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Familial and Personal Medical History of Cancer and Nervous System Conditions among Adults with Glioma and Controls

Margaret Wrensch,[1] Marion Lee,[1] Rei Miike,[1] Beth Newman,[2] Geoffrey Barger,[3] Richard Davis,[4] John Wiencke,[1] and John Neuhaus[1]

The causes of glioma, the most common type of primary malignant brain tumor, are poorly understood. This study compared the personal and first-degree familial medical histories of 462 adults newly diagnosed with glioma in the San Francisco Bay Area between August 1, 1991, and March 31, 1994, with those of 443 controls who were frequency-matched on age, sex, and ethnicity. Cases and controls had equivalent personal histories of cancers other than brain cancer and most nervous system conditions, but they differed significantly regarding histories of epilepsy, seizures, or convulsions 3 or more years prior to diagnosis (odds ratio = 3.3, 95% confidence interval (CI) 1.4–7.9), chickenpox (odds ratio = 0.4, 95% CI 0.3–0.6), and shingles (odds ratio = 0.5, 95% CI 0.3–0.8). Four cases (less than 1%) and no controls had known genetic disorders (three had neurofibromatosis and one had tuberous sclerosis). Cases and controls had similar family histories of cancer and seizures. However, the odds ratio for a validated family history of primary brain tumor was 2.3 (95% CI 1.0–5.8). These results suggest that although family history of any cancer probably is not an important risk factor for adult glioma, a family history of brain tumors may play a role. Variation in exposure to or biologic response to common viral infections might play a greater role in the etiology of adult glioma than family history. *Am J Epidemiol* 1997;145:581–93.

brain neoplasms; family characteristics; glioma; nervous system diseases

Editor's note: *A companion article by Wrensch et al. appears on page 594 of this issue.*

Despite dramatic recent advances in the molecular genetics and biology of brain tumors (1–4), very little is known about the causes of most primary brain cancers (5–7). The most common form of brain cancer in adults, glioblastoma multiforme, is almost always debilitating and rapidly fatal (8). Treatment prospects have not improved measurably for these tumors in over 20 years (9, 10). Inferences from many previous epidemiologic studies of brain cancer have been hindered by a variety of methodological problems such as small sample sizes, incomplete case series including only living or deceased cases, and inadequate or potentially biased control groups. Few etiologic hypotheses have emerged that clearly warrant wide-scale investigation (5–7). One such hypothesis is that a family history of cancer, brain tumors, or other nervous system diseases/disorders might increase the risk of brain cancer.

Certain heritable syndromes such as Li-Fraumeni familial cancer syndrome or tuberous sclerosis may involve glioma (7), and inherited defects in the p53 gene have been demonstrated in certain subsets of glioma patients (11). Thus, it is clear that a (probably small) proportion of brain tumors is due to identifiable inherited susceptibility. Familial aggregation studies (7, 12), although inconclusive, have found relative risks ranging from 1.0 to 3.7 for cancer at any site in family members of brain tumor cases (compared with controls) and risks ranging from 0.8 to 9.0 for brain tumors in family members of brain tumor cases, with most studies reporting relative risks greater than 1.0. Most of these previous findings did not reach statistical significance. Given this and other limitations of these studies with generally consistent findings of possibly increased risk, it seemed reasonable to examine whether relative risks of cancer, brain tumors, or

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Abbreviation: CI, confidence interval.
[1] Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, CA.
[2] Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC.
[3] Department of Neurology, School of Medicine, Wayne State University, Detroit, MI.
[4] Departments of Pathology and Neurosurgery, School of Medicine, University of California, San Francisco, CA.
Reprint requests to Dr. Margaret Wrensch, Box 0560, University of California School of Medicine, San Francisco, CA 94143-0560.

other nervous system conditions were increased for families of glioma cases as compared with controls in a population-based study.

The overall aim of our ongoing study of the genetic epidemiology of adult glioma is to investigate associations of familial and environmental factors with brain cancer; to determine whether familial associations may be due to common environmental exposures; and to test specific genetic models of disease occurrence in families of brain cancer cases. This first report from the San Francisco Bay Area Adult Glioma Study compares the familial and personal medical histories of cancer and certain nervous system conditions in adults with glioma to those of controls.

MATERIALS AND METHODS

Case ascertainment

All histologically confirmed incident cases of glioma (*International Classification of Disease for Oncology*, second edition (13), morphology codes 9380–9481) in adults aged 20 years or more that were diagnosed in six San Francisco Bay Area counties (Alameda, Contra Costa, Marin, San Mateo, San Francisco, and Santa Clara counties) between August 1, 1991, and March 31, 1994, were eligible for inclusion. Cases were ascertained within 2–8 weeks of diagnosis using the Northern California Cancer Center's rapid case ascertainment system, which searched hospital pathology, radiotherapy, and inpatient and outpatient records in the six Bay Area counties to identify cases. The cases, or next-of-kin for deceased cases, were first sent a letter describing the study and then were telephoned to arrange an in-person interview. Eligibility criteria for the cases included the ability of the case or proxy to be interviewed in English.

Ascertainment of controls

Through random-digit dialing (using methods described by Waksberg (14) and refined by Harlow and Davis (15)), we obtained a group of controls who were frequency-matched to cases with regard to age (5-year age groups), sex, and ethnicity (white, black, Hispanic, Asian, and other). Telephone area code, three-digit prefix, and the next two digits of cases' telephone numbers were the initial sampling units. For each sampling unit, two-digit suffixes were generated from random number tables, and the resulting telephone numbers were called until the necessary eligible matches were found. We sent a letter to eligible controls and then telephoned them to arrange an in-person interview. Eligibility criteria for controls included competence in English and residency in the San Francisco Bay Area.

Interviews

Structured interviews were conducted in English with consenting cases (or their proxies) and controls in their homes or another location of their choosing. Prior to the interview, subjects were sent a packet of materials describing the topics to be covered in the interview so that the respondent could obtain any information required.

The interviewer asked for detailed family medical information and data to facilitate validation of the reported information. For each first-degree relative (biologic parent, sibling, or child), we asked for the person's name, sex, age, date of birth, vital status (if deceased, age at death and date, cause, and place of death), and whether or not the relative had any of a list of specific medical conditions of interest. The primary conditions of interest were cancer (by primary site, if known), brain tumor, senility or dementia, mental retardation, and epilepsy, seizures, or convulsions. A list of secondary interest included stroke, heart disease or heart attack, colonic polyposis, Gardner's syndrome, Turcot's syndrome, pituitary tumor, multiple sclerosis, poliomyelitis, Parkinson's disease, meningitis, encephalitis, neurofibromatosis, learning disability, emotional or psychiatric disorder or mental illness, adrenal disease or disorder, and thyroid disease or disorder. For any positive response for a given condition, we asked about age at first diagnosis. In addition, we asked for the address and telephone number of each living relative and the name, address, and telephone number of the best informant for each deceased relative.

The interviewer then asked the case or control whether he or she had had any of the specified conditions, and the age at onset for any positive response. In addition to the conditions listed above, we also asked about personal histories of chickenpox and shingles, since both of these conditions are caused by varicella-zoster virus, which may have nervous system involvement. For cases, the interviewer asked about any conditions present prior to the brain tumor diagnosis. The remainder of the questionnaire asked for information on potential environmental and demographic risk factors for glioma.

Partway through the study, we developed and began to administer a very short telephone interview (approximately 5 minutes) for nonparticipating controls so that they could provide information on factors that might have influenced or been associated with control participation.

Because a major aim of this study was to clarify the role of family medical history, we are currently conducting extensive positive and negative validation of

reported medical conditions for relatives. Results of this validation will be presented separately.

Data analysis and statistical methods

We computed odds ratios for cases versus controls, as well as 95 percent confidence intervals, using the SAS program Logistic (16). Three analyses were performed for each variable: all cases versus all controls; self-reporting cases versus all controls; and cases for whom a proxy reported versus all controls. Although cases and controls were frequency-matched with regard to age, sex, and ethnicity, odds ratios comparing individual attributes of cases versus controls were adjusted for sex and for individual year of age as a continuous variable, to allow for the differences in age and sex distributions between self-reporting and non-self-reporting cases. Odds ratios comparing familial attributes of cases versus controls were controlled for the cases' or controls' individual year of age. All comparisons were additionally adjusted for education, family income, and ethnicity (white vs. nonwhite). Because the additional adjustment did not meaningfully alter any of the odds ratios, only the age-adjusted comparisons are presented here.

If information on family history of a certain condition was not available, a specific procedure was followed. First, the entire array of responses from the subject's family (parents, siblings, children) was examined for missing data; if information on all items was missing, then family history for all conditions was designated as missing. Similarly, if a subject had been adopted and nothing was known of his/her first-degree relatives, family history for all conditions was designated as missing. For parents, if either the mother or the father was reported to have the specific condition, the parental history of the condition was called positive. If neither parent was reported to have the specific condition, the parental history of the condition was called negative. If information was missing for either the mother or the father and the other parent was not reported to have the condition, the parental history of the condition was designated as missing. For siblings, if any sibling was reported to have the condition, the sibling history of the condition was called positive. If at least one sibling's history was known and was negative, and there were no siblings with a positive history, the sibling history of the condition was called negative. If information was missing for all siblings, the sibling history was called missing. Children's history of each condition was categorized using the same rules as those applied to siblings. Family history of a condition for all relatives was called positive if any parent, sibling, *or* child was positive. Family history of the condition for all relatives was called negative if parents', siblings', *and* children's histories of the condition were all negative. If either the parental, sibling, or children's history was missing and there was no positive history given, family history for all relatives was called missing.

RESULTS

Case ascertainment and interviews

The Northern California Cancer Center identified 603 eligible cases. We completed interviews for 492 cases (82 percent); 12 percent declined to participate, physicians refused contact with 2 percent, and we were unable to locate or contact 25 cases (4 percent) or suitable proxies. Fifty-seven percent of participating cases and 60 percent of nonparticipants were men. Participants were significantly younger, on average, than nonparticipants (54.4 years (standard deviation 16.7) vs. 59.4 years (standard deviation 15.7); $p = 0.004$), reflecting the poorer survival generally observed with increased age at diagnosis (8, 10). On average, we interviewed self-reporting cases within 4 months of diagnosis and proxies within 8 months of the case's diagnosis. Proxy interviews were necessary for 46 percent of the cases because of the case's death or disability. Table 1 shows the distributions of participating cases by age, race, and original pathologist's diagnosis.

TABLE 1. Age, race/ethnicity, and original pathologist's diagnosis for 492 participants with glioma in the San Francisco Bay Area Adult Glioma Study, 1991–1995

	%
Age (years)	
20–29	7
30–39	17
40–49	16
50–59	19
60–69	17
70–79	20
≥80	4
Race/ethnicity	
White	83
Black	5
Asian	6
Hispanic	4
Other	2
Original diagnosis	
Glioblastoma multiforme	51
Astrocytoma	34
Mixed glioma	6
Ependymoma	1
Oligodendroglioma	4
Other	4

Control ascertainment and interviews

Seven hundred and fifty-four apparently eligible controls were obtained through random-digit dialing of 6,612 telephone numbers. Of 5,858 numbers that did not yield eligible controls, 49 percent were either business numbers (n = 1,024), fax or modem numbers (n = 347), or nonworking numbers (n = 1,495). For 9 percent (n = 547) of the numbers, there was no response after 10 attempts; 26 percent (n = 1,502) of the enumerated numbers resulted in contact but no eligible household member; and 5 percent (n = 283) of households contacted refused to provide information. Finally, 0.6 percent (n = 37) of respondents were eligible but were too ill to be interviewed; 4 percent (n = 231) did not speak English; and 7 percent (n = 392) were eligible but the quota for their age/sex/ethnic group had already been filled. Of the 754 apparently eligible controls, initial contact indicated that two were relatives of cases, 11 lived out of the area, and nine did not speak sufficient English to be interviewed. Interviews were completed with 63 percent (462/732) of the remaining eligible controls; 32 percent (n = 236) declined to participate, and 5 percent could not be reached for interview.

Of controls who refused the full interview, 74 percent (101/137) agreed to the abbreviated telephone interview. (The denominator for this rate differs from the total number of refusing controls, because the telephone-interview option for refusers was instituted after the study was under way.) The participation rate we obtained for controls is similar to that being obtained in comparable studies in the San Francisco Bay Area.

Comparison of participating and nonparticipating controls

Table 2 compares 101 controls who completed the short telephone interview (referred to as nonparticipants) with 462 participating controls. The average ages of participating and nonparticipating controls were very similar. The percentages reporting having a mother or sibling with cancer were nearly identical. Although participants were somewhat more likely than nonparticipants to report having a father with cancer (24 percent of participants vs. 19 percent of nonparticipants), the difference was not statistically significant (p = 0.28). Those who were willing to participate were more likely to be white, female, and college-educated than nonparticipants.

Case-control demographic data

To create a data set for analyses in which cases and controls were successfully frequency-matched with regard to race/ethnicity, we deleted 9 cases and 13 controls because they were categorized as being of "other" ethnicity (a heterogeneous group that included American Indians, Pacific Islanders, Pakistanis, Polynesians, and Middle Easterners). Furthermore, we also deleted 21 cases and 6 controls to make the 5-year age distributions similar for cases and controls. Thus, the data set constructed for the analyses included 462 cases and 443 controls.

TABLE 2. Selected characteristics of participating and nonparticipating controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995

Variable	Participating controls (n = 462)	Nonparticipating controls (n = 101)
Mean age (years)	53.7 (17.2)†	53.2 (18.1)
Percent male	55	58
Percent white*	85	76
Percent college-educated*	46	34
Percent reporting that mother had cancer	23	24
Percent reporting that father had cancer	24	19
Percent reporting that a sibling had cancer	18	16

* $p < 0.05$.
† Numbers in parentheses, standard deviation.

Table 3 gives the demographic characteristics of cases and controls and compares the cases by proxy reporting status. The age, sex, and ethnicity distributions of cases and controls were very similar, by study design. Self-reporting cases were, on average, 17 years younger than cases for whom a proxy was necessary. This reflects the more rapid decline of cases with later age at disease onset (8, 10). Self-reporting cases tended to have higher family incomes and educational attainment than proxy-reported cases after adjustment for the other factor, age, sex, and severity of original diagnosis (measured as glioblastoma, grade 4 astrocytoma, or highly anaplastic astrocytoma vs. other histologies); the odds ratio for having 16 or more years of education was 1.6 (95 percent confidence interval (CI) 1.0–2.6), and the odds ratio for having a yearly household income of $70,000 or more was 1.8 (95 percent CI 1.0–2.9). In contrast, neither education nor income was significantly associated with severity of original diagnosis after adjustment for the other factor, age, sex, and the reporting status of the cases (for education, odds ratio = 1.0, 95 percent CI 0.7–1.7; for income, odds ratio = 1.2, 95 percent CI 0.8–1.9). Self-reporting cases were also slightly more likely to be male and white than cases for whom a proxy reported.

A higher proportion of controls than of proxy-reported cases had 16 or more years of education, but

TABLE 3. Demographic characteristics of glioma cases and controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995

Variable	Controls (*n* = 443)		Cases							
			All cases (*n* = 462)			Self-reporting cases (*n* = 249)			Proxy-reported cases (*n* = 213)	
	No.	%	No.	%	OR*,† (95% CI*)	No	%	OR† (95% CI)	No	%	OR† (95% CI)
Mean age (SD*)	54.2 (16.6)		53.9 (16.5)			46.0 (14.3)			63.2 (13.9)		
% male		54.6		56.5			58.6			54.0	
Race											
White	391	88.3	408	88.3		221	88.8		187	87.8	
Black	13	2.9	13	2.8		7	2.8		6	2.8	
Asian	21	4.7	24	5.2		12	4.8		12	5.6	
Hispanic	18	4.1	17	3.7		9	3.6		8	3.8	
Education (years)											
<16	240	54.3	278	61.1	0.7	127	51.6	1.0	151	72.2	0.5
≥16	202	45.7	177	38.9	(0.6–0.96)	119	48.4	(0.7–1.3)	58	27.8	(0.4–0.8)
Household income (dollars/year)											
<70,000	301	70.3	295	67.4	1.1	141	58.5	1.5	154	78.2	0.8
≥70,000	127	29.7	143	32.6	(0.8–1.5)	100	41.5	(1.1–2.1)	43	21.8	(0.5–1.3)

* OR, odds ratio; CI, confidence interval; SD, standard deviation.
† Odds ratios are for cases compared with controls, adjusted for sex and individual year of age.

there was no difference in the educational distributions of self-reporting cases and controls. In contrast, the annual household incomes of controls and cases for whom a proxy reported were similar, but approximately 40 percent more self-reporting cases than controls had annual household incomes greater than or equal to $70,000.

Personal medical histories of cases and controls

Table 4 compares reported medical conditions for cases and controls. Epilepsy, seizures, or convulsions were significantly more common in cases than in controls both before diagnosis (cases) or study entry (controls) and more than 3 years before diagnosis or study entry. The only other medical conditions for which there were significant differences between cases and controls were chickenpox and shingles, controls being significantly more likely to report either condition than cases.

Overall, cases and controls were almost equally likely to have had cancer previously. Cases were somewhat likely, but not significantly less likely than controls, to have had heart disease, a learning disability, a psychiatric disorder, or a thyroid disorder. Cases for whom a proxy reported were twice as likely as controls to have had a stroke, but the result did not achieve statistical significance. A higher proportion of cases than of controls also reported having had colonic polyps, but the results were not significant.

Senility or dementia, mental retardation, Parkinson's disease, meningitis, poliomyelitis, multiple sclerosis, encephalitis, pituitary or adrenal disorders, Turcot's or Gardner's syndrome, and acquired immunodeficiency syndrome or human immunodeficiency virus positivity were reported too infrequently among cases and controls for meaningful statistical comparisons, but results generally did not differ notably between the two groups (table 5). Three cases had neurofibromatosis and one had tuberous sclerosis, both known genetic conditions; no controls reported having these conditions.

Familial medical histories

Family size and age distributions. Cases' and controls' family sizes were very similar (table 6). The average ages and years of birth of cases' and controls' parents did not differ. Cases had somewhat older siblings and children than did controls, both being on average 1 year older. Nearly identical proportions of cases' and controls' fathers and children were deceased. A somewhat higher but not significantly higher proportion of cases' mothers and siblings than of controls' mothers and siblings were deceased. As

TABLE 4. Personal medical histories* of glioma cases and controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995

Variable	Controls (n = 443)		Cases								
			All cases (n = 462)			Self-reporting cases (n = 249)			Proxy-reported† cases (n = 213)		
	No.	%	No.	%	OR‡,§ (95% CI‡)	No.	%	OR§ (95% CI)	No.	%	OR§ (95% CI)
Other cancer¶											
Yes	51	11.6	52	11.4	1.0	22	8.9	1.2	30	14.4	0.9
No	390	88.4	404	88.6	(0.7–1.5)	225	91.1	(0.7–2.2)	179	85.6	(0.5–1.5)
Epilepsy, seizures, or convulsions											
Yes	7	1.6	43	9.5	6.7	31	12.6	6.4	12	5.8	4.9
No	434	98.4	411	90.5	(3.0–15.2)	216	87.4	(2.7–15.1)	195	94.2	(1.8–13.1)
Epilepsy, seizures, or convulsions diagnosed >3 years previously											
Yes	7	1.6	23	5.1	3.3	18	7.3	3.3	5	2.4	1.9
No	434	98.4	431	94.9	(1.4–7.9)	229	92.7	(1.3–8.2)	202	97.6	(0.6–6.4)
Heart disease											
Yes	40	9.0	38	8.3	0.9	12	4.8	0.9	26	12.4	0.9
No	402	91.0	420	91.7	(0.6–1.5)	237	95.2	(0.4–1.7)	183	87.6	(0.5–1.5)
Stroke											
Yes	12	2.7	16	3.5	1.3	1	0.4	0.2	15	7.1	2.0
No	431	97.3	443	96.5	(0.6–2.8)	248	99.6	(0.03–1.9)	195	92.9	(0.9–4.3)
Psychiatric problems											
Yes	21	4.7	21	4.6	1.0	10	4.0	0.7	11	5.2	1.4
No	422	95.3	437	95.4	(0.5–1.8)	238	96.0	(0.3–1.6)	199	94.8	(0.7–3.1)
Learning disability											
Yes	11	2.5	9	2.0	0.8	6	2.4	0.6	3	1.4	0.97
No	430	97.5	446	98.0	(0.3–1.9)	242	97.6	(0.2–1.8)	204	98.6	(0.3–3.6)
Thyroid condition											
Yes	34	7.7	30	6.6	0.9	12	4.8	0.9	18	8.6	0.9
No	407	92.3	427	93.4	(0.5–1.5)	237	95.2	(0.5–2.0)	190	91.4	(0.5–1.6)
Chickenpox											
Yes	348	84.1	267	70.1	0.4	177	75.3	0.5	90	61.6	0.3
No	66	15.9	114	29.9	(0.3–0.6)	58	24.7	(0.3–0.8)	56	38.4	(0.2–0.5)
Shingles											
Yes	42	9.6	22	4.9	0.5	8	3.2	0.5	14	6.9	0.5
No	398	90.4	428	95.1	(0.3–0.8)	240	96.8	(0.2–1.0)	188	93.1	(0.3–1.0)
Colonic polyps											
Yes	3	0.7	10	2.2	3.4	4	1.6	4.0	6	2.9	3.4
No	439	99.3	447	97.8	(0.9–12.4)	244	98.4	(0.9–18.3)	203	97.1	(0.8–14.0)

* Medical conditions prior to diagnosis for cases and prior to interview for controls.
† Proxy-reported cases were, on average, 17 years older than self-reporting cases.
‡ OR, odds ratio; CI, confidence interval.
§ Odds ratios are for cases compared with controls, adjusted for sex and individual year of age.
¶ Cancer other than glioma.

TABLE 5. Additional information from the personal medical histories* of glioma cases and controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995

Medical condition	Controls (n = 443)		Cases					
			All cases (n = 462)		Self-reporting cases (n = 249)		Proxy-reported cases (n = 213)	
	No.†	%	No	%	No.‡	%	No.§	%
Senility	0	0	1	0.2	0	0	1	0.5
Mental retardation	0	0	1	0.2	0	0	1	0.5
Poliomyelitis	6	1.4	4	0.9	4	1.6	0	0
Parkinson's disease	2	0.4	2	0.4	0	0	2	1.0
Meningitis	4	0.9	3	0.6	2	0.8	1	0.5
Multiple sclerosis	1	0.2	2	0.4	2	0.8	0	0
Encephalitis	1	0.2	4	0.9	1	0.4	3	1.4
Tuberous sclerosis	0	0	1	0.2	1	0.4	0	0
Neurofibromatosis	0	0	3	0.7	2	0.8	1	0.5
Other neurologic conditions	3	0.7	4	0.9	2	0.8	2	1.0
Pituitary gland disorder	0	0	1	0.2	1	0.4	0	0
Adrenal gland disorder	2	0.4	0	0	0	0	0	0
AIDS¶ or HIV¶ positivity	2	0.4	3	0.6	1	0.4	2	1.0

* Medical conditions prior to diagnosis for cases and prior to interview for controls.

† Information was given as unknown for one subject each for poliomyelitis, Parkinson's disease, and AIDS and for two subjects each for dyslexia and pituitary gland disorder.

‡ Information was given as unknown for one case each for dyslexia, tuberous sclerosis, and adrenal gland disorder and for two cases for "other neurologic conditions."

§ Information was given as unknown for six cases for dyslexia and "other neurologic conditions"; for three cases for poliomyelitis, Parkinson's disease, meningitis, and encephalitis; and for two cases for the remaining tabled conditions.

¶ AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

expected, given the younger average age of self-reporting cases compared with proxy-reported cases, their relatives' ages also were lower and their family sizes smaller.

Family history of cancer. Overall, cases and controls had very similar reported family histories of cancer at any site (table 7). (When examining the proportions of cases with positive family histories of cancer or other age-related conditions, it is important to remember that proxy-reported cases were much older on average than self-reporting cases.) There were no notable differences between cases and controls for family histories of cancer at the more commonly reported primary sites: breast, lung, and colon/rectum. For proxy-reported cases, cases' mothers were less likely than controls' mothers to be reported to have cancer. Cancer histories reported for cases' and controls' fathers and siblings were very similar. Cases' children were 2.2–2.6 times more likely than controls' children to be reported to have had cancer, but the result did not achieve statistical significance.

Eighteen cases were reported to have a child with cancer; the children's average age at cancer diagnosis was 35 years (range, 19–50 years). Primary sites included six cancers of the skin, three cases of Hodgkin's disease, three breast cancers, four cancers of the uterus or cervix (one in a woman who also had breast cancer), one rectal cancer, one thyroid cancer, and one with site unknown. For controls, 10 cancers were reported among nine children in eight families; the children's average age at diagnosis was 32 years (range, 4–54 years). Primary sites included one skin cancer, one case of Hodgkin's disease, four breast cancers (two individuals in the same family had breast cancer), one stomach cancer (in a woman who also had breast cancer), and one case each of cancer of the bladder, uterus, and kidney.

Family history of brain tumors. Using unvalidated information provided by index subjects, the odds ratio for a first-degree family history of brain tumor was 1.7 (95 percent CI 0.9–3.2, p = 0.10) (table 8). Among the 29 case relatives reported to have a brain tumor, 18 tumors were confirmed as primary brain tumors via medical reports or death certificates; two were considered probable based on details given by the index subject; six were probably not primary brain tumors according to the death certificates; and three lacked sufficient information for definitive classification. Among the 19 control relatives reported to have a brain tumor, seven tumors were confirmed by medical reports or death certificates; one was considered probable based on details given by the index subject; one was considered probable based on information from another relative in addition to the index subject; six

TABLE 6. Age, year of birth, and vital status for first-degree relatives of cases and controls, San Francisco Bay Area Adult Glioma Study, 1991–1995

	No. with information	Average no. per family	Mean age*	Average birth year	% deceased
Mothers					
Controls (n = 443)	437		70.4 (14.3)†	1912	49.7
Cases					
All cases (n = 462)	459		69.4 (14.8)	1912	54.8
Self-reporting cases (n = 249)	249		66.2 (13.2)	1919	39.0
Proxy-reported cases‡ (n = 213)	210		73.1 (15.7)	1903	73.7
Fathers					
Controls (n = 443)	436		68.4 (13.6)	1908	65.9
Cases					
All cases (n = 462)	454		68.1 (13.2)	1908	66.9
Self-reporting cases (n = 249)	245		66.8 (12.4)	1916	52.5
Proxy-reported cases‡ (n = 213)	209		69.8 (14.0)	1898	83.6
Siblings					
Controls (n = 443)	1,243	2.9	49.3 (19.7)	1938	21.7
Cases					
All cases (n = 462)	1,252	2.8	51.0 (18.8)	1937	23.3
Self-reporting cases (n = 249)	600	2.4	44.1 (16.9)	1946	12.8
Proxy-reported cases‡ (n = 213)	652	3.1	57.6 (18.3)	1929	33.0
Children					
Controls (n = 443)	827	1.9	29.7 (14.5)	1963	3.6
Cases					
All cases (n = 462)	899	2.0	31.2 (14.7)	1961	4.0
Self-reporting cases (n = 249)	395	1.6	24.7 (13.9)	1968	2.3
Proxy-reported cases‡ (n = 213)	504	2.4	36.3 (13.2)	1956	5.4

* Current age of the relative or his/her age at death.
† Numbers in parentheses, standard deviation.
‡ Proxy-reported cases were, on average, 17 years older than self-reporting cases.

were probably not primary brain tumors according to the death certificates; and four lacked sufficient information for definitive classification. For both cases and controls, reported brain tumors that were not confirmed as primary brain tumors on death certificates usually were metastatic brain tumors from lung cancer. Using confirmed or probable primary brain tumors only for analyses, nine of 399 controls and 20 of 381 cases had a probable positive family history, giving an odds ratio of 2.3 (95 percent CI 1.0–5.8, p = 0.03). A more conservative calculation would consider all cases and controls with missing or uncertain family histories to be negative; in such a case, the comparison is between nine of 443 controls and 20 of 462 cases, giving an odds ratio of 2.2 (95 percent CI 0.9–5.2, p = 0.05). (The 95 percent confidence interval and p value give different results here because the confidence interval calculation uses Yates' correction and the p value calculation does not.)

On average, the 20 cases with a validated family history of brain tumors were significantly older at diagnosis than either the 361 cases with a negative family history of brain tumors or the 81 cases with an unknown or uncertain family history (mean ages at diagnosis were 63.8 years (standard deviation 12.9), 52.4 years (16.6), and 58.3 years (15.5), respectively; in analysis of variance, $p < 0.001$).

Other nervous system conditions. Case and control family histories of epilepsy, seizures, or convulsions did not differ considerably or consistently (table 8). Although results were not statistically significant, a sibling history of senility or dementia was nearly twice as common among self-reporting cases as among controls and nearly three times as common among proxy-reported cases as among controls. Cases were more likely than controls to have a relative with mental retardation, but the results were compatible with chance.

DISCUSSION

The results of this study suggest that although family history of any cancer probably is not an important risk factor for adult glioma, a family history of brain tumors may play a role.

TABLE 7. Family history of cancer among first-degree relatives of glioma cases and controls, San Francisco Bay Area Adult Glioma Study, 1991–1995

	Controls (n = 443)			Cases										
				All cases (n = 462)				Self-reporting cases (n = 249)				Proxy-reported cases¶ (n = 213)			
	%	No. +*	N†	%	No. +	N†	OR§ (95% CI)	%	No. +	N†	OR§ (95% CI)	%	No. +	N†	OR§ (95% CI)
All relatives															
Any cancer#	52.0	213	410	51.6	216	419	1.0 (0.8–1.4)	41.7	96	230	0.9 (0.6–1.3)	63.5	120	189	1.2 (0.8–1.8)
Breast cancer	9.4	38	406	10.6	43	406	1.2 (0.8–1.9)	8.8	20	227	1.4 (0.8–2.5)	12.8	23	179	1.1 (0.6–2.0)
Lung cancer	9.4	38	405	8.9	36	403	1.0 (0.6–1.6)	7.9	18	227	1.1 (0.6–2.0)	10.2	18	176	0.9 (0.5–1.6)
Colorectal cancer	8.4	34	407	6.7	27	402	0.8 (0.5–1.4)	4.4	10	228	0.6 (0.3–1.3)	9.8	17	174	1.0 (0.6–2.0)
Any cancer#															
Parents	41.4	171	413	36.3	150	413	0.8 (0.6–1.1)	34.3	80	233	0.9 (0.6–1.2)	38.9	70	180	0.9 (0.6–1.2)
Mothers	23.1	99	428	18.0	79	439	0.7 (0.5–1.0)	19.2	47	245	1.0 (0.7–1.5)	16.5	32	194	0.6 (0.4–0.9)
Fathers	24.1	101	419	22.5	93	414	0.9 (0.7–1.3)	20.6	48	233	0.8 (0.6–1.3)	24.9	45	181	1.1 (0.7–1.7)
Siblings	18.6	74	399	20.8	83	400	1.3 (0.9–1.8)	10.6	23	218	0.9 (0.5–1.6)	33.0	60	182	1.4 (0.9–2.2)
Children	2.4	8	330	5.2	18	345	2.3 (0.96–5.3)	3.0	5	169	2.6 (0.8–8.4)	7.4	13	176	2.2 (0.9–5.5)

* No. +, number of subjects with positive family histories.
† N, number of subjects with nonmissing family histories, as defined in the text.
‡ OR, odds ratio; CI, confidence interval.
§ Odds ratios are for cases compared with controls, adjusted for age.
¶ Proxy-reported cases were, on average, 17 years older than self-reporting cases.
# Does not include brain tumors (see table 8).

TABLE 8. Family history of brain tumors and selected nervous system conditions among first-degree relatives of glioma cases and controls, San Francisco Bay Area Adult Glioma Study, 1991–1995

	Controls (n = 443)			Cases										
				All cases (n = 462)				Self-reporting cases (n = 249)				Proxy-reported cases¶ (n = 213)			
	%	No. +*	N†	%	No. +	N†	OR‡,§ (95% CI‡)	%	No. +	N†	OR§ (95% CI)	%	No. +	N†	OR§ (95% CI)
Brain tumor#															
All relatives	4.7	19	401	7.6	29	384	1.7 (0.95–3.2)	3.2	7	222	0.8 (0.3–2.0)	13.6	22	162	2.8 (1.4–5.4)
Parents	1.7	7	406	2.5	10	393	1.5 (0.6–4.1)	0.9	2	227	0.6 (0.1–2.9)	4.8	8	166	2.8 (0.97–8.1)
Siblings	2.3	9	399	3.7	15	401	1.7 (0.8–4.1)	1.4	3	218	0.7 (0.2–2.8)	6.6	12	183	2.5 (1.0–6.3)
Children	1.2	4	330	1.2	4	345	1.0 (0.2–3.8)	1.2	2	169	1.2 (0.2–6.5)	1.1	2	176	0.9 (0.2–5.0)
Epilepsy, seizures, or convulsions															
All relatives	7.2	29	401	8.4	33	391	1.2 (0.7–2.0)	6.6	15	227	1.0 (0.5–1.9)	11.0	18	164	1.6 (0.9–3.1)
Parents	2.2	9	405	1.8	7	396	0.8 (0.3–2.1)	0.9	2	230	0.4 (0.1–1.8)	3.0	5	166	1.5 (0.5–4.8)
Siblings	1.8	7	399	3.0	12	401	1.7 (0.7–4.4)	2.8	6	218	1.2 (0.4–3.7)	3.3	6	183	2.4 (0.7–7.6)
Children	4.2	14	330	4.9	17	345	1.2 (0.6–2.4)	4.7	8	169	1.3 (0.5–3.3)	5.1	9	176	1.2 (0.5–2.9)
Senility or dementia															
All relatives	6.8	27	400	9.7	37	382	1.6 (0.96–2.8)	5.8	13	225	1.3 (0.7–2.7)	15.3	24	157	1.9 (1.0–3.4)
Parents	5.9	24	405	6.9	27	390	1.3 (0.7–2.3)	4.8	11	230	1.2 (0.6–2.5)	10.0	16	160	1.4 (0.7–2.7)
Siblings	0.9	4	399	2.5	10	401	2.7 (0.8–8.8)	0.9	2	218	2.2 (0.4–12.3)	4.4	8	183	2.9 (0.8–9.8)
Mental retardation															
Siblings and children	1.2	5	429	2.3	10	438	2.0 (0.7–5.9)	2.9	7	241	2.8 (0.8–9.2)	1.5	3	197	1.2 (0.3–5.2)
Siblings	0.9	4	399	1.5	6	401	1.5 (0.4–5.4)	2.3	5	218	2.4 (0.6–9.4)	0.6	1	183	0.4 (0.04–4.1)
Children	0.3	1	330	1.2	4	345	3.9 (0.4–34.7)	1.2	2	169	4.8 (0.4–55.7)	1.1	2	176	4.1 (0.4–48.2)

* No. +, number of subjects with positive family histories.
† N, number of subjects with nonmissing family histories, as defined in the text
‡ OR, odds ratio, CI, confidence interval.
§ Odds ratios are for cases compared with controls, adjusted for age.
¶ Proxy-reported cases were, on average, 17 years older than self-reporting cases.
# Results for confirmed brain tumors among relatives are presented in the text.

Comparability of case and control information

Concerns could arise about differential reporting and data quality between our cases and controls, because of the necessary use of proxies to obtain information for some cases (17). Although the original design called for individual matching to permit matching by proxy respondent, it seemed impractical and of limited scientific value to conduct interviews with proxies of controls. First, adding the puzzling requirement for proxy controls and informing potential controls that someone other than themselves might have to participate would have further hindered recruitment. Second, proxy data for controls would not necessarily be comparable to proxy data for cases; a devastating illness could well influence the relationship between two people and the information they have about one another. Third, since we are conducting extensive validation of family histories, we are able to determine the effect, if any, of proxy status on the reporting of relatives' medical conditions. Fourth, analyses were stratified by the case's proxy status, allowing assessment of consistency of effect. More specifically, we have more confidence in effects seen in both proxy- and self-reporting case groups. Fifth, removing the requirement of matching on proxy status allowed frequency matching of controls, which considerably facilitated both control recruitment and statistical analyses.

The observed differences in the educational attainment and annual household incomes of self-reporting and proxy-reported cases did not appear to be related to the severity of the disease as measured by original diagnosis. Since survival data are not yet available for the cases, we cannot rule out the possibility that education and income might have been associated with survival independently of the severity of the original diagnosis, and therefore with the proxy reporting status of the cases. It is also possible that proxies might have underreported cases' education or household income in comparison with what the cases themselves would have reported. Interpretation of the observed educational differences between proxy-reported cases and controls is difficult, given the unexplained difference in education between proxy-reported and self-reporting cases.

Personal medical history

The finding that cases were more likely than controls to have a history of seizures more than 3 years prior to diagnosis has been observed in other studies (18, 19). Cohort studies of people with epilepsy have found the rate of brain tumors to decrease with time since epilepsy diagnosis and with total duration of medication use, suggesting that seizures might be an early symptom of brain tumors (20–23). However, neither cohort nor case-control findings are incompatible with the hypothesis that seizures or seizure medications might increase brain tumor risk, but only among susceptibles and then only for a limited time period. The current study cannot distinguish between these two interpretations, nor can it distinguish the possible role of seizures from the role of seizure medications, since virtually everyone with seizures is treated with medication.

One aim of this study was to assess whether viral or other infections with nervous system involvement might be associated with the risk of brain tumors. The conditions we asked about (poliomyelitis, meningitis, encephalitis, acquired immunodeficiency syndrome or human immunodeficiency virus positivity, and chickenpox and shingles) were meant not to form an exhaustive list but rather to include infections of which the subjects might have been aware. With the exception of chickenpox and shingles, too few subjects reported histories of the other infections for meaningful comparison. The possibility that glioma cases may have a reduced history of chickenpox and shingles has not been reported previously. It has been reported that cases were less likely than controls to have allergies or colds or other infections (18, 19). Although this could and has been interpreted to indicate that controls are protected from this and other cancers by regular immunologic stimulation, it might also be possible that cases historically respond differently than people who do not become cases to antigenic stimulation or viral attacks. In an accompanying report, we follow up on this finding with regard to serologic evidence of infection by varicella-zoster virus among cases and controls (24).

Aside from these conditions, the medical histories of cases and controls appeared very similar. Four cases, all of whom were in their mid-thirties at diagnosis, had genetic conditions (neurofibromatosis and tuberous sclerosis) known to predispose people to brain tumors (7, 25–27). This finding indicates that these genetic disorders probably are not an important cause of most adult gliomas, accounting for less than 1 percent of cases. However, given the fact that neurofibromatosis-1 has an incidence of approximately 1 in 3,000 persons while tuberous sclerosis has a maximum estimated incidence of 1 in 10,000 persons, the odds ratios for these conditions among glioma cases in this population-based series clearly are quite large (the odds ratio for neurofibromatosis was 20; that for tuberous sclerosis was 22).

Family medical history

Overall, first-degree relatives of cases did not exhibit an increased history of cancer in comparison with controls. Although cases' children were somewhat more likely to be reported to have cancer than children of controls, the results were compatible with chance. Furthermore, no types of cancer clearly emerged as being more common in cases' children, and ages at diagnosis appeared to be very similar for cases' and controls' children. This observed lack of familial association is not likely to be due to selection bias among controls, because participating and nonparticipating controls reported very similar family histories of cancer. Although firm conclusions await validation, a recent study reported relatively good sensitivity (0.82–0.87) and specificity (0.97) for reporting of colorectal cancer among first-degree relatives of colorectal cancer cases and controls (28). The observed lack of association also is not likely to be due to differences in family size, family age distributions, or birth cohorts, because cases and controls were very similar with regard to these familial attributes. In addition, since adjustment for education, income, and ethnicity did not alter the odds ratios, these factors probably were not important confounders of familial cancer in this study.

The issue of a family history of brain tumors among cases versus controls remains unresolved, results being of borderline significance among confirmed familial cases. Our findings neither clearly implicate nor clearly eliminate such a history as an important risk factor in adult glioma; only 4 percent of cases had a confirmed family history of brain tumors. Although the study was designed to have adequate power to detect a modest 1.5 odds ratio for family history of cancer at any site, there was 80 percent power to detect only a large odds ratio of 4.5 for a family history of brain tumor in cases versus controls. The observation that cases with a confirmed family history were significantly older than those without one does not favor an obvious role for inheritance of a major susceptibility gene for early-onset glioma. However, inherited susceptibility may play some role in the observed familial aggregation of brain tumors. Ongoing analyses with compound regressive models may shed further light on the underlying genetic mechanisms of this aggregation.

Two other studies have reported an elevated but nonsignificant incidence of mental retardation in families of brain tumor cases (29, 30). Because of the low prevalence of mental retardation, it probably is not feasible to conduct a large enough study to verify these findings. However, because mental retardation might well involve substantial chromosomal alterations, these families might make good candidates for more detailed genetic studies.

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