Risk Factors for Gliomas and Meningiomas in Males in Los Angeles County

Susan Preston-Martin, Wendy Mack, and Brian E. Henderson

Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California 90033

ABSTRACT

Detailed job histories and information about other suspected risk factors were obtained during interviews with 272 men aged 25–69 with a primary brain tumor first diagnosed during 1980–1984 and with 272 individually matched neighbor controls. Separate analyses were conducted for the 202 glioma pairs and the 70 meningioma pairs. Meningioma, but not glioma, was related to having a serious head injury 20 or more years before diagnosis (odds ratio (OR) = 2.3; 95% confidence interval (CI) = 1.1–5.4), and a clear dose–response effect was observed relating meningioma risk to number of serious head injuries (P for trend = 0.01; OR for ≥ 3 injuries = 6.2; CI = 1.2–31.7). Frequency of full-mouth dental X-ray examinations after age 25 related to both glioma (P for trend = 0.04) and meningioma risk (P for trend = 0.06). Glioma, but not meningioma risk, related to duration of prior employment in jobs likely to involve high exposure to electric and magnetic fields (P for trend = 0.05). This risk was greatest for astrocytoma (OR for employment in such jobs for > 5 years = 4.3; CI = 1.2–15.6). More glioma cases had worked in the rubber industry (discordant pairs 6/1) and more worked in hot processes using plastics (9/1). More meningioma cases had jobs that involved exposure to metal dusts and fumes (discordant pairs 13/5), and six of these cases and two controls worked as machinists. Finally, there was a protective effect among glioma pairs relating to frequency of use of vitamin C and other vitamin supplements (P for trend = 0.004); the OR for use at least twice a day was 0.4 (CI = 0.2–0.8).

INTRODUCTION

The age-adjusted incidence rate for primary tumors of the brain and cranial meninges (called BT) in Los Angeles County is about 8/100,000/year. Therefore, more than 600 BT are diagnosed each year among Los Angeles County residents. Eighty-six % of all primary BT are gliomas or meningiomas. Studies of the etiology of brain tumors in adults have suggested the importance of exposure to ionizing radiation (1–5), physical trauma (4–7), farm residence (8–10), familial aggregation (11–12), and various occupational exposures such as vinyl chloride monomer (13–15), rubber (16–19), formaldehyde (20–22), and electric and magnetic fields (23–25). This paper describes a case-control study of gliomas and meningiomas diagnosed in men in Los Angeles County from 1980 to 1984. The purpose of this study was to investigate the importance of occupational exposures and of other suggested risk factors for this disease.

MATERIALS AND METHODS

Cases. The patients were black and white men with a glioma or meningioma first diagnosed during 1980–1984. Any man who was a resident of Los Angeles County and 25–69 years of age at the time his BT was diagnosed was eligible for inclusion if he was alive and able to be interviewed. We decided to only include personal interviews with the subjects themselves because of the level of detail we sought on job history and other experiences. Because we decided not to accept interviews with proxy respondents, we were unable to include a large proportion of otherwise eligible cases because they were deceased or were too ill or impaired to participate in an interview. The Los Angeles County Cancer Surveillance Program identified the cases (26). All diagnoses had been microscopically confirmed. A total of 478 patients were identified. The hospital and attending physician granted us permission to contact 396 (83%) patients. We were unable to locate 22 patients, 38 chose not to participate, and 60 were aphasic or too ill to complete the interview. We interviewed 277 patients (74% of the 374 patients contacted about the study or 58% of the initial 478 patients). An additional 161 patients who were otherwise eligible were deceased, only 10 of these were meningioma patients. Controls. We sought a neighborhood control for each of these 277 patients by use of a procedure that defines a sequence of houses on specified neighborhood blocks. Our goal was to interview the first male resident in the sequence who corresponded to the patient in race and age (birth year within 5 years of birth year of the patient). We would not interview a match until we ascertained that there were no available matches at houses visited earlier in the sequence. If no one was home at the time of the visit, we left a return envelope, an explanatory letter and a brief questionnaire about the age, sex and race of household members at the residence and made a follow-up visit after several days. In 210 instances, the first appropriate person agreed to be interviewed. In 62 neighborhoods, the first match refused, but we were able to locate and interview another matched control in the sequence. For any patient, we visited 40 housing units and made three return visits before we conceded failure to secure a matched control. We were unable to obtain a control in five neighborhoods. In all, we identified and interviewed 272 controls. These 272 controls and the corresponding 272 cases were included in the analysis.

The Interview. A questionnaire sought information on various life experiences that had occurred 2 years or more prior to the year of diagnosis of the case. The first and longest section obtained a detailed job history including information on specific job tasks and materials used. After the work history was obtained, specific questions were asked about exposures, on any job, to each of: 45 substances; five processes (e.g., welding); radiation or radioactive materials; and farming and various related exposures. Questions were also asked about occupational illness or injury. There were also questions about head trauma; head X-rays; relatives with nervous system tumors or cancer; and consumption of tobacco, alcohol, vitamin supplements, and certain foods. It was not feasible for interviews to be conducted blindly, but all questions were asked in a standard manner. Both members (case and control) of each matched pair were interviewed by the same interviewer and both were interviewed by the same method, either in person or by telephone. Interviews were conducted from August 1980 through December 1985.

Statistical Analysis. In the analysis of dichotomous exposure variables, we used matched OR (the ratio of discordant pairs) to estimate relative risks and used the exact binomial test to calculate associated P values and CIs. Conditional logistic regression models were used for the dose-response analysis of a single variable considered at more than two levels, for tests of trend, and for multivariate analyses (27). If, for any variable, the information for either the patient or the control was not known, we excluded the pair from the relevant analysis. All statistical significance levels (P values) cited are based on a likelihood ratio test and are two-sided for occupational factors and for tobacco and alcohol use. P Values are one-sided for other variables which were asked to test one-directional hypotheses relating to variables such as X-rays, head trauma, and vitamin use. However, the 95% confidence intervals (CI) shown are two-sided. In tests for trend, factors are considered as continuous variables whenever possible.

Analyses of occupational data compared the distributions of cases and controls by blue versus white collar and by major occupation (10...
groups) and industry groups (11 groups). Comparisons were also made of the numbers who worked in specific occupations or industries or specific groups of occupations or industries that had been identified in the literature as having apparent excesses of brain tumors. Similarly, comparisons were made for each of the 45 substances, five processes, and other exposures queried separately as well as the hundreds of substance exposures reported during the initial job history.

RESULTS

Analyses used data for 202 glioma pairs and 70 meningioma pairs. Only a few pairs were black (11 glioma and five meningioma pairs). Glioma cases and controls were similar with regard to median birthyear (1938 for both); mean age at date of diagnosis of the case (45.2 years for cases; 45.1 for controls); and mean number of years of education (13.3 versus 13.7). Meningioma pairs were also similar with regard to these variables: median birthyear (1924 versus 1926); mean age (55.3 versus 54.5); and mean years of education (13.1 for both). The distribution by histological type is shown in Table 1.

**Serious Head Trauma.** Table 2 compares cases and controls on prior serious head injury. “Serious head injury” was defined to include all head injuries occurring before reference year (2 years before the year of diagnosis of the case) that led to loss of consciousness, dizziness, or a medical consultation. Men who had a serious head injury 20 or more years before the year of diagnosis of the case had a significantly increased risk of meningioma, but not of glioma. Head injury appeared not to be associated with glioma risk no matter what the assumed latent period (interval between first head injury and diagnosis). The increase in meningioma risk was greater after an interval of 20 years than after intervals of 5, 10, or 30 years. In a dose-response analysis, the meningioma risk increased with an increase in the number of serious head injuries. (ORs for 0, 1, 2, and 3+ head injuries 10 or more years prior to diagnosis = 1.0, 1.6, 2.3, and 4.6; P trend = 0.01).

**Exposure to X-Rays.** Table 3 compares cases and controls on prior dental radiography. Questions were asked about frequency of any type of dental X-ray examination and frequency of full-mouth X-ray series in particular for two periods (up to age 25; after age 25). Whether or not subjects had ever been exposed to dental X-rays was not a good discriminator because about 90% of all controls had such an exposure. Exposure to dental X-rays before age 25 was less common than exposure after age 25, and exposure to full-mouth X-ray examinations (which use an average of 18 intraoral films) was less common than exposure to dental X-rays of any type. Few men had full-mouth exams before age 25. Glioma risk increased with an increase in the frequency (from never to yearly) of full-mouth examinations after age 25; a similar trend was seen for meningiomas. Both glioma and meningioma risk also increased with an increase in the frequency of exposure to dental X-rays of any type before age 25, although these trends did not reach statistical significance. The way these questions were asked did not allow for an analysis by calendar year of exposure; the per film dose from dental radiography had declined dramatically since 1920 and as recently as the 1960s was many times higher than it is today (28). Cases and controls were similar with regard to medical radiography of the head before reference year. Pairs in which either the case or the control had exposure to the brain or cranial meninges from radiation treatment to the head or neck prior to reference year (3 cases; 3 controls) were excluded from all X-ray analyses.

**Occupational History.** Some significant case-control differences related to major occupational categories. Compared to their controls, more glioma cases had spent the majority of their working years in blue collar jobs [discordant pairs, 46/31; OR = 1.5; P (two-sided) = 0.09]. This difference was attributable mainly to more cases working as transport or equipment operatives (discordant pairs 7/3; OR = 2.3; P = 0.22) or as laborers (11/3; OR = 3.7; P = 0.05). Of those who spent the majority of their working years as laborers, nine cases and no controls worked as warehousemen, freight and material handlers, or stock handlers and they held such jobs for an average of 12 years. Seven of these nine said they were exposed to various types of dust (two to chlorine), three to acids, and one each to methylethylketone, formaldehyde, petroleum products, plastics, and rubber.

Similar proportions of meningioma cases and controls spent the majority of their working years in blue versus white collar jobs, but more meningioma cases worked in service jobs for more than 5 years (discordant pairs, 10/4; OR = 2.5; P = 0.12). Five cases versus six controls worked as policemen, security guards, or detectives; the mean years at these jobs was 16.5 for cases versus 9.0 for controls. Three cases and no controls were professional cooks. Three cases worked an average of 17 years...
Table 3 Comparison of male brain tumor cases (glioma and meningioma) and controls on frequency of exposure to dental radiography, Los Angeles County, 1980–1984

<table>
<thead>
<tr>
<th>Frequency of dental X-rays up to age 25</th>
<th>Gliomas</th>
<th>Meningiomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or &lt; every 5 years</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Every 2–5 years</td>
<td>0.15</td>
<td>0.7</td>
</tr>
<tr>
<td>Once a year</td>
<td>0.09</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 5 Other job exposures positively associated with occurrence of brain tumors (gliomas and meningiomas) in men, Los Angeles County, 1980–1984

<table>
<thead>
<tr>
<th>Gliomas</th>
<th>Meningiomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubber processing</td>
<td>6/1 6.0 0.7, 276.0</td>
</tr>
<tr>
<td>Used any other type of plastic</td>
<td>13/6 2.2 0.8, 6.9</td>
</tr>
<tr>
<td>Synthetics (nylons, rayons, etc.)</td>
<td>6/1 6.0 0.7, 276.0</td>
</tr>
</tbody>
</table>

As Janitors compared to 1 control who worked as a janitor for 4 years.

In addition, more meningioma cases worked as a manager or administrator for more than 5 years (17/6; OR = 2.8; P = 0.03). Nothing striking emerged, however, in an analysis by specific jobs held.

Employment in occupations likely to involve high exposure to electric and magnetic fields appeared to increase risk of gliomas but not meningiomas (Table 4). The association was strongest with astrocytomas (OR for working in such jobs > 5 years = 4.3; CI = 1.2–15.6). Risk increased with an increase in the number of years working in these occupations (P for trend = 0.008). The occupations in this rubric are listed in a footnote to Table 4.

No subjects worked in the manufacture of polyvinylchloride, but 14 glioma cases versus seven controls had jobs that involved contact with other plastics (i.e., other than polyvinylchloride, polystyrene, polyethylene, or polyurethane; discordant pairs, 13/6; Table 5). A comparison by job type showed that nine cases and one control worked in the manufacture of plastic products or heated plastic to melt it down, whereas similar numbers of cases and controls cut or shaped plastic (four cases; four controls) or used plastic materials for bonding or covering (one case; two controls). Most subjects did not know the name of the plastic compound they used.

More cases than controls answered yes when asked if they had ever worked in rubber processing (discordant pairs: glioma, 6/1; meningioma, 3/2; Table 5). In addition, when giving their job histories, more cases had volunteered previously (in the occupational history section of the questionnaire) that they were exposed to rubber or rubber dust when asked about substances they came in contact with (discordant pairs: glioma, 7/2; meningioma, 4/0; Table 5). Four subjects worked in tire plants: two glioma cases worked 24 and 9 years, and one meningioma case and one meningioma control each worked 2 years in the manufacture of rubber tires.

Six glioma cases and one control had jobs working with synthetics (e.g., nylon, rayon, and other polyesters), but only one of these seven (one case) worked in the manufacture of synthetics and the other six worked only with the finished product. Three of the cases (and no controls) had volunteered previously that their jobs involved working with rayon, and one
of these worked with rayon for 12 years.

There were no remarkable differences between cases and controls in job exposure to specific petroleum products such as paints, lacquers, or coal tar, soot, or pitch; but more meningioma cases than controls said they had worked with other petroleum products such as gasoline or kerosene at least weekly (18/5, Table 5). Ten of these cases and three controls used gasoline or another petroleum-based solvent to clean their hands or clean items they worked with, and seven cases and four controls used it daily as a fuel and inhaled the fumes. Three cases and three controls used airplane fuel. Ten meningioma cases and five controls used cooling, cutting, or lubricating oils, and most used these daily (eight cases; four controls). Seven meningioma cases and two controls had daily exposure to inks and most mixed inks or worked with wet inks (four cases; one control).

Information volunteered about specific job exposures in the occupational history section of the questionnaire suggested that kerosene might be an exposure of interest (nine meningioma cases; four controls), but most exposures appeared relatively trivial (e.g., “occasionally filled a kerosene lamp”), and only two of the nine cases used kerosene at least weekly.

More meningioma cases had jobs that involved exposure to metal dust and fumes (discordant pairs 13/5; Table 5). Among those with metal dust exposure, six cases and two controls worked as machinists and both cases and controls worked as machinists for an average of 5 years. Similar numbers of cases and controls were exposed to metals as welders (two cases, two controls), inspectors (two cases, one control) or as laborers of various sorts (four cases, two controls).

No other significant case-control differences were apparent in the analysis of occupational factors. This analysis included comparisons on the 37 specific substances and five specific jobs queried as well as comparisons by job titles, industry of employment, and information given about exposures in the job history section of the questionnaire. Some comparisons were made by grouping job titles or exposures in an attempt to confirm associations reported in the literature. A similar number of cases and controls worked in the aircraft industry (glioma, 34 cases and 34 controls; meningioma, 13 cases and 14 controls). Also, cases and controls were similar with respect to job exposure to ionizing radiation.

Other Exposures. Table 6 compares cases and controls on smoking status and consumption of alcoholic beverages. There were no remarkable differences between cases and controls with regard to history of cigarette smoking when we considered age started smoking, amount smoked, years smoked, and pack-years of exposure (1 pack-year is equivalent to smoking a pack a day for a year, i.e., 7300 cigarettes). The only significant difference in relation to consumption of beer, wine, and hard liquor was that fewer meningioma cases than controls were beer drinkers (i.e., drank beer at least once a month). No differences were apparent in maximum amount of alcohol drunk regularly.

There were no significant differences between cases and controls in their consumption of various cured meats or of citrus fruits. Among glioma pairs, a significant protective effect was associated with the use of vitamin supplements, and increasing protection related to increasing frequency of use (one-sided P for trend = 0.004). The OR for use at least twice a day was 0.4 (95% CI = 0.24–0.77). The protective effect was somewhat stronger for use of vitamin C tablets than for other vitamin preparations. Among meningioma pairs, no protective effect of vitamin supplements was seen but a protective effect was seen for consumption of citrus fruit (OR for ate citrus five or more times a week = 0.4; P = 0.07; P for trend = 0.12). Also, meningioma risk appeared to increase with increasing consumption of all types of cured meats combined, but this finding was not statistically significant.

Fewer cases than controls had ever lived on a farm, and among the glioma pairs this difference was statistically significant (OR = 0.5; P = 0.016). When just those subjects who lived on a farm were considered, fewer cases reported exposure to various farm animals, crops, pesticides, and fertilizers. In an analysis by decade when they worked on a farm, the only significant finding was that more glioma cases did farm work in the 1950s (discordant pairs, 6/1; OR = 6.0; P = 0.05).

The same number of cases and controls had blood relatives with cancer (discordant pairs: glioma, 42/42; meningioma, 12/12). More meningioma cases had two or more relatives with cancer (10/3; OR = 3.3; P = 0.02), but there was nothing remarkable about the site distribution of these cancers. A similar number of cases and controls had relatives with nervous system tumors. Two meningioma cases had a close blood relative with a meningioma (one had a son diagnosed at age 17, the other a sister diagnosed at age 61). No cases had a prior primary brain or other nervous system tumor, and no controls had nervous system tumors.

DISCUSSION

The present study has limited generalizability because it includes only living subjects who were able to be interviewed. Although interviewers could not be blinded as to case or control status, they were blinded as to the study hypotheses, and every effort was made to conduct interviews with cases and controls in a like manner.

The study does support various associations reported previously such as the association of brain tumors with various occupational factors, (e.g., working in the rubber industry) and with frequent full mouth dental X-rays; however, not all such previously reported differences are statistically significant here. This study does not support other previously suggested associations. For example, we see no increase in risk related to cigarette smoking or wine drinking. The hypothesis that exposure to N-nitroso compounds causes brain tumors has gained limited support from the association with employment in the rubber industry and from the clearly protective effect seen for gliomas of frequent use of vitamin C and other vitamin supplements (both discussed below). Finally, this study, by comparing data for the two major histological groups of primary brain tumors, has helped to clarify the relative importance of suspected risk factors such as head trauma in the etiology of each.

Serious Head Trauma. The possibility of recall bias must be considered in all such case-control interview studies, but it is of particular concern when investigating factors such as trauma
which among lay persons is often thought to relate to tumor development. The concern is that direct questions about head injuries may be answered more completely by brain tumor patients than controls because patients may already have thought an injury caused their tumor; this phenomenon is called “differential recall.” For this reason, we limited our analysis of this variable to “serious head injuries” (i.e., those injuries that resulted in a medical visit, loss of consciousness, or dizziness) that occurred 2 or more years before the year of diagnosis. The fact that head trauma was found to be a risk factor for meningioma but not for glioma provides further reassurance that this finding is not attributable to differential recall. Also, it supports findings from other recent case-control studies which did not find an association of head trauma with gliomas (29) but did find an association with meningiomas (4, 5). In the present study, the association was strongest with serious head injury 20 or more years prior to the year of diagnosis, and risk increased with an increase in the number of serious head injuries. A few dramatic case reports suggest that trauma can lead to the development of meningioma. For example, a boiler explosion drove a wire 1 cm long into the brain of a man who 20 years later was found to have a large meningioma with the wire at its center (30). Another man, who struck his head when he was thrown from a stretcher by a bomb explosion, developed a small lump on his head at the site of the injury. Twenty years later, the lump began to gradually increase in size and after 5 years was surgically removed and histologically diagnosed as a meningioma (7). The present study further suggests that head trauma is an important factor in the development of meningiomas, and that it is unlikely to be an important factor in the development of gliomas.

Exposure to X-Rays. Both major tumor types, on the other hand, appear to be related to the frequency of full-mouth dental X-rays after age 25. There was also the suggestion of a relationship with the frequency of exposure to dental X-rays (of any type) before age 25. Meningiomas have been related previously to frequency of full-mouth dental X-ray series and to young age at first full-mouth series (4, 5). In addition, the risk for brain tumors of all histological types in young people age 15–24 was increased among those who had five or more full-mouth examinations starting at least 10 years before diagnosis (31). A recent study of gliomas in adults, however, did not find an association with having ever had dental X-rays (29). This variable (ever versus never had dental X-rays) is likely, however, to be a poor discriminator. It does not correlate well with total exposure from dental radiography (28), and, in the present data set, about 90% of controls ever had their teeth X-rayed. A better indicator of exposure from dental radiography is total number or frequency of dental X-ray examinations, in particular full-mouth examinations. Dental X-rays account for most of the exposure of the head from diagnostic radiography, and cumulative exposure from dental X-rays can be quite high (in a recent study of cases and controls of similar ages to those in the present study, 37% had >5 rads and 4% >50 rads exposure to the parotid gland, 28).

Since dental X-ray examinations are not particularly memorable events, recall of them may be poor. We have asked similar questions about dental radiography in several studies including one that validated interview information by a review of dental charts. Results of this validation study suggest that any misclassification in interview data on dental X-rays is similar for cases and controls and that these data are good enough to use alone in the analysis of case-control studies (28).

Ionizing radiation can cause brain tumors, and a recent follow-up of the Israeli tinea capitis cohort suggests that this association is stronger for meningiomas (RR = 9.5) than for gliomas (RR = 2.6; Ref. 32). We were unable to evaluate this potential difference in our study because our data on exposure to X-rays and other sources of ionizing radiation was limited. However, a test for interaction between tumor type and full mouth X-ray frequency after age 25 was not statistically significant implying no differential risk by histological type for this X-ray variable.

Occupational History. We confirmed the association of glioma with previous employment in the rubber industry (OR = 6.0). Several earlier studies have found a similar association (29, 33–35) but others have not (36, 37). Four of the five positive studies found the association to be specific to working in the manufacture of tires, and the fifth study gave no information on type of job held in the rubber industry (29). The three negative studies, on the other hand, looked at employment in other branches of the industry or in the industry as a whole. In our study, two glioma cases, one meningioma case, and one meningioma control were employed in the manufacture of tires. Tire plants have been found to have high levels of contamination with various N-nitroso compounds (N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosomorpholine, and N-nitrosodiphenylamine) in the air, soil, floor scrapings, steam condensate, and compounding chemicals (38). Hot processes such as tire curing had the highest levels of volatile N-nitroso compounds, in particular N-nitrosomorpholine. Various other N-nitroso compounds (in particular the nitrosoureas) have been shown experimentally to cause brain tumors in a variety of species (39, 40).

The association with exposure to vinyl chloride reported previously (14, 41) was not found in our study. The possible association we found of gliomas with working in hot processes using other plastics needs to be investigated in other studies.

We also confirmed an association of gliomas, in particular astrocytomas, with duration of employment in jobs involving more than the usual exposure to electric and magnetic fields. This association with gliomas (23, 25) and with astrocytomas in particular (24) has been reported previously. Although it is tempting to assume that this increase is attributable to increased exposure to extremely low frequency electromagnetic radiation, the mechanism for such an effect is not understood and the possible association of brain tumor risk with other exposures common to this industry (such as organic solvents) must be considered (24).

More meningioma cases than controls reported exposure to metal dust and fumes and this difference was attributable to more cases working as machinists. Machinists and other precision metal workers have been shown to have an elevated brain tumor risk (43). In addition, more of our meningioma cases used metal working fluids such as cooling and cutting oils. Such fluids have been shown to contain N-nitroso compounds (38).

Descriptive studies have shown that glioma incidence and mortality rates are highest among those in the highest social classes regardless of whether social class is defined by census tract of residence or by occupation (43–45). The present study, in contrast, found an increase in glioma risk associated with employment (for most of one’s working years) in blue collar jobs. The most striking difference in this group was that nine cases and no controls had worked as warehousemen or freight handlers. The most common exposures mentioned in relation to these jobs were dusts of various sorts (seven cases) and acids (three cases).

Compared to controls, more of our meningioma cases worked
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