neill, Mr D Peterson, Ms F Taylor, Prof J van Dellon (Charing Cross Hospital); Dr JJ Bending (Eastbourne District Hospital); Mr PR Bullock, Mr C Chandler, Mr B Chitnavis, Mr L Doey, Mr RW Gullan, Prof CE Polkey, Mr R Selway, Mr MM Sharr, Ms L Smith, Prof AJ Strong, Mr N Thomas (King's College Hospital); Dr GM Sadler (Maidstone Hospital); Dr S Short (Mount Vernon Hospital); Prof S Brandner, Mr AD Cheesman, Miss JP Grieve, Mr WJ Harkness, Dr R Kapoor, Mr ND Kitchen, Mrs T Pearce, Mr MP Powell, Dr J Rees, Prof F Scaravilli, Prof DT Thomas, Mr LD Watkins (National Hospital for Neurology and Neurosurgery); Mr AR Aspoas, Mr S Bavetta, Mr J C Benjamin, Mr KM David, Mr JR Pollock, Dr E Sims (Oldchurch Hospital); Mrs J Armstrong, Mr J Akinwunmi, Mr G Critchley, Mr L Gunasekera, Mr C Hardwidge, Mr JS Norris, Dr PE Rose, Mr PH Walter, Mr PJ Ward, Dr M Wilkins (Princess Royal Hospital); Prof TZ Aziz, Prof D Kerr, Mr PJ Teddy (Radcliffe Infirmary); Ms M Allen, Ms T Dale, Mr R Bradford, Prof AP Dhillon, Mr NL Dorward, Ms D Farraday-Browne, Dr DJ McLaughlin, Mr RS Maurice-Williams, Dr K Pigott, Ms B Reynolds, Ms C Shah, Mr C Shieff, Dr EM Wilson (Royal Free Hospital); Mr F Afshar, Mr HE Ellamushi, Prof PM Richardson, Mr HI Sabin, Mr J Wadley (Royal London Hospital); Professor M Brada, Dr FH Saran, Mrs D Traish (Royal Marsden Hospital); Dr S Whitaker (Royal Surrey County Hospital); Dr PN Plowman (St. Bartholomew's Hospital); Mrs Carole Bramwell, Prof A Bell, Mr F Johnston, Mr H Marsh, Mr A Martin, Mr PS Minhas, Miss A Moore, Mr S Stapleton, Dr S Wilson (St. George's Hospital); Dr RP Beaney (St Thomas' Hospital).

References

- Hochberg F, Toniolo P, Cole P, Salcman M. Nonoccupational 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.
- Schlehofer B, Blettner M, Becker N, Martinsohn C, Wahrendorf J. Medical risk factors and the development of brain tumors. *Cancer* 1992;69:2541-7.
- 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 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.
- Wiemels 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.
- 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.
- Schwartzbaum J, Jonsson F, Ahlbom A, Preston-Martin S, Lonn S, Soderberg KC, Feychting M. Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. *Int J Cancer* 2003;106:423-8.
- Schwartzbaum J, Ahlbom A, Malmer B, Lonn S, Brookes AJ, Doss H, Debinski W, Henriksson R, Feychting M. Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. *Cancer Res* 2005;65:6459-65.
- Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 2005;60:1098-111.
- Burnet M. Cancer: a biological approach. *Br Med J* 1957;841-7.
- Cardis E, Kilkenny M. International case-control study of adult brain, head and neck tumours: results of the feasibility study. *Radiat Protect Dosim* 1999;83:179-83.
- Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren M, McKinney PA. Mobile phone use and risk of glioma in adults: a UK case-control study. *Br Med J* 2006;332:883-7.
- WHO. International statistical classification of diseases and related health problems, 10th revision. Geneva: World Health Organization, 1992.
- WHO. International classification of diseases for oncology, 3rd edn. Geneva: World Health Organization, 2000.
- OPCS. General practitioner morbidity statistics. London: Office of Populations Censuses and Surveys, 1992.
- Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the north. New York: Croom. Helm., 1988.
- Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55 (Suppl 1):S2-S10.
- Preston-Martin S, Mack W. Neoplasms of the nervous system. In: Schottenfeld D, Fraumeni JF, Jr, eds. *Cancer epidemiology and prevention*, 2nd edn. New York: Oxford University Press, 1996. 1231-81.
- Cox DR, Hinkley DV. Theoretical statistics. London: Chapman & Hall, 1974.
- StataCorp. Stata statistical software: release 8.0. College Station, Texas: Stata Corporation, 2003.
- Hjern A, Hedberg A, Haglund B, Rosen M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. *Clin Exp Allergy* 2001;31:908-14.
- ESRC/JISC Census Programme, 2001. Original Data Depositor-2001 Census. Census Area Statistics (Scotland) and Census Area Statistics (England & Wales) [computer file]. Census Dissemination Unit, MIMAS (University of Manchester)/Census Interaction Data Service (University of Leeds).

24. Wiemels JL, Wiencke JK, Patoka J, Moghadassi M, Chew T, McMillan A, Miike R, Barger G, Wrensch M. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Res* 2004;64:8468–73.
25. 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.
26. Wrensch M, Weinberg A, Wiencke J, Miike R, Barger G, Kelsey K. Prevalence of antibodies to four herpesviruses among adults with glioma and controls. *Am J Epidemiol* 2001;154:161–5.
27. Wrensch M, Weinberg A, Wiencke J, Miike R, Sison J, Wiemels J, Barger G, DeLorenze G, Aldape K, Kelsey K. History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. *Am J Epidemiol* 2005;161:929–38.
28. Ryan P, Hurley SF, Johnson AM, Salzberg M, Lee MW, North JB, McNeil JJ, McMichael AJ. Tumours of the brain and presence of antibodies to *Toxoplasma gondii*. *Int J Epidemiol* 1993;22:412–9.
29. Goedert JJ, Cote TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, et al. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998;351:1833–9.
30. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. *AIDS* 1999;13:839–43.
31. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–45.
32. Gandini S, Lowenfels AB, Jaffee EM, Armstrong TD, Maisonneuve P. Allergies and the risk of pancreatic cancer: a meta-analysis with review of epidemiology and biological mechanisms. *Cancer Epidemiol Biomarkers Prev* 2005;14:1908–16.
33. Turner MC, Chen Y, Krewski D, Ghadirian P, Thun MJ, Calle EE. Cancer mortality among US men and women with asthma and hay fever. *Am J Epidemiol* 2005;162:212–21.
34. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. *Int J Cancer* 2006;118:3124–32.
35. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoevasion: from immunosurveillance to tumor escape. *Nat Immunol* 2002;3:991–8.
36. Hopper JL, Bishop DT, Easton DF. Population-based family studies in genetic epidemiology. *Lancet* 2005;366:1397–406.
37. Dix AR, Brooks WH, Roszman TL, Morford LA. Immune defects observed in patients with primary malignant brain tumors. *J Neuroimmunol* 1999;100:216–32.
38. Walker PR, Calzascia T, Dietrich PY. All in the head: obstacles for immune rejection of brain tumours. *Immunology* 2002;107:28–38.
39. Behin A, Hoang-Xuan K, Carpentier AF, Delattre JY. Primary brain tumours in adults. *Lancet* 2003;361:323–31.
40. Eriksson NE, Mikoczy Z, Hagmar L. Cancer incidence in 13811 patients skin tested for allergy. *J Investig Allergol Clin Immunol* 2005;15:161–6.
41. Hagstromer L, Ye W, Nyren O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. *Arch Dermatol* 2005;141:1123–7.
42. CBTRUS. Statistical report: primary brain tumors in the United States 1997–2001. Chicago: Central Brain Tumor Registry of the United States, 2004.
43. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101–8.
44. Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the UK diagnostic criteria for atopic dermatitis in a population setting. UK diagnostic criteria for Atopic Dermatitis Working Party. *Br J Dermatol* 1996;135:12–7.
45. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;104:600–8.
46. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults. *Allergy* 2001;56:377–84.
47. ISAAC. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;351:1225–32.
48. ECRHS. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687–95.
49. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, Jarvis D, Kuenzli N, Leynaert B, Luczynska C, Neukirch F, Svanes C et al. The European Community Respiratory Health Survey: what are the main results so far? *European Community Respiratory Health Survey II. Eur Respir J* 2001;18:598–611.