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Risk factors for oligodendroglial tumors: A pooled international study

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Oligodendroglial tumors are rare subtypes of brain tumors and are often combined with other glial tumors in epidemiological analyses. However, different demographic associations and clinical characteristics suggest potentially different risk factors. The purpose of this study was to investigate possible risk factors for oligodendroglial tumors (including oligodendroglioma, anaplastic oligodendroglioma, and mixed glioma). Data from 7 case–control studies (5 US and 2 Scandinavian) were pooled. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for age group, gender, and study site. Data on 617 cases and 1260 controls were available for analyses. Using data from all 7 studies, history of allergies and/or asthma was associated with a decreased risk of anaplastic oligodendroglioma (OR = 0.6; 95% CI: 0.4–0.9), and history of asthma only was associated with a decreased risk of oligodendroglioma (OR = 0.5; 95% CI: 0.3–0.9) and anaplastic oligodendroglioma (OR = 0.3; 95% CI: 0.1–0.9). A family history of brain tumors was associated with an increased risk of anaplastic oligodendroglioma (OR = 2.2; 95% CI: 1.1–4.5). Having had chicken pox was associated with a decreased risk of oligodendroglioma (OR = 0.6; 95% CI: 0.4–0.9) and anaplastic oligodendroglioma (OR = 0.5; 95% CI: 0.3–0.9) in the US studies. Although there is some overlap in risk factors between oligodendroglial tumors and gliomas as a group, it is likely that additional factors specific to oligodendroglial tumors have yet to be identified. Large, multi-institution international studies will be necessary to better characterize these etiological risk factors.

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Oligodendroglial tumors are often slow-growing brain tumors with cells that resemble oligodendrocytes. The World Health Organization subclassifies these tumors into low-grade (Grade II) oligodendrogliomas and high-grade (Grade III) anaplastic oligodendrogliomas.[1] Tumors that contain both neoplastic oligodendrocytic and astrocytic cells are labeled mixed gliomas or oligoastrocytomas. Oligodendroglial tumors are included in the larger category of glioma, which also consists of the more common histologies of glioblastoma and astrocytoma, as well as ependymomas, and other tumor histologies. Oligodendrogliomas are rare, with an incidence in the USA of 0.32/100 000 person years (adjusted to the US Standard Population) for the years 2000–2004.[2] Anaplastic oligodendrogliomas and mixed gliomas are extremely rare, with 2000–2004 incidences of 0.17/100 000 and 0.18/100 000, respectively. The incidence of these tumors in Denmark and the Scandinavian countries is similar to that in the USA.[3,4] In Denmark, the oligodendroglioma/anaplastic oligodendroglioma combined incidence was 0.45/100 000 person years (adjusted to the World Standard Population) for the years 2000–2002.[3]

Because oligodendroglial tumors are rare, it is difficult for any single clinical series to assemble a large enough number of cases to explore etiological risk factors. These tumors are often combined with other glial tumors in analyses for epidemiological studies, which makes it difficult to disentangle the association between the risk factors under study and the association with either oligodendroglioma or glioma. However, these tumors have age, gender, and ethnic distributions and clinical characteristics different from other glial tumors, suggesting potentially different risk factors. The mean age at diagnosis for those with grade II oligodendroglioma and mixed glioma (41 years) and grade III anaplastic oligodendroglioma (~49 years) is younger than for those with glioblastoma (62–64 years), the most frequent glioma histology.[2,5] The male-to-female incidence ratio is smaller (incidence rate ratio [IRR]: 1.17 vs 1.66, respectively), and the white to black IRR is larger (2.69 vs 2.00) for those with oligodendroglioma compared with glioblastoma.[2] In addition, the 5-year relative survival in patients with oligodendroglioma (72%), mixed glioma (58%), and anaplastic oligodendroglioma (45%) is significantly better than in those with glioblastoma (3%).[2] As the characteristics of those with mixed glioma tend to be intermediate to either the pure oligodendrocytic or astrocytic tumors, they are included in this study with the other oligodendrocytic tumors. The identification of 1p/19q loss in ~70% of oligodendrogliomas[6–8] and its correlation with improved survival and better response to DNA-damaging therapies[9–13] suggest that the etiology of oligodendroglial tumors may differ from that of other gliomas.

Factors previously found to be associated with the larger category of glioma (which includes oligodendroglial tumors),[14] such as ionizing radiation, family history of brain tumors, and allergic disease, may also be specifically associated with oligodendroglial tumors. The purpose of this study was to investigate the possible risk or protective factors for oligodendroglial tumors. To this end, data from 7 studies (5 case–control studies conducted in the USA and 2 case–control studies in Sweden and Denmark) were pooled and analyzed. The results are presented here.

Methods

Data for the current study were obtained from 7 previously conducted case–control studies: (a) the University of Texas MD Anderson Cancer Center Harris County Case–Control Study; (b) the National Cancer Institute (NCI) Multicenter Study of Environment and Health; (c) the National Institute for Occupational Safety and Health (NIOSH)/Centers for Disease Control (CDC) Upper Midwest Health Study; (d) the University of California at San Francisco (UCSF) Genetic and Molecular Epidemiology of Adult Glioma Study; (e) University of Illinois at Chicago (UIC)/Duke University study; (f) the Swedish Interphone Study; and (g) the Danish Interphone Study. This collaborative data analysis was identified as a priority and conducted through the Brain Tumor Epidemiology Consortium, an organization established to develop multicenter international collaborations to better understand the etiology, outcomes, and prevention of brain tumors (http://epi.grants.cancer.gov/btec/).[14] Details of the study design for each of the studies included here have been previously described[15–21] and are briefly outlined below.

(i) The University of Texas MD Anderson Cancer Center Harris County Case–Control Study was a modified population-based case–control study of adults (≥20 years) with newly diagnosed, histologically confirmed primary brain tumors diagnosed between 1992 and 2006.[20] Oligodendroglial tumors were pathology reviewed by either K.A. or the neuropathologist on call at the time of surgery. Population-based controls were frequency-matched to cases (1:1) by gender, race, and age.

(ii) The NCI Multicenter Study of Environment and Health was a hospital-based case–control study of adults (>18 years of age) with newly diagnosed, histologically confirmed glioma or neuroepithelial tumor, meningioma, or acoustic neuroma diagnosed between June 1994 and August 1998.[15] Oligodendroglial tumors did not undergo a pathology review. Hospital-based controls were frequency-matched (1:1) by hospital, age ± 10 years, gender, race/ethnicity, and distance of residence from the hospital.

(iii) The NIOSH/CDC Upper Midwest Health Study was a population-based case–control study of adults (aged 18–80 years) with histologically confirmed intracranial glioma newly diagnosed between January 1995 and January 1997.[16] Oligodendroglial diagnoses were originally reviewed by a study-specific neuropathologist, but tumor tissue, as available, was sent to K.A. for a pathology re-review. For this study, controls (identified through driver's license or Medicare files) who had donated blood were pair-matched to oligodendroglial tumor cases by state of residence, gender, race, and age ± 5 years (where possible).

(iv) The UCSF Genetic and Molecular Epidemiology of Adult Glioma Study was a population-based case–control study of adult (≥18 years) glioma cases newly diagnosed during 1991–1994 (Series 1), 1997–1999 (Series 2), and 2001–2004 (Series 3).[17,18] Interviews changed slightly across series. In addition, cases referred to the UCSF Neuro-oncology Clinic from 2002 to 2006 were also recruited to participate, regardless of their residence. Oligodendroglial tumors underwent a pathology review by K.A. or by 2 other study neuropathologists. Population-based controls obtained through random-digit-dialing were frequency-matched by age, gender, and ethnic group.

(v) The UIC/Duke brain tumor SPORE study was a hospital-based case–control study of adults (≥18 years) with histologically confirmed glioma newly diagnosed between 2003 and 2008.[19] Oligodendroglial tumors, for which tissue was available, underwent a pathology review by a single neuropathologist collaborating on that study. For the current study, controls were randomly selected from the pool of all friend controls and were frequency-matched to the selected cases by age (± 5 years), gender, race, and hospital.

(vi) The Swedish Interphone Study was a population-based study of adults (aged 20–69) with a confirmed primary brain glioma, meningioma, acoustic neuroma, or parotid gland tumor newly diagnosed between 2000 and 2002.[21] The population-based tumor registry was also reviewed regularly to identify cases. One pathologist reviewed all oligodendroglial tumors, and then T.B. and H.B. reviewed them together. Population-based controls were frequency-matched on year of birth (± 5-year groups), gender, and study region.

(vii) The Danish Interphone Study was a population-based study of adults (aged 20–69) with a confirmed primary brain glioma, meningioma, acoustic neuroma, or malignant parotid gland tumor newly diagnosed between 2000 and 2002.[21] The population-based tumor registry was also reviewed regularly to identify cases. One pathologist reviewed all oligodendroglial tumors, and then T.B. and H.B. reviewed them together. Population-based controls were frequency-matched on year of birth (± 5-year groups) and gender.

The study design and privacy protection features were reviewed and approved by the respective institutional review boards (Denmark also had approval from the National Ethical Committee System and the National Data Protection Board) at all 7 study sites, and all participants signed an informed consent form upon enrollment in the original study. Care was taken to ensure comparability of information across studies. From each study, patients with oligodendroglioma (ICD-O-3[22] code 9450), anaplastic oligodendroglioma (ICD-O-3 code 9451), and mixed glioma (ICD-O-3 code 9382) were identified and frequency-matched by age (± 5 years), gender, and race to controls at the same study site at a ratio of 1 case to 2 controls.

Demographic, clinical, and survey data (obtained via in-person interview, telephone interview, or web-based survey) without any direct identifiers were provided from each study. Risk factors selected for analysis were based on protective and risk factors investigated for other glial tumors, primarily glioblastomas and astrocytomas, and were available in the survey data from at least 3 study sites. Crude variables using data collapsed from the questionnaires from each study were created, and general categories of exposure variables compiled for this study included selected environmental exposures (solvent exposure, pesticide exposure, paint exposure, farm exposure, and water source), family history of tumors, viral exposures, medical and dental exposure to ionizing radiation, medical history (including head trauma, allergies, autoimmune diseases, selected medication usage, etc.), tobacco and alcohol use, and sociodemographic factors. For the allergy variable, surveys from MD Anderson, UIC/Duke, NCI, and UCSF series 2 inquired about medical personnel-diagnosed allergies, while surveys from Sweden and Denmark inquired about medical personnel-diagnosed hayfever. The NIOSH survey inquired about the ever use of prescription medications for allergies/hayfever prior to 1993. For UCSF series 3, allergies were self-reported in the survey, which resulted in a much higher prevalence of allergies in this population than in any of the other study populations. Therefore, a variable was created for individuals having at least 2 allergies, at least one of which was a pollen, food, animal/insect, or drug allergy, as this allergy combination correlated best with physician-diagnosed allergies in UCSF Series 2.

Frequencies and means were calculated using SAS version 9.1.3 (SAS, 2007).[23] Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age group, gender, and study site. For analyses of those variables collected solely in the US studies, race and year of interview were also included as adjustment variables. One subject was excluded from these analyses due to

missing race data. For histology-specific analyses, cases within each histologic subtype were compared with all frequency-matched controls for that study site. Study sites that did not include a specific variable in its survey were not included in the analysis of that variable. To determine whether there was heterogeneity among study sites, an interaction term for each exposure variable by study site was run separately for oligodendroglioma, anaplastic oligodendroglioma, and mixed glioma. For those exposures with a statistically significant interaction term ($P < .05$), stratum-specific models by study site were run. Survey data from 49 case and 9 control subjects were obtained by proxy respondents and these data were included in the final analyses. The magnitude of the results and the conclusions did not differ with the exclusion of proxy respondents (data not shown). Owing to potential differences in the pathology and the small number of cases resulting in wide CIs, histology-specific results for mixed glioma were omitted from some analyses and not included in Tables 3 and 4, although significant results were noted in the results section.

Results

Data on 617 cases (329 oligodendroglioma; 146 anaplastic oligodendroglioma; 142 mixed glioma) and 1260 controls were identified and pooled for analyses. Demographic characteristics of cases and controls by study site are presented in Table 1. For all tumors in all study sites combined, there were no differences by gender, race (for US sites only), age group, highest education level completed or marital status for those with oligodendroglioma, anaplastic oligodendroglioma, or mixed glioma compared with control subjects (Table 2). Within specific histologic types, there were more females and subjects aged 18–29 with oligodendroglioma compared with control subjects. No differences for either gender or age were noted for those with anaplastic oligodendroglioma or mixed glioma (Table 2).

For analyses including all 7 sites, ORs adjusted for gender, age group, and study site could be calculated (Table 3). The risk of anaplastic oligodendroglioma was increased in those with a family history of any brain tumor (OR = 2.2; 95% CI: 1.1–4.5). Significant heterogeneity between Scandinavian sites and US sites was found for family history of other cancers, with the Scandinavian sites finding a significantly increased risk in those with oligodendroglioma (OR = 4.0; 95% CI: 1.7–9.6) compared with the US sites for which no association was found (OR = 1.0; 95% CI: 0.7–1.3). Asthma and/or allergies were associated with a decreased risk of anaplastic oligodendroglioma (OR = 0.6; 95% CI: 0.4–0.9) and with a borderline significantly reduced risk for mixed glioma (OR = 0.6; 95% CI: 0.3–1.0) but were not statistically significantly associated with oligodendroglioma (OR = 0.9; 95% CI: 0.6–1.2). Asthma alone was associated with a decreased risk of both oligodendroglioma (OR = 0.5; 95% CI: 0.3–0.9) and anaplastic oligodendroglioma (OR = 0.3; 95% CI: 0.1–0.9). Significant heterogeneity was found between the Scandinavian and US sites for ever having allergies. In those with oligodendroglioma, allergies were significantly associated with an increased risk of disease for the Scandinavian sites (OR = 4.6; 95% CI: 1.3–15.5), but no increased risk was observed for the US sites (OR = 1.0; 95% CI: 0.7–1.4). A history of epilepsy or seizures was associated with an increased risk for all three histologies (data not shown for mixed glioma). Although there was significant heterogeneity among the US sites for this variable, the site-specific ORs were all in the same direction and differed only in the magnitude of the risk (data not shown). For oligodendrogliomas, head trauma was associated with a modestly increased risk (OR = 1.3; 95% CI: 1.0–1.8), while medical X-rays were inversely associated with oligodendroglioma (OR = 0.7; 95% CI: 0.5–1.0) and anaplastic oligodendroglioma (OR = 0.6; 95% CI: 0.4–1.0). No significant associations were noted for ever smoking, family history of cancers other than brain, eczema, regular antihistamine use, left-handedness, radiation treatment, or ever exposure to dental X-rays.

For variables that were reported by only US study sites, ORs were adjusted for gender, race, age group, year of diagnosis or interview, and study site (Table 4). Having had chicken pox was associated with a decreased risk of oligodendroglioma (OR = 0.6; 95% CI: 0.4–0.9) and anaplastic oligodendroglioma (OR = 0.5; 95% CI: 0.3–0.9). Compared with the use of a public water source, use of bottled water was inversely associated with oligodendroglioma (OR = 0.4; 95% CI: 0.2–0.9).

Table 1. Demographic characteristics of case subjects diagnosed with oligodendroglioma (OGD), anaplastic oligodendroglioma (AO), or mixed glioma (MG), and control subjects from 5 US and 2 international case–control studies

Study site	*n*, Cases OGD/AO/MG	*n*, Controls	% White, case/control	% Male, case/control	Mean age at diagnosis/interview, case/control (y)
MD Anderson	99 (51/36/12)	204	85.9/87.8	51.5/52.0	41.4/42.3
NCI	85 (46/9/30)	172	94.1/93.6	51.8/52.3	41.1/40.8
NIOSH	108 (74/12/22)	216	98.2/95.8	50.0/50.0	43.8/44.8
UCSF	198 (92/43/63)	400	83.8/84.5	60.1/59.5	44.9/45.2
UIC/Duke	62 (34/26/2)	144	91.9/97.9	40.3/47.9	42.9/46.0
Sweden	33 (7/13/13)	64	NA/NA	51.5/51.6	51.6/51.3
Denmark	32 (25/7/0[a])	60	NA/NA	46.9/46.7	43.8/44.3

[a]Data on mixed gliomas were not provided. Should the study site abbreviations be identified?

Table 2. Demographics by histology for cases compared with frequency-matched controls from 7 sites

Characteristic	Oligodendroglioma ($n = 329$), %	Anaplastic oligodendroglioma ($n = 146$), %	Both OGD and AO ($n = 475$), %	Mixed glioma ($n = 142$), %	All tumor types ($n = 617$), %	Controls ($n = 1,260$), %
Gender						
Male	47.1[a]	59.6	51.0	58.5	52.7	53.3
Race (US sites only; 1 missing)						
Asian	3.1	2.3	2.9	4.6	3.3	3.2
Black, NH	0.6	0.8	0.7	0.8	0.7	0.8
Hispanic	5.3	4.5	5.1	0.8	4.1	3.7
Other	1.6	3.0	2.0	0.8	1.7	1.6
White, NH	89.4	89.5	89.4	93.0	90.2	90.8
Age group						
18–29	15.2[a]	8.9	13.3	14.1	13.5	12.1
30–39	31.3	21.9	28.4	26.1	27.9	27.1
40–49	31.0	26.0	29.5	29.6	29.5	28.4
50–59	12.5	21.9	15.4	16.2	15.6	17.8
60–69	7.0	15.8	9.7	9.9	9.7	10.7
70–79	2.4	4.8	3.2	3.5	3.2	3.2
80+	0.6	0.7	0.6	0.7	0.7	0.7
Education						
HS or less	34.4	36.6	35.0	34.5	34.9	30.6
Some college	49.5	45.5	48.3	50.7	48.9	51.8
Post-grad	16.1	17.9	16.7	14.8	16.2	17.6
Marital status						
Married	69.0	74.0	70.5	59.9	68.1	64.6
Never married	17.3	11.6	15.6	18.3	16.2	19.0
Widowed/ divorced/ separated	13.7	14.4	13.9	21.8	15.7	16.4

[a]$P < .05$ (χ^2 test for the association between each case type with controls). Abbreviations need to be identified/defined in a footnote for each table.

No significant associations were noted for ever regular alcohol drinking, diabetes, antidepressant use, anti-inflammatory use, solvent exposure, paint exposure, pesticide exposure, or farm exposures.

Discussion

Oligodendroglial tumors are rare tumors often grouped with other glial tumors in epidemiological studies.[20,24–39] A summary of possible risk factors that have been investigated for glioma is available in the review by Bondy et al.[14] Known risk factors for glioma include inherited genetic syndromes and exposure to high-dose ionizing radiation.[32,33] Epilepsy/seizures, a family history of brain tumors, and mutagen sensitivity have all previously been associated with an increased risk of glioma, while allergies/asthma and chicken pox have been associated with a decreased risk of glioma.[14] Smoking, alcohol consumption, dental X-rays, and head injury are not believed to be associated with the risk of glioma. Other nongenetic risk factors that have been investigated include cellular telephone use,[25,29] diet,[36] anti-inflammatory drug use,[20] pesticides,[28] exogenous hormones,[26,30] and other lifestyle factors.[24] Information on many of these risk factors was available for pooled analysis in the current study. Whereas genetic risk factors have been investigated in glial tumors[27,31,37] and recent GWAS studies have found 3–5 chromosomal regions associated with glioma,[34,35] the specific aims of this study did not include genetic analyses and, therefore, genetic risk factors were not evaluated.

Similarities were found in the risk factors in this analysis and those previously identified for gliomas.[14] Family history of brain tumors was associated with an increased risk of anaplastic oligodendroglioma, while allergies and/or asthma and chicken pox were associated with a decreased risk. No significant association of allergies with oligodendroglioma was found, but there was a significantly decreased risk for those with asthma. Although there is the possibility that the power was too low to detect an association with allergies, the number of oligodendroglioma cases in this study was much larger than the number of cases with anaplastic oligodendroglioma. Interestingly, allergies were associated with a significantly increased risk of oligodendroglioma in the Scandinavian sites, although previous analyses of all gliomas combined have shown reduced risk estimates.[21] The small number of cases

Table 3. Adjusted ORs for data on selected exposures collected at 5 US and 2 Scandinavian sites for oligodendroglioma (OGD), anaplastic oligodendroglioma (AO), and both tumor types compared with frequency-matched controls

Exposure	Oligodendroglioma, adj. OR[a] (95% CI)	Anaplastic oligodendroglioma, adj. OR[a] (95% CI)	Both tumor types, adj. OR[a] (95% CI)	# Cases OGD/AO	# Controls	Study sites excluded[c]
Ever smoker	0.9[f] (0.7, 1.2)	0.9 (0.7, 1.4)	0.9 (0.8, 1.2)	328/146	1255	None
Family history of brain tumor	1.6 (0.9, 3.1)	**2.2[d] (1.1, 4.5)**	**1.8[d] (1.1, 3.1)**	271/122	995	2, 6
Family history of cancer	1.1[e] (0.8, 1.4)	1.1 (0.7, 1.5)	1.1 (0.9, 1.3)	324/144	1230	None
Asthma	**0.5[d] (0.3, 0.9)**	**0.3[d] (0.1, 0.9)**	**0.4[d] (0.2, 0.7)**	174/92	674	1, 3, 4.1
Allergies[b]	1.1[e] (0.8, 1.6)	0.6 (0.4, 1.1)	0.9 (0.7, 1.3)	245/97	880	1, 4.1
Asthma and/or allergies[b]	0.9 (0.6, 1.2)	**0.6[d] (0.4, 0.9)**	**0.7[d] (0.6, 1.0)**	222/122	869	3, 4.1
Eczema	0.6 (0.3, 1.3)	0.4 (0.1, 1.3)	0.5 (0.3, 1.0)	136/72	541	1, 3, 4.1, 4.2
History of seizures	**6.7[d,f] (4.3, 10.6)**	**8.7[d] (5.0, 15.2)**	**7.0[d] (4.7, 10.5)**	248/130	1036	3
Antihistamine use	1.0 (0.6, 1.4)	1.2 (0.7, 1.9)	1.0 (0.8, 1.4)	229/123	866	2, 4.1, 7
Dominant hand						
Left vs right	1.2 (0.6, 2.3)	1.1 (0.4, 2.8)	1.1 (0.6, 2.0)	122/64	494	1, 3, 4.1, 4.2
Both vs right	1.1 (0.3, 3.4)	0.9 (0.1, 7.5)	1.0 (0.4, 3.0)			
Radiation treatment	1.1 (0.5, 2.6)	1.3 (0.5, 3.4)	1.2 (0.6, 2.3)	327/146	1247	None
Dental X-rays	0.8 (0.5, 1.2)	1.3 (0.5, 2.9)	0.9 (0.6, 1.3)	212/86	772	1, 4.1, 4.3
Medical X-rays to the head and neck	**0.7[d] (0.5, 1.0)**	**0.6[d] (0.4, 1.0)**	**0.7[d] (0.5, 0.9)**	179/80	731	1, 3, 4.3
Any trauma to the head	1.3 (1.0, 1.8)	1.0 (0.6, 1.5)	1.2 (0.9, 1.6)	267/110	1037	5, 7

[a]Unconditional logistic regression, adjusting for age group, gender, and site.
[b]Allergies for the Denmark and Sweden data only includes hay fever.
[c]1 = MD Anderson; 2 = NCI; 3 = NIOSH; 4.1 = UCSF Series 1; 4.2 = UCSF Series 2; 4.3 = UCSF Series 3; 5 = UIC/Duke; 6 = Sweden; 7 = Denmark.
[d]$P < .05$.
[e]P value for test for heterogeneity was $<.05$ between US and Scandinavian sites. For oligodendroglioma, site-specific adj. OR (95% CI) for family history of other cancers for Scandinavian and US sites, respectively, was 4.0 (1.7, 9.6) and 1.0 (0.7, 1.3); for allergies for Scandinavian and US sites, respectively, was 4.6 (1.3, 15.5) and 0.9 (0.6, 1.3).
[f]P value for interaction term with site was $<.05$ among US sites with available data. For oligodendroglioma, site-specific adj. OR (95% CI) for smoking ranged from MD Anderson: 0.4 (0.2, 0.9) to Duke/UIC: 2.3 (1.0, 5.3); for history of seizures ranged from NIH: 1.2 (0.4, 3.9) to Duke/UIC: 35.2 (4.0, 311.2); For anaplastic oligodendroglioma, site-specific adj OR (95% CI) for medical X-rays ranged from UCSF: 0.4 (0.1, 0.9) to NIH: 2.6 (0.7, 10.4).

from the Scandinavian sites may explain some of the variability in risk compared with the US study sites. In addition, differences in data collection or study design between studies (for example, hayfever versus all allergies; in-person interview versus self-completed survey, differences in wording of survey questions, etc.) may have resulted in some heterogeneity or bias. Also, differences in age distribution between controls and cases for each histologic subtype may have resulted in a lack of efficiency to detect an association. Alternately, it is possible that allergies may not protect against oligodendroglioma as they have been observed to do for other glial tumors.[14,17,20,21,38,39] The allergy results presented in this study are similar to the results of Schwartzbaum et al.,[40] where allergies were inversely associated with high-grade, but not low-grade, gliomas. The only protective factors associated with oligodendroglioma were ever having had asthma and ever having had chicken pox, suggesting that other factors not explored here may be associated with a risk of oligodendroglioma. Although seizures were associated with an increased risk in all 3 histologic subtypes, it is highly likely that for some proportion of the cases the seizures represent an early symptom rather than an etiological risk factor. Detailed examination of this association would be required; however, we were not able to assess this variable in depth. Similarly, the apparent protective effect of medical X-rays for those with oligodendroglioma may be due to a bias in recall or reporting. No significant associations with mixed glioma were identified, although the number of cases was small compared with the number of oligodendroglioma and anaplastic oligodendroglioma subjects in this study.

As oligodendroglial tumors are a rare glioma subtype, few studies are able to look at risk factors separately for each of the histologic types presented here. Pooling data

Table 4. Adjusted ORs for data on select exposures collected only at 5 US sites for oligodendroglioma (OGD), anaplastic oligodendroglioma (AO), and both tumor types compared with frequency-matched controls

Exposure	Oligodendroglioma, adj. OR[a] (95% CI)	Anaplastic oligodendroglioma, adj. OR[a] (95% CI)	Both tumor types, adj. OR[a] (95% CI)	# Cases OGD/AO	# Controls	Study sites excluded[b]
Ever regular alcohol drinker	0.8 (0.6, 1.2)	0.7 (0.5, 1.2)	0.8 (0.6, 1.1)	287/120	1092	None
Diabetes I or II	0.8 (0.4, 1.9)	0.7 (0.2, 2.0)	0.8 (0.4, 1.5)	192/108	754	3, 4.1
Chicken pox	**0.6[c] (0.4, 0.9)**	**0.5[c] (0.3, 0.9)**	**0.6[c] (0.4, 0.8)**	172/100	731	2, 3
Antidepressant use	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)	0.8 (0.6, 1.2)	177/104	745	2, 3
Anti-inflammatory use	0.9 (0.6, 1.4)	0.9 (0.5, 1.4)	0.9 (0.6, 1.3)	148/98	586	2, 3, 4.1
Solvent exposure	0.9 (0.7, 1.3)	1.2 (0.7, 2.0)	1.0 (0.7, 1.4)	203/83	733	4.1, 4.2, 4.3
Paint exposure	1.4 (1.0, 2.0)	1.4 (0.8, 2.4)	1.3 (1.0, 1.7)	225/100	834	4.1, 4.2
Pesticide exposure	1.1 (0.7, 1.6)	1.6 (0.8, 3.2)	1.2 (0.8, 1.7)	223/99	826	4.1, 4.2
Farm exposures	0.7 (0.5, 1.1)	0.8 (0.5, 1.4)	0.8 (0.5, 1.1)	200/81	760	1, 2
Water source						
Private vs public	1.0 (0.7, 1.6)	1.6 (0.8, 3.1)	1.1 (0.8, 1.7)	199/83	727	4.1, 4.2, 4.3
Bottled vs public	**0.4[c] (0.2, 0.9)**	0.5 (0.2, 1.3)	**0.4[c] (0.2, 0.8)**			

[a]Unconditional logistic regression, adjusting for age group, gender, race, site, and interview year.
[b]1 = MD Anderson; 2 = NCI; 3 = NIOSH; 4.1 = UCSF Series 1; 4.2 = UCSF Series 2; 4.3 = UCSF Series 3; 5 = UIC/Duke.
[c]*P* value $< .05$.

across study sites can help to focus future studies on risk factors that may be uniquely relevant to these histologies. However, there are several limitations to these data including pooling cases and controls from studies with different study designs. First, because all of the studies used a case–control study design, we used controls from each primary study frequency-matched to cases from the same primary study. However, controls from 3 US and both international sites were selected in a population-based manner, whereas controls from the other 2 US studies were hospital-based and friend controls. There is the potential that hospital and friend controls may be over-matched on some of the exposure variables selected for analysis which would bias our estimates toward the null (or underestimate the effects). Second, the questions on the surveys were often asked in a similar but not identical way, which necessitated the combination of data at a broad level (eg, yes/no) rather than using specific details for many of the variables. Standardized surveys that ask questions in a similar format would be necessary to probe these variables in more detail. As not all study sites had race data available, we did not control for this variable in the analyses including all 7 study sites. However, the final results were similar when restricted to including only the 5 US study sites, where race was included in the model. Third, differences in the distribution of age groups in cases compared with controls for the specific subgroup analyses may have resulted in a lack of efficiency to detect an association if exposure to the variable was more likely to occur later in life or if the association was due to cumulative exposure over time. However, results similar to the histologic-specific results were found for the analysis of oligodendrogliomas and anaplastic oligodendrogliomas combined, where the distribution for cases and controls was very similar.

Additionally, classification of oligodendroglial tumors has changed over time. With the identification of loss of 1p/19q as a positive prognostic indicator,[12,41,42] the incidence of oligodendroglial tumors rose throughout the 1990s.[43] Since the early 2000s, the features of oligodendroglioma have become better recognized, loss of 1p/19q has become a common clinical marker for identification of these tumors,[44] and the incidence of oligodendroglioma in the USA has begun to decline.[43] Therefore, cases and controls ascertained over different time periods may reflect differential classification, and it is possible that the results may have been influenced by these changes. Reanalysis of data collected pre-2000 (including data from NCI, NIOSH/CDC, UCSF Series 1 and 2) and post-2000 (including data from MD Anderson, UIC/Duke, UCSF Series 3) was conducted to investigate possible differential classification over time. Significant heterogeneity was found between those studies conducted prior to the year 2000 and those conducted in 2000 or later for being an ever smoker, having a family history of cancer, having any trauma to the head, and having a history of diabetes and chicken pox (data not shown). Heterogeneity between sites for smoking and family history of cancer was already noted in Table 3. For chicken pox, the estimates for both time periods were in the same direction, reflecting a difference in magnitude but not direction. These differences may be due to differences in the time periods (including differences in classification), small numbers in the subgroup analyses, or, as different studies were included in the different time periods, differences by study site (including differences in population, how the data were collected, etc). Although there were some differences pre- and post-2000, the primary conclusions presented in this paper did not change. To further address this, restriction

of the analysis to tumors that were pathology reviewed and, even further, to those tumors pathology reviewed by one neuropathologist (K.A.), did not materially change the results presented in Tables 3 and 4.

The rarity of oligodendroglial tumors requires collaboration among researchers at multiple institutions to provide the large numbers of subjects needed to identify potential risk or protective factors. Using survey data from previously conducted studies, some overlap between oligodendroglial tumors and all gliomas as a group was found for some risk factors, such as family history of brain cancer, and protective factors, such as asthma, allergies, and chicken pox. It is likely, however, that there are other risk factors yet to be identified specific to oligodendroglial tumors. Large multi-institution international studies focused on these and other risk factors are needed to further clarify the etiology of oligodendroglial tumors.

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