

ASSOCIATION OF ADULT GLIOMA WITH MEDICAL CONDITIONS, FAMILY AND REPRODUCTIVE HISTORY

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A population-based case-control study of 416 histologically diagnosed, incident gliomas in adults was carried out in Melbourne, Australia, to determine whether past medical, family or reproductive histories are risk factors for developing glioma. A total of 422 controls were selected from the Australian electoral roll and matched to cases for age, sex and post code of residence. An increased risk of developing glioma was observed among first-born individuals OR (95% CI) 2.0 (1.4–2.9). It is possible that this effect is due to residual confounding by socio-economic status or that it is a chance finding. Alternatively, it may be that this is due to some other effect linked to the first pregnancy, such as maternal age, birth weight or circumstances of delivery. There was no apparent association between the development of glioma and other neuropsychiatric or general medical conditions or with family history or reproductive history. Allergies (asthma and eczema) were not associated with a decreased risk of glioma, as has previously been suggested. *Int. J. Cancer* 71:203–207, 1997.

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Glioma is the most common primary brain malignancy in adults, accounting for approximately 75% of all primary adult brain tumours (Green *et al.*, 1976). The prognosis is poor, with a median survival of less than 12 months (Axtell *et al.*, 1983; Whittle *et al.*, 1991) and an increasing incidence over the last 30 years (Davis *et al.*, 1991). The causes of glioma are unknown, and related to this, no preventive strategy is available. Although many possible risk factors for brain tumours have been suggested, there is still no dominant hypothesis. A wide range of genetic and environmental factors have been investigated. While some evidence exists implicating certain work chemicals (Burch *et al.*, 1987; Preston-Martin and Mack, 1991; Morrison *et al.*, 1992), investigations of a wide range of genetic and environmental factors have been inconclusive (Burch *et al.*, 1987; Wrensch and Barger, 1990; Schiffer, 1991; Ryan *et al.*, 1992; Zampieri *et al.*, 1994).

A role has been suggested for genetic factors in the aetiology of glioma (Schiffer, 1991; Wrensch and Barger, 1990), but this is not consistent in all studies (Choi *et al.*, 1970). This is based on the following: the difference in distribution of ABO blood groups between brain tumour patients and controls (Selverstone and Cooper, 1961; Zampieri *et al.*, 1994), the association of brain tumours with genetically determined disorders (Schiffer, 1991), some evidence of familial aggregation of brain tumours (Schiffer, 1991) and familial clustering of brain tumours with breast and lung cancers (Wrensch and Barger, 1990; Zampieri *et al.*, 1994).

A number of exploratory case-control studies have been reported which examine the association of medical conditions, family and reproductive history in cases with glioma and controls. There are few consistent findings. There is some evidence that allergies may decrease the risk of glioma (Hochberg *et al.*, 1990; Ryan *et al.*, 1992; Schlehofer *et al.*, 1992a). Although in one report the authors suggested that the reproductive and hormonal status of the individual may influence the risk of brain tumour, they present scant evidence for this as all 95% confidence intervals (CIs) for the odds ratios (ORs) are wide and include 1.0 (Schlehofer *et al.*, 1992b).

The aim of our study was to investigate the association between glioma and a number of specific medical conditions and aspects of

family and reproductive history in the largest case-control study of glioma conducted to date.

METHODS

Case and control subject selection

Cases were defined as people with histologically confirmed primary glioma (ICD-0 codes 938–946) diagnosed between July 1987 and December 1991, who were aged 20–70 years at diagnosis and lived in Melbourne or 4 other major Victorian cities. Residents of these areas account for 85% of the population of the state of Victoria. Case subjects were identified by screening the medical records of 14 Melbourne hospitals, which together provide most of the neurosurgical services within Victoria. Completeness of ascertainment was checked by reference to the Victorian Cancer Registry, to which notification of the incident cases of cancer is required by law. We sought approval on an individual basis from the attending neurosurgeon to approach each subject. A letter inviting the patient to participate in an interview was sent. If the patient did not contact the study office, he or she was telephoned or further letters were sent. If the patient had died, a proxy subject was interviewed. Proxies were chosen in the following order of priority: spouse (or partner), children, siblings and other relatives or friends.

Over the study period, we identified and attempted to recruit 627 eligible case. The attending neurosurgeons refused permission to approach 76 patients, we were unable to contact 67 patients, 15 patients refused to participate, 49 proxy subjects refused interview and 4 patients did not speak English sufficiently well to be interviewed. We conducted 416 case interviews, 234 (56.3%) with the index subject and 182 (43.7%) with a proxy. Case participation, therefore, represented 66% of those eligible and 86% of those contacted.

Of the 416 participating cases, 166 (39.9%) were women and 250 (60.1%) were men (Table I). In comparison, a higher percentage of the 211 eligible patients who did not participate were women (43.6%), but this difference was not statistically significant. Participating case subjects were younger than those who did not participate (48.9 vs. 53.3 years, $t = -3.65$, $df = 625$, $p = 0.0003$). In addition, participating cases lived in post code areas with a higher socio-economic status than non-participating cases, as measured by the indicator of disadvantage, which is based on the

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TABLE I – CHARACTERISTICS OF SUBJECTS

	Cases	Controls
Number	416	422
Mean age ¹ (SD)	48.9 (14.3)	50.2 (14.3)
Sex (% females)	166 (39.9)	170 (40.3)
Educational level ² (%)		
Secondary or less	181 (43.5)	175 (41.5)
Technical	127 (30.5)	134 (31.8)
University	103 (24.8)	112 (26.6)
Proxy interviews (%)	234 (56.3)	

¹At reference date (date of diagnosis for cases and selection of controls).—²Data missing for 5 cases and 1 control.

census data. The mean score ($\pm$ standard deviation) for this index was 103.6 ($\pm$ 7.3) for the participating cases and 102.1 ($\pm$ 7.6) for the non-participating cases ($t = 2.54$, $df\ 624$, $p = 0.012$).

Initially, we planned to recruit 2 control subjects per case, individually matched for gender and age (± 5 years), from a random sample of people listed on the Victorian electoral roll who lived in the areas from which the cases were recruited. Enrolment on the electoral roll is compulsory, and an estimated 85% of those eligible were listed on the roll in 1989 (Hurley, 1990). Due to budgetary constraints, we revised our target to one control per case, and in some instances the control subject was recruited before the case subject, using the age-gender distribution of cases predicted from the Victorian Cancer Registry incidence data. The control selection procedure, therefore, more closely resembled frequency matching than individual matching. Potential controls were considered ineligible if they had a history of stroke, epilepsy or brain tumour.

Controls were recruited by first sending an invitation letter, which described the project as a study aimed at investigating the causes of certain illnesses affecting the nervous system. If the subject did not reply, we attempted to obtain a telephone number and 3 contact attempts were made. If a telephone number could not be obtained, we sent a second invitation letter. An index subject was interviewed for each case, irrespective of whether a proxy or index case subject was interviewed.

A total of 968 potential control subjects were selected from the electoral roll, of whom 288 could not be contacted (either because letters were returned or because the subject did not respond to the letter and a telephone number could not be found); 14 had moved interstate or overseas; 2 were too ill; 5 had died; 7 gave a history of stroke, epilepsy or brain tumour; and 230 refused interview. We therefore interviewed 422 control subjects, representing 43.5% of those identified as potentially eligible and 64.7% of those eligible subjects who were contacted. Of the participating controls, 710 (40.3%) were women and 252 (59.7%) were men. Compared with the participating control subjects, the group of potential controls who did not participate had a higher percentage of women (45.6% vs. 40.3) and were younger (49.8 vs. 50.2 years), though neither difference was statistically significant. However, as for case subjects, participating controls lived in areas with a higher socioeconomic status than those of non-participating controls (mean indicator of disadvantage: 104.2 ± 6.7 vs. 102.6 ± 7.6 , $t = 3.38$, $df = 964$, $p = 0.0007$). Of these, 423 were interviewed, representing 45% of those eligible and 65% of those contacted.

Data collection

The study instrument was a detailed questionnaire based on an instrument provided by the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) programme of the International Agency for Research on Cancer (IARC, Lyon, France) and sought details of exposure to a wide range of factors previously reported as possible risk factors for developing brain tumour. The questionnaire was administered in the participant's home by a research nurse.

Statistical methods

Exposure status was determined from a subject's experience up to 2 years before the time of diagnosis (cases) or interview (controls) to allow for a period of tumour induction to avoid recording changes in exposure related to early disease.

Standard statistical methods for the analysis of case-control studies were used throughout. Logistic regression analysis was used to control for the matching variables (age and sex) and to adjust for any confounders. A variable was considered a confounder if it altered the risk associated with an exposure by 10% or more. Relative risks were estimated using the method of maximum likelihood, and the 95% CIs were based on the standard error of coefficient estimated and the normal approximation. Significant tests at 5% were performed by referring the likelihood ratio statistic to the χ^2 distribution. In some instances, analyses were repeated including only index subject interviews (*i.e.*, excluding proxies).

RESULTS

There was no significant difference in age and sex distribution or educational level among cases and controls (Table I).

Medical history

Previous neurological disease was not associated with a significant risk of developing glioma (meningitis OR [95% CI] 1.7 [0.6–4.7], medically diagnosed depression 0.8 [0.5–1.4]) (Table II). Brain abscess, multiple sclerosis, spinal tumour, schizophrenia, neurofibromatosis and tuberous sclerosis were also examined, but for each condition less than 2 cases or controls were found.

TABLE II – ASSOCIATION OF MEDICAL CONDITIONS AND GLIOMA

Exposure	Cases ¹ (n = 416)	Controls ¹ (n = 422)	Odds ratio ² (95% CI)	Odds ratio ² (index subjects only) ³ (95% CI)
Meningitis				
Yes	10	6	1.7 (0.6–4.7)	2.2 (0.7–7.1)
No	405	416		
Depression				
Yes	28	35	0.8 (0.5–1.4)	1.0 (0.5–2.0)
No	382	387		
Asthma				
Yes	36	46	0.8 (0.5–1.2)	0.76 (0.5–1.3)
No	371	367		
Eczema				
Yes	29	34	0.9 (0.5–1.4)	1.0 (0.1–1.3)
No	377	384		
Diabetes				
Yes	4	12	0.3 (0.1–1.1)	0.7 (0.2–2.2)
No	400	404		
Anaemia				
Yes	3	2	1.7 (0.3–10.2)	1.1 (0.8–1.5)
No	409	419		
Gastrectomy				
Yes	2	5	0.4 (0.1–2.2)	1.04 (0.1–10.3)
Fever				
Nil	159	137	1.00	1.00
≤ 1 /year	218	258	0.7 (0.5–1.0)	0.8 (0.5–1.3)
> 2 /year	33	26	1.1 (0.6–1.9)	0.8 (0.4–1.8)
Blood group:				
O	85	105	1.0	1.0
A	59	63	1.1 (0.7–1.8)	0.7 (0.3–1.8)
B	12	19	0.8 (0.4–1.7)	0.6 (0.1–2.1)
AB	5	9	0.7 (0.2–2.2)	0.8 (0.5–1.5)
Other cancers				
Yes	16	29	0.6 (0.3–1.1)	0.5 (0.2–1.2)
No	396	391		

¹The numbers do not always equal 416 or 422 because of missing data.—²Odds ratio obtained by logistic regression adjusting for age and sex.—³Analyses repeated including only index subject interviews (*i.e.*, excluding proxies).

Other medical conditions were examined to see whether they affected the risk of glioma (Table II). There was no significant association between allergies (either asthma or eczema), diabetes, anaemia, a previous gastrectomy or a history of regular episodes of fever and the risk of developing glioma (Table II). Results were similar when proxy respondents were excluded. Although information on blood group was available on only 38.7% of cases and 40.0% of controls, there was no evidence that blood group affected the risk of glioma (Table II).

A reduced, but inconclusive, reduction in glioma risk was found for the presence of other (second) cancers, OR 0.6 (0.3–1.1). Similar results were observed when proxy interviews were excluded. There was no significant difference in the types of malignancy found in cases and controls. The following malignancies were found in cases: skin/bone ($n = 4$), genito-urinary ($n = 6$), bowel ($n = 1$), breast ($n = 2$), lymphoproliferative ($n = 2$) and lung ($n = 1$). The following malignancies were found in controls: skin/bone ($n = 13$), genito-urinary ($n = 6$), bowel ($n = 5$), breast ($n = 3$), lymphoproliferative ($n = 1$) and lung ($n = 1$).

Genetic factors

Having a first-degree relative with epilepsy, OR 0.9 (0.5–1.9); brain or spinal tumours, OR 0.7 (0.3–1.4); or other cancers, OR 1.1 (0.8–1.4) was not associated with an increased risk of glioma (Table III). In this study, there was no family with an aggregation of cancers. The number of cases and controls with more than one relative with either epilepsy or malignancy was similar. There was no difference in the family history of cancer in glioma cases aged less than 50 years at diagnosis (26.5%) and in the control population aged less than 50 years (29.5%). There was no difference in the relative type who had cancer among cases and controls (data not shown). Only 2 cases had a relative with neurofibromatosis. No cases or controls had any relatives with tuberous sclerosis.

Social and reproductive history

The risk of glioma was increased in first-born individuals, OR (95% CI) 2.0 (1.4–2.9), adjusted for age and sex (Table IV). This result persisted after adjusting for post code and educational level, OR 2.3 (1.4–3.5). To determine whether this effect was confounded by being an only child, we repeated the analysis by excluding the 32 individuals who were only children. The OR for first-born (excluding only children) and adjusted for confounders was 2.3 (1.4–3.7). The OR for being an only child, adjusting for confounders, was 1.5 (0.6–3.7). Birth rank, apart from first-born status, was not associated with the risk of glioma (p for trend = 0.21).

There was no difference in the number of cancers in the relatives of the first-born who had glioma (33.6%) compared to those who

were not first-born but had glioma (40.3%). There was no difference in the number of cancers in their parents and other first-degree relatives or in the age at which they developed cancers (data not shown).

Whether a woman had ever been pregnant, OR 1.1 (0.6–2.1); her menopausal status, OR 0.9 (0.5–1.4); and whether she had had a previous hysterectomy, OR 0.9 (0.5–1.4) did not significantly affect the risk of developing glioma (Table IV). When we performed these analyses excluding proxy interviews, similar results were observed.

DISCUSSION

Our large case-control study of 416 cases of histologically confirmed glioma did not demonstrate an association between glioma and general medical conditions, a family history of other neurological or malignant conditions, or reproductive or hormonal status in women. Being first-born children was associated with glioma (OR [95% CI] 2.0 [1.4–2.9]), independent of age or socio-economic factors, OR 2.3 (1.4–3.5).

The mechanism for the observed effect of being first-born on the risk of glioma is unknown, though it has also been observed in other studies (MacMahon, 1962; Choi *et al.*, 1970). This could not be explained by being an only child as excluding individuals who were only children from the analysis did not significantly affect the results, 2.3 (1.4–3.7). It is possible that this effect is due to residual confounding by socio-economic status or that it is a chance finding. Alternatively, this effect may be due to some other effect linked to the first pregnancy, such as the age of the mother, birth weight or circumstances of delivery, that was not examined in our study.

Some data suggest that general activation of the immune system, *e.g.*, in individuals with allergies (Ryan *et al.*, 1992; Schlehofer *et al.*, 1992a) or who have had regular episodes of fever (Schlehofer *et al.*, 1992a), may reduce the risk of glioma. However, our study does not support this. Care must be taken in interpreting these findings as the response to questions regarding past history of infections or allergies may be subject to response bias and may result in misclassification. No attempt was made in any of the above studies to validate the responses to these subjective questions.

The genetic disorders most frequently reported to be associated with an increased incidence of brain tumours are von Recklinghausen's disease (neurofibromatosis) (Asai *et al.*, 1991; Matsui *et al.*, 1993), tuberous sclerosis (Rieger *et al.*, 1991; Louis and von Deimling, 1995) and immunodeficiency diseases (Moulinier *et al.*, 1994). In this study, we had few individuals or first-degree relatives with either tuberous sclerosis or neurofibromatosis. Our

TABLE III – NEUROLOGICAL DISEASE AND MALIGNANCIES IN FIRST-DEGREE RELATIVES OF GLIOMA CASES AND CONTROLS

Disease	Cases ¹	Controls ¹	Odds ratio ² (95% CI)	Odds ratio ² (index subjects only) ³ (95% CI)
Epilepsy				
Yes	17 (16 × 1 relative, 1 × 2 relatives)	18 (16 × 1 relative, 2 × 2 relatives)	0.9 (0.5–1.9)	0.9 (0.5–1.9)
No	391	400		
Brain or spinal tumour				
Yes	13 (12 × 1 relative, 1 × 2 relatives)	19 (18 × 1 relative, 1 × 2 relatives)	0.7 (0.3–1.4)	0.7 (0.3–1.4)
No	393	399		
Other cancers				
Yes	131 (114 × 1 relative, 12 × 2 relatives, 1 × 4 relatives)	132 (119 × 1 relative, 11 × 2 relatives, 1 × 3 relatives)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
No	274	283		

¹The numbers do not always equal 416 or 422 because of missing data. ²Odds ratio obtained by multiple logistic regression adjusting for age and sex. ³Analyses repeated including only index subject interviews (*i.e.*, excluding proxies).

TABLE IV – SOCIAL AND REPRODUCTIVE HISTORIES OF GLIOMA CASES AND CONTROLS

	Cases	Controls	Odds ratio (95% CI)	Odds ratio (index subjects only) ³ (95% CI)
First-born				
Yes	94	56	2.0 (1.4–2.9) ¹	2.0 (1.4–3.0) ¹
No	221	263	2.3 (1.4–3.5) ²	2.4 (1.3–3.6) ²
Number of siblings				
0	21	11	1.0	1.0
1–3	224	224	0.5 (0.3–1.1)	0.6 (0.2–1.2)
4–6	96	93	0.6 (0.3–1.2)	0.6 (0.3–1.2)
>6	32	51	0.3 (0.1–0.8)	0.4 (0.1–0.9)
Previous pregnancies				
Yes	141	143	1.1 (0.6–2.1)	0.7 (0.3–1.5)
No	23	26		
Hysterectomy				
Yes	30	33	0.9 (0.6–1.7)	1.3 (0.6–3.1)
No	128	137		
Menopausal				
Yes	85	92	0.9 (0.5–1.4)	0.92 (0.4–2.2)
No	77	76		

¹ $p = 0.003$.²Adjusted for age, sex, post code and educational level.³Analyses repeated including only index subject interviews (*i.e.*, excluding proxies).

observation that there is no difference in the number of first-degree relatives who had either brain or other cancers is consistent with previous reports (van de Wiel, 1960; Ikizler *et al.*, 1992). However, some family studies have reported a significant increase in central nervous system (Choi *et al.*, 1970) and other cancers (Lynch *et al.*, 1973; Wrensch and Barger, 1990) in relatives of patients with brain tumours. For example, 34 families have been described in which an individual with brain tumour had 2 or more relatives with breast cancer (Lynch *et al.*, 1973), and there has been some evidence suggesting familial clustering of brain, breast and lung cancers (Wrensch and Barger, 1990). This suggests that these families are probably rare among glioma patients in general.

Interest in possible associations between brain tumours and family history of neurological disease was stimulated by a report showing an excess of epilepsy in siblings of children with brain tumours (Gold *et al.*, 1970). This was further supported by a study that examined the relatives of glioma cases compared with the relatives of their wives and showed excesses of epilepsy, meningi-

tis, mental retardation and Parkinson's disease among the relatives of the glioma cases (Wrensch and Barger, 1990). However, as with a number of other reports, our study does not support any such associations (van de Wiel, 1972; Ryan *et al.*, 1992).

Conflicting results have been observed in studies examining the distribution of ABO blood types in patients with brain tumours. One study demonstrated significantly more cases that were blood group A or AB (Selverstone and Cooper, 1961), while in another study, a significant excess of individuals with blood group A was observed in males but not in females (Garcia *et al.*, 1963). However, our findings are consistent with several studies that showed no difference in the distribution of blood groups between cases and controls with glioma (Choi *et al.*, 1970; Zampieri *et al.*, 1994).

Female hormonal changes appear to play a role in the aetiology of meningioma (Preston-Martin *et al.*, 1982). It has been suggested that female hormonal changes may be associated with glioma (Schlehofer *et al.*, 1992b). However, that study showed no clear evidence for this as all the risk estimates were null. In our study based on larger numbers, no such association was found.

This population-based case-control study of 416 histologically diagnosed, incident gliomas in adults examined whether past medical, family or reproductive histories are risk factors for developing glioma. Being first-born was a risk factor for developing glioma. Although this could be a result of residual confounding by, *e.g.*, socio-economic status or a chance finding, it may be due to other factors associated with being first-born, such as maternal age, birth weight or birth circumstances that were not examined in our study. In contrast, there was no evidence to support other characteristics of the individual, such as past medical, family or reproductive histories, which have previously been hypothesized to be risk factors for developing glioma.

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