Case-Control Study of Use of Nonsteroidal Antiinflammatory Drugs and Glioblastoma Multiforme

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Received for publication July 8, 2003; accepted for publication January 12, 2004.

Evidence from epidemiologic and experimental studies suggests that use of nonsteroidal antiinflammatory drugs (NSAIDs) reduces risk of colon and breast cancer. The association between use of aspirin and other NSAIDs and risk of adult glioblastoma multiforme (GBM) was evaluated among 236 incident GBM cases and 401 population-based controls frequency-matched on age, gender, and ethnicity from the San Francisco Bay Area Adult Glioma Study. Cases (or proxies) and controls were interviewed in person between May 1997 and August 2000. Cases with self-reported GBM reported less use of at least 600 pills of all types of NSAIDs combined during the 10-year prediagnostic period than did controls (odds ratio (OR) = 0.53, 95% confidence interval (CI): 0.3, 0.8). Findings were consistent for aspirin (OR = 0.51, 95% CI: 0.3, 0.8), ibuprofen (OR = 0.41, 95% CI: 0.2, 0.8), and naproxen/other NSAIDs (OR = 0.34, 95% CI: 0.1, 0.8). GBM cases also reported less use of acetaminophen than did controls (OR = 0.51, 95% CI: 0.3, 1.0). Eliminating participants who initiated NSAID use within 2 years of diagnosis yielded similar results. These findings show an inverse association between NSAID use and GBM. Further studies are warranted to determine whether NSAIDs might be effective in the inhibition of GBM development or progression.

acetaminophen; anti-inflammatory agents, non-steroidal; case-control studies; glioblastoma

Abbreviations: CI, confidence interval; NSAID(s), nonsteroidal antiinflammatory drug(s); OR, odds ratio.

Glioblastoma multiforme, a highly malignant astrocytic tumor (1), is the most common primary malignant brain tumor and usually results in debility or rapid death (1–3). Treatment prospects for this tumor have not improved significantly in the past two decades (2, 4, 5). Although epidemiologic studies of glioma have implicated numerous environmental risk factors (e.g., radiation, chemical carcinogens, or infections/viruses), only therapeutic radiation exposure has been convincingly established to be causal (2). Thus, there currently are no prevention strategies for glioblastoma multiforme other than reducing high-dose ionizing radiation exposure to the head.

Numerous case-control and cohort studies have evaluated the potentially preventive activity of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) against colorectal cancer and adenoma, with regular use of aspirin and other nonprescription NSAIDs being largely supportive of a reduced risk (6–12). Clinical trials examining aspirin use in relation to colorectal cancer risk show mixed results ranging from a significant reduction in risk of large bowel adenoma recurrence among consistent aspirin users (13, 14) to moderate reduction of adenoma recurrence (15) to no association between aspirin use and colorectal cancer (16, 17).

Both epidemiologic studies and animal-model experiments have also provided evidence that NSAIDs inhibit chemically induced tumors and that regular use of analgesic agents may be associated with reduced risk of cancers of the bladder (8, 18, 19), breast (8, 20, 21), esophagus (8, 22), lung
Diagnosed, histologically confirmed glioma (23–25), ovary (26), prostate (27–30), stomach (22, 24, 31), liver (8), pancreas (32), and tongue (33).

NSAIDs can impair the arachidonic acid cascade, inhibiting the synthesis of prostaglandins by interfering with cyclooxygenase, the rate-limiting enzyme of the cascade. Prostaglandins, the mediators of inflammation, have a potential role in carcinogenesis through direct mutagenesis, tumor cell proliferation, tissue invasiveness, metastasis, immune suppression, and hormone responsiveness (23, 34–36). In addition, angiogenesis or new blood vessel formation contributes to tumor growth and the spread of solid tumors and is accompanied by, if not dependent on, prostaglandin- and cyclooxygenase-2-driven inflammation (37–41). Aspirin irreversibly blocks prostaglandin hydroxy endoperoxide (prostaglandin H₂) formation (42–44), while ibuprofen and other NSAIDs compete for the active site of the enzyme with the substrate, arachidonic acid (44, 45). NSAIDs inhibit angiogenesis through direct effects on endothelial cells, a process that has both prostaglandin-dependent and -independent components (46). Other evidence suggests that NSAIDs may inhibit cancer independently of their effects on prostaglandin synthesis. For example, aspirin can interrupt intracellular signaling pathways via inhibition of phospholipase activity (47, 48), and aspirin inhibits the growth of rat glioma cells in vitro and in vivo (49). Thus, anticarcinogenic effects of NSAIDs may result from their inhibition of cell proliferation, tumor growth, promotion, and metastasis; blockage of prostaglandin-induced immunosuppression; or interference with prostaglandin-induced angiogenesis (26, 27, 31, 34, 35, 50–52).

To our knowledge, no previous epidemiologic study has specifically examined associations between NSAID use and specific subtypes of brain tumors. The need for research in this area is essential, given that astrocytic brain tumors and colorectal cancer arise from common cellular origins—neuroepithelial cells and epithelial cells, respectively—and perhaps share common preventive mechanisms as well. In addition, a small percentage of primary brain tumors are associated with hereditary disorders (1), including Turcot’s syndrome, which is clinically characterized by the concurrence of a primary brain tumor, either medulloblastoma or glioblastoma, and multiple colorectal adenomas (53, 54). In the present study, we examined the association between use of aspirin and other NSAIDs and risk of glioblastoma multiforme. In this paper, we emphasize results for glioblastoma multiforme, since these tumors are more homogenous than glioma as a whole and therefore may be more likely to share a common etiology (1, 3).

**MATERIALS AND METHODS**

**Case ascertainment**

Men and women newly diagnosed with glioblastoma multiforme (*International Classification of Diseases for Oncology, Second Edition* (55), morphology codes 9380–9481) residing in any of six San Francisco Bay Area counties (Alameda, Contra Costa, Marin, San Mateo, San Francisco, and Santa Clara) between May 1997 and August 2000 were eligible for the study. The Northern California Cancer Center’s rapid case ascertainment system searched hospital pathology, radiotherapy, and inpatient and outpatient records in the six Bay Area counties to identify and ascertain cases within 2–8 weeks of diagnosis. If subjects’ physicians did not refuse, subjects were sent a letter describing the study and were then telephoned for arrangement of an in-person interview. Proxies were sought for subjects unable to participate because of disability or death. Additional eligibility criteria included the ability of the case or proxy to be interviewed in English. Subsequent to the interview, pathology specimens were obtained and the diagnosis was reviewed by a single neuropathologist, Dr. Kenneth Aldape (M. D. Anderson Cancer Center, Houston, Texas). This report includes cases he classified as cases of glioblastoma multiforme.

**Ascertainment of controls**

Controls, who were frequency-matched according to age (in 5-year groups), gender, and ethnicity (White, Black, Hispanic, Asian, or other), were obtained through random digit dialing using methods described by Waksberg (57) and refined by Harlow and Davis (58). Frequency-matching of controls was to all glioma cases, not just those with glioblastoma multiforme. The initial sampling units included telephone area code, three-digit prefix, and the next two digits of the telephone numbers of all cancer cases in the study counties from 1996. These select numbers were obtained from the Northern California Cancer Center. Two-digit suffixes were generated from random number tables for each sampling unit, and the resulting telephone numbers were called until the necessary eligible matches were found. Controls’ eligibility criteria included competence in English and residency in the same San Francisco Bay Area counties in which cases were identified. Eligible controls were mailed a letter and were then telephoned for arrangement of an in-person interview.

**Interviews**

In-person structured interviews using questionnaires and show-cards were conducted in English with consenting cases (or their proxies) and controls in their homes or at a location of their choosing. Subjects were sent a packet of materials describing the topics to be covered in the interview so the respondent could obtain any required information before the interview occurred. Subjects were asked about personal and familial medical history, demographic characteristics, occupational history, radiographic exposures, diet, and smoking, among other topics. Subjects were offered a brief telephone interview if they declined the full in-person interview.

As part of the subject’s personal medical history, the interviewer asked for information on all medications taken during the previous 10 years (10 years before diagnosis for cases), including NSAIDs and acetaminophen. Although acetamin-
ophen is not categorized as an NSAID, it is a centrally active analgesic and antipyretic agent used for many of the same reasons for which people take NSAIDs, so it was included in the question as one of the drugs of interest (59). Subjects were shown a list of drugs including generic and brand names of aspirin, acetaminophen, ibuprofen, naproxen, and 11 other prescription NSAIDs. They were then asked whether, during the past 10 years (or 10 years prior to diagnosis for cases), they had taken a total of 600 or more pills of any of these drugs. The figure 600 was chosen in an attempt to classify only persons who regularly used NSAIDs as users (e.g., approximately 60 pills per year or at least one pill per week for 10 years); this definition of a regular NSAID user (as opposed to a sporadic user or a nonuser), which relies on a criterion of at least one pill per week for at least 6 months, has been used in several studies to classify “regular” NSAID use (26, 50–52, 60, 61). If the respondent answered “yes” to this initial question, the interviewer then asked whether, during that time period, he or she had taken any aspirin, ibuprofen, naproxen, other NSAIDs, or acetaminophen. For each category of analgesic for which use was reported, subjects were then asked how many times per day, week, month, or year the drug had been taken during the past 10 years. The questionnaire also asked about year of first use and total number of months or years of use for each category of analgesic for which use was reported. Information on specific dosages for the specific types of medications was not requested.

Data analysis and statistical methods

Unconditional logistic regression models (62) were used to estimate odds ratios and 95 percent confidence intervals comparing all glioma cases and controls and glioblastoma multiforme cases and controls. The reference category comprised persons who reported not consuming at least 600 NSAID pills during the 10-year prediagnostic or preinterview period. For examination of duration of NSAID use (i.e., period of time between initiation of use to cessation of use in any dose), numbers of years of use for the specific types of analgesic agents were categorized into below-median and above-median categories based on the median values in the control distributions. Because information on the different potencies/dosages of the drugs was not requested, we do not report frequencies. Three separate analyses were performed for each category of NSAIDs: all controls versus all cases, all controls versus self-reported cases, and all controls versus proxy-reported cases. Although cases and controls were frequency-matched with regard to age, gender, and ethnicity, odds ratios were adjusted for age (as a continuous variable) to control for residual confounding and because the glioblastoma multiforme case group was older on average than the overall case and control groups. In all of the models, age was also entered as a quadratic function, and the likelihood ratio test was used to determine whether the quadratic term added significantly ($p < 0.05$) to the model. All comparisons were additionally adjusted for gender, education, family income, and ethnicity. To reduce the potential for differential data quality due to proxy reporting, in the results we emphasize associations for self-reported cases. Although all glioma cases were also compared with controls, we highlight analyses restricted to glioblastoma multiforme cases, because glioma is a very heterogeneous collection of diseases and glioblastoma multiforme was the only histologic grouping with sufficient numbers for meaningful separate analysis. Descriptive statistics were generated using SAS (62). All $p$ values were two-tailed.

RESULTS

Case ascertainment and interviews

We obtained full interviews with 403 (79 percent) of 510 eligible glioma patients, of whom 241 (60 percent) were diagnosed with glioblastoma multiforme by the review pathologist. Table 1 summarizes reasons for nonparticipation. On average, self-reported cases were interviewed within 3 months of diagnosis and proxies within 6 months of the case’s diagnosis. Proxy interviews comprised 41 percent (99/241) of completed interviews because of the death or disability of some cases. Of the case-proxy interviews, most were completed with spouses or children (48 percent and 37 percent, respectively) and the remainder were completed with parents, other relatives, or friends. Data on NSAID use were missing for five glioblastoma multiforme cases, who were therefore eliminated from the analyses.

Control ascertainment and interviews

Random digit dialing of 9,282 telephone numbers produced 541 apparently eligible controls (5.8 percent), of whom 74 percent (402/541) consented to a full interview. One control was missing data for NSAID use and was eliminated from subsequent analyses. Details on the specific reasons for exclusion of controls and the distribution of random digit dialing calls are shown in table 1.

Case-control demographic data

Table 2 shows the distribution of demographic characteristics of glioblastoma multiforme cases and controls and compares the cases by reporting status. The median age of cases was 62 years, while the controls were younger, on average, with a median age of 56 years, because of the frequency-matching of controls to all glioma cases and not just those with glioblastoma multiforme. Self-reported cases were 11 years younger, on average, than cases for which a proxy was required, reflecting the poorer survival observed for cases with increasing age at diagnosis (5, 63). In addition, self-reported cases were significantly more likely to have household incomes at or above $70,000 per year than both controls and proxy-reported cases.

NSAID use

Self-reported glioblastoma multiforme cases were less likely than controls to report use of at least 600 pills of all types of NSAIDs combined during the 10-year prediagnostic or preinterview period (table 3; odds ratio (OR) = 0.53, 95 percent confidence interval (CI): 0.3, 0.8). These findings

Am J Epidemiol 2004;159:1131–1139
TABLE 1. Ascertainment of cases and controls and participation and number of subjects with glioblastoma multiforme after neuropathology review, San Francisco Bay Area Adult Glioma Study, 1997–2000

<table>
<thead>
<tr>
<th>Subject ascertainment</th>
<th>No. of subjects</th>
<th>Telephone calls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Full interview</td>
<td>403</td>
<td>402</td>
</tr>
<tr>
<td>Accepted brief telephone interview only</td>
<td>23</td>
<td>68</td>
</tr>
<tr>
<td>Refused to enter study</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Language problem</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Too ill for interview</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Inability to locate subject</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Patient’s physician refused permission or pathology specimen was unavailable</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Distribution of random digit dialing telephone calls

<table>
<thead>
<tr>
<th>Distribution</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in service</td>
<td>1,591</td>
<td>17.1</td>
</tr>
<tr>
<td>Business line</td>
<td>1,218</td>
<td>13.1</td>
</tr>
<tr>
<td>Fax/modem</td>
<td>700</td>
<td>7.5</td>
</tr>
<tr>
<td>No response after 10 calls</td>
<td>1,417</td>
<td>15.3</td>
</tr>
<tr>
<td>Refusal</td>
<td>1,541</td>
<td>16.6</td>
</tr>
<tr>
<td>Language or health problems</td>
<td>559</td>
<td>6.0</td>
</tr>
<tr>
<td>Multiple lines</td>
<td>73</td>
<td>0.8</td>
</tr>
<tr>
<td>Respondent too young</td>
<td>24</td>
<td>0.3</td>
</tr>
<tr>
<td>Quota full</td>
<td>1,513</td>
<td>16.3</td>
</tr>
<tr>
<td>Ineligible</td>
<td>80</td>
<td>0.9</td>
</tr>
<tr>
<td>Out of area</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Good match*</td>
<td>562</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Total†                                               | 510   | 541   | 9,282 |

Confirmed glioblastoma multiforme                     | 241   |       |

* Of 562 good matches obtained from random digit dialing, the study closed before 20 persons could be contacted, and one person proved to be related to a case; thus, there were 541 eligible controls.
† Of the eligible cases and controls, 79% and 74%, respectively, gave a full interview.

TABLE 2. Sociodemographic characteristics of glioblastoma multiforme cases and controls, San Francisco Bay Area Adult Glioma Study, 1997–2000

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 401)</th>
<th>All cases (n = 236)</th>
<th>Self-reported cases (n = 137)</th>
<th>Proxy-reported cases (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>53.9</td>
<td>58.1</td>
<td>62.0</td>
<td>52.5</td>
</tr>
<tr>
<td>Race (% White)*</td>
<td>83.3</td>
<td>85.2</td>
<td>84.7</td>
<td>85.9</td>
</tr>
<tr>
<td>Income group (% earning &lt;$70,000/year)†</td>
<td>61.1</td>
<td>61.5</td>
<td>51.2</td>
<td>76.4</td>
</tr>
<tr>
<td>Education (% with &lt;16 years)‡</td>
<td>51.0</td>
<td>56.8</td>
<td>50.4</td>
<td>65.9</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>56.0</td>
<td>62.0</td>
<td>57.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Interquartile range for age</td>
<td>43–67</td>
<td>51–71.5</td>
<td>47–66</td>
<td>56–76</td>
</tr>
</tbody>
</table>

* Categories other than White included African Americans, Chinese, Japanese, other Asians, Filipinos, Mexicans, other Latinos, and others.
† There were eight missing values for controls, eight missing values for self-reported cases, and 10 missing values for proxy-reported cases.
‡ There was one missing value for controls and two missing values for proxy-reported cases.
were consistent for each type of NSAID, aspirin, ibuprofen, naproxen and/or other NSAIDs, and acetaminophen (which, as we noted above, does not have strong antiinflammatory properties). No differences were found for use of any type of NSAID or acetaminophen among proxy-reported glioblastoma multiforme cases and controls (table 3). Adjustment for other potentially confounding variables, including gender, ethnicity, income, and education, did not meaningfully alter any result; therefore, only age-adjusted odds ratios are presented.

Self-reporting men and women with glioblastoma multiforme were less likely than controls to report NSAID use, and findings were similar for each type of NSAID, as well as acetaminophen, among males and females (table 4).

Cases may have initiated NSAID use in response to headaches or other symptoms of the disease. Consequently, we repeated the analyses excluding cases who had initiated use within 2 years of diagnosis and found results similar to those noted above (see table 3). That is, fewer subjects with glioblastoma multiforme than controls reported use of 600 or more pills of only aspirin-containing NSAIDs (age-adjusted OR = 0.88, 95 percent CI: 0.4, 1.7), though the results were not significant, and less likely to report use of 600 or more pills of only ibuprofen-containing compounds (age-adjusted OR = 0.27, 95 percent CI: 0.0, 2.1), but results were unstable because of small sample sizes. There were too few users of only naproxen/other NSAIDs for analysis.

Similar results were obtained for comparisons of all glioma cases with controls, with the odds ratios being only somewhat closer to the null. In particular, fewer self-reported glioma cases than controls indicated use of at least 600 pills of all types of NSAIDs combined (OR = 0.76, 95 percent CI: 0.5, 1.1), aspirin (OR = 0.70, 95 percent CI: 0.5, 1.0), ibuprofen (OR = 0.70, 95 percent CI: 0.5, 1.1), naproxen/other NSAIDs (OR = 0.50, 95 percent CI: 0.3, 0.96), and acetaminophen (OR = 0.92, 95 percent CI: 0.6, 1.5). No association was found between any type of NSAID or acetaminophen and glioma among proxy-reported glioma cases and controls (results not shown).

### Table 3. Age-adjusted* odds ratios for use of nonsteroidal antiinflammatory agents among glioblastoma multiforme cases and controls, San Francisco Bay Area Adult Glioma Study, 1997–2000

<table>
<thead>
<tr>
<th>NSAID† variable</th>
<th>No. of controls (n = 401)</th>
<th>All cases (n = 236)</th>
<th>Self-reported cases (n = 137)</th>
<th>Proxy-reported cases (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>OR†‡, 95% CI†‡</td>
<td>No.</td>
</tr>
<tr>
<td>Use of ≥600 NSAID pills in the past 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>138</td>
<td>75</td>
<td>0.76, 0.5, 1.1</td>
<td>32</td>
</tr>
<tr>
<td>No</td>
<td>263</td>
<td>161</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Aspirin and/or other NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>112</td>
<td>58</td>
<td>0.70, 0.5, 1.0</td>
<td>25</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Ibuprofen and/or other NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>80</td>
<td>36</td>
<td>0.70, 0.4, 1.1</td>
<td>14</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Naproxen and/or other NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>40</td>
<td>17</td>
<td>0.59, 0.3, 1.1</td>
<td>6</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Acetaminophen and other NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>51</td>
<td>31</td>
<td>0.92, 0.6, 1.5</td>
<td>11</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>105</td>
<td>56</td>
</tr>
</tbody>
</table>

* Adjustment for gender, ethnicity, income, and education did not meaningfully alter the results; therefore, only age-adjusted odds ratios are presented.
† NSAID(s), nonsteroidal antiinflammatory drug(s); OR, odds ratio; CI, confidence interval.
‡ Additionally adjusted for age².
To our knowledge, this is the first study to have compared NSAID use among glioblastoma multiforme cases and controls. The principal findings were that cases with self-reported glioblastoma multiforme were less likely than controls to report use of 600 or more NSAID pills within the 10 years prior to diagnosis, with the associations being similar among men and women across the various categories of NSAIDs. If future studies corroborate this finding, NSAIDs might be considered candidates for prevention of this rapidly fatal tumor. This observed inverse association also extends existing hypotheses regarding the protective role of aspirin and other NSAIDs in the reduction of certain cancers to include brain cancer.

Results from two previous cohort studies evaluating brain cancer in relation to aspirin use were similar to results for our proxy-reported group, which consisted more of older patients and/or patients with rapidly progressing glioblastoma multiforme (8, 66). Thun et al. (8) found an increased risk of death from brain and nervous system cancers for men (but not women) with use of aspirin on occasion (OR = 1.35, 95 percent CI: 1.03, 1.77), 1–15 times per month (OR = 1.42, 95 percent CI: 1.08, 1.87), and 16 or more times per month (OR = 1.40, 95 percent CI: 1.03, 1.92) relative to no use, though there was no dose-response trend. Limitations of Thun et al.’s cohort study included the facts that data on the actual dose and number of aspirin were missing for a large portion of their study population, all types of brain and nervous system cancers (benign and malignant) were grouped into one heterogeneous group, mortality rather than incidence was considered, death certificates rather than pathology reports were used for case identification, and no analysis was presented to account for the possible increased use of aspirin in response to brain tumor symptoms such as headache (8). Friis et al. (66) also found an increased standardized incidence ratio for brain cancer among low-dose aspirin users; however, this increased risk was due to an excess of brain cancers in the first year of follow-up (standardized incidence ratio = 4.7, 95 percent CI: 3.4, 6.3) among persons receiving either one low-dose aspirin prescription (standardized incidence ratio = 6.2, 95 percent CI: 4.1, 9.1) or 2–4 prescriptions (standardized incidence ratio = 3.5, 95 percent CI: 2.0, 5.7). The standardized incidence ratio for brain cancer was 1.0 (95 percent CI: 0.6, 1.5) for the follow-up period of 1–4 years and was further decreased to 0.5 (95 percent CI: 0.2, 1.2) for the follow-up period of 5 or more years. The latter value is similar in magnitude to the odds ratio we observed in this study. It is likely that the increased risk of brain cancer in the first year of follow-up could be an artifact and due to use of low-dose aspirin as treatment for symptoms of the brain cancer itself, such as headache or other symptoms suggestive of thrombotic cerebral diseases.

There are several potential limitations to consider when interpreting the results of the present case-control study. Although proxy-reported glioblastoma multiforme cases and controls had similar histories of NSAID use, data quality for proxy-reported cases may have differed from that of cases and controls interviewed directly. As a consequence of high

**DISCUSSION**

Results from two previous cohort studies evaluating brain cancer in relation to aspirin use were similar to results for our proxy-reported group, which consisted more of older patients and/or patients with rapidly progressing glioblastoma multiforme (8, 66). Thun et al. (8) found an increased risk of death from brain and nervous system cancers for men (but not women) with use of aspirin on occasion (OR = 1.35, 95 percent CI: 1.03, 1.77), 1–15 times per month (OR = 1.42, 95 percent CI: 1.08, 1.87), and 16 or more times per month (OR = 1.40, 95 percent CI: 1.03, 1.92) relative to no use, though there was no dose-response trend. Limitations of Thun et al.’s cohort study included the facts that data on the actual dose and number of aspirin were missing for a large portion of their study population, all types of brain and nervous system cancers (benign and malignant) were grouped into one heterogeneous group, mortality rather than incidence was considered, death certificates rather than pathology reports were used for case identification, and no analysis was presented to account for the possible increased use of aspirin in response to brain tumor symptoms such as headache (8). Friis et al. (66) also found an increased standardized incidence ratio for brain cancer among low-dose aspirin users; however, this increased risk was due to an excess of brain cancers in the first year of follow-up (standardized incidence ratio = 4.7, 95 percent CI: 3.4, 6.3) among persons receiving either one low-dose aspirin prescription (standardized incidence ratio = 6.2, 95 percent CI: 4.1, 9.1) or 2–4 prescriptions (standardized incidence ratio = 3.5, 95 percent CI: 2.0, 5.7). The standardized incidence ratio for brain cancer was 1.0 (95 percent CI: 0.6, 1.5) for the follow-up period of 1–4 years and was further decreased to 0.5 (95 percent CI: 0.2, 1.2) for the follow-up period of 5 or more years. The latter value is similar in magnitude to the odds ratio we observed in this study. It is likely that the increased risk of brain cancer in the first year of follow-up could be an artifact and due to use of low-dose aspirin as treatment for symptoms of the brain cancer itself, such as headache or other symptoms suggestive of thrombotic cerebral diseases.

There are several potential limitations to consider when interpreting the results of the present case-control study. Although proxy-reported glioblastoma multiforme cases and controls had similar histories of NSAID use, data quality for proxy-reported cases may have differed from that of cases and controls interviewed directly. As a consequence of high

**TABLE 4. Age-adjusted* odds ratios for use of nonsteroidal antiinflammatory agents among self-reported glioblastoma multiforme cases and controls, by gender, San Francisco Bay Area Adult Glioma Study, 1997–2000**

<table>
<thead>
<tr>
<th>NSAID† variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of controls (n = 216)</td>
<td>No. of cases (n = 85)</td>
</tr>
<tr>
<td>Use of ≥600 NSAID pills in the past 10 years</td>
<td>79  23  0.62  0.3, 1.1</td>
<td>59  9  0.42  0.2, 0.9</td>
</tr>
<tr>
<td>Yes</td>
<td>137  62</td>
<td>126  43</td>
</tr>
<tr>
<td>No</td>
<td>72  21  0.63  0.3, 1.1</td>
<td>40  4  0.25  0.1, 0.7</td>
</tr>
<tr>
<td>Aspirin and/or other NSAIDs</td>
<td>137  62</td>
<td>126  43</td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>42  9  0.46  0.2, 1.0</td>
<td>38  5  0.40  0.1, 1.1</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>137  62</td>
<td>126  43</td>
</tr>
<tr>
<td>Ibuprofen and/or other NSAIDs</td>
<td>21  3  0.27  0.1, 1.0</td>
<td>19  3  0.44  0.1, 1.6</td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>137  62</td>
<td>126  43</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>26  8  0.64  0.3, 1.5</td>
<td>25  3  0.33  0.1, 1.2</td>
</tr>
<tr>
<td>Naproxen and/or other NSAIDs</td>
<td>137  62</td>
<td>126  43</td>
</tr>
<tr>
<td>Used ≥600 pills</td>
<td>26  8  0.64  0.3, 1.5</td>
<td>25  3  0.33  0.1, 1.2</td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>137  62</td>
<td>126  43</td>
</tr>
</tbody>
</table>

* Adjustment for gender, ethnicity, income, and education did not meaningfully alter the results; therefore, only age-adjusted odds ratios are presented. Odds ratios were also adjusted for age².

† NSAID(s), nonsteroidal antiinflammatory drug(s); OR, odds ratio; CI, confidence interval.
TABLE 5. Age-adjusted* odds ratios for duration of use of nonsteroidal antiinflammatory agents among glioblastoma multiforme cases and controls, San Francisco Bay Area Adult Glioma Study, 1997–2000

<table>
<thead>
<tr>
<th>NSAID† variable</th>
<th>No. of controls</th>
<th>All cases</th>
<th>Self-reported cases</th>
<th>Proxy-reported cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>OR†,‡</td>
<td>95% CI†</td>
<td>No.</td>
</tr>
<tr>
<td>Use of ≥600 aspirin and/or other NSAID pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>1.00</td>
<td>105</td>
</tr>
<tr>
<td>Below median duration¶</td>
<td>49</td>
<td>28</td>
<td>0.71</td>
<td>0.4, 1.2</td>
</tr>
<tr>
<td>Above median duration¶</td>
<td>63</td>
<td>29</td>
<td>0.66</td>
<td>0.4, 1.1</td>
</tr>
<tr>
<td>Use of ≥600 ibuprofen and/or other NSAID pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>1.00</td>
<td>105</td>
</tr>
<tr>
<td>Below median duration¶</td>
<td>36</td>
<td>8</td>
<td>0.32</td>
<td>0.1, 0.7</td>
</tr>
<tr>
<td>Above median duration¶</td>
<td>44</td>
<td>28</td>
<td>1.04</td>
<td>0.6, 1.8</td>
</tr>
<tr>
<td>Use of ≥600 naproxen and/or other types of NSAID pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>1.00</td>
<td>105</td>
</tr>
<tr>
<td>Below median duration¶</td>
<td>17</td>
<td>9</td>
<td>0.75</td>
<td>0.3, 1.7</td>
</tr>
<tr>
<td>Above median duration¶</td>
<td>22</td>
<td>8</td>
<td>0.50</td>
<td>0.2, 1.2</td>
</tr>
<tr>
<td>Use of ≥600 acetaminophen and other NSAID pills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;600 pills</td>
<td>263</td>
<td>161</td>
<td>1.00</td>
<td>105</td>
</tr>
<tr>
<td>Below median duration¶</td>
<td>22</td>
<td>11</td>
<td>0.72</td>
<td>0.3, 1.5</td>
</tr>
<tr>
<td>Above median duration¶</td>
<td>29</td>
<td>20</td>
<td>1.08</td>
<td>0.6, 2.0</td>
</tr>
</tbody>
</table>

* Adjustment for gender, ethnicity, income, and education did not meaningfully alter the results; therefore, only age-adjusted odds ratios are presented.
† NSAID(s), nonsteroidal antiinflammatory drug(s); OR, odds ratio; CI, confidence interval.
‡ Additionally adjusted for age.
§ Linear trend: p = 0.0093.
¶ The cutpoint for duration (below median vs. above median) was based on the median number of years the specific NSAID was used among controls. Numbers of controls above and below the median differ depending on the number of controls falling at the median value. The median number of years of use was 10 for aspirin, 5 for ibuprofen, 3 for naproxen/other NSAIDS, and 10 for acetaminophen.

rates of fatality from glioblastoma multiforme, this study had a large percentage of proxy respondents. We did not obtain proxy data for controls, because such data would not necessarily be comparable to proxy data from cases, since the diagnosis of a debilitating illness could influence a case informant/proxy to recall information differently than a control informant/proxy (67). In addition, proxies may not possess adequate knowledge of NSAID consumption by cases, which could produce biased odds ratios. For these reasons, we believe that results from self-reports are more likely to be valid, and we have placed more emphasis on those associations.

Reporting bias is also a potential problem among the self-reported cases and controls. Differential misclassification would result if the cancer diagnosis served as a stimulus for cases to recall any exposures more or less thoroughly than controls. For example, cases reported exposure information after learning of their diagnoses, which could have led to information errors that biased the results. However, the questionnaire collected data on a variety of exposures, placing no particular emphasis on any specific items, and there were no suggestions in the literature or media that NSAIDs were likely to be an important factor in the risk of brain tumors. There is little reason to believe that cases were more likely than controls to recall analgesic use, but if this were so, the result would be odds ratios greater than 1, rather than the inverse associations shown in this study. It is also possible that cases might underreport NSAID use because of deficits in recall secondary to their brain tumors. In an attempt to evaluate this bias, we examined information on utilization of some other commonly used medications, such as antihistamines, sleeping aids, and tranquilizers, among others.

Patients with self-reported cases indicated similar or increased use of some medications in comparison with controls, including antihistamines (OR = 1.1, 95 percent CI: 0.65, 2.0) and sleeping aids (OR = 5.1, 95 percent CI: 1.3, 20.5); this argues against consistent underreporting of commonly used medications in the self-reported case group.

Another potential source of exposure misclassification relates to our asking and classifying as users those who took a total of 600 or more pills of any NSAID or acetaminophen. Thus, subjects classified as nonusers might have included persons who may have consumed up to 599 pills over the referent period, making them more similar to persons classified as users who consumed 600–700 pills than to never users. If this hypothesized source of misclassification was present in a large proportion of the sample, the odds ratio characterizing the association between NSAIDs and glioblastoma multiforme would be biased towards the null. In addition, respondents may have failed to include cold or allergy preparations containing NSAIDs, since there are hundreds of such products on the market which respondents may have used without realizing their NSAID content. Nevertheless, this potential source of misclassification
would also be nondifferential with respect to case status and would therefore also bias the odds ratios towards the null.

A primary difficulty in studying the relation between NSAID use and glioblastoma multiforme is obtaining an accurate measure of use before tumor induction. This problem is important in both case-control and cohort studies, because the disease process may change NSAID consumption and because the latency time between tumor induction and clinical symptoms of glioblastoma multiforme is not known. In this study, after exclusion of cases whose NSAID use was initiated in the 2 years before diagnosis, the associations between NSAID use and glioblastoma multiforme remained, suggesting that results were probably not affected by subclinical disease.

Another potential problem with this study is that we were unable to determine whether the association was specific to particular NSAIDs, because people who take one type of antiinflammatory or analgesic agent also tend to take other types. The result would be that the protective effects observed among self-reported cases for the various types of NSAIDs could all have been driven by use of one type. However, results from separate analyses of self-reported users of only aspirin-containing compounds and only ibuprofen-containing compounds still tended to show protective effects against glioblastoma multiforme. This lends support to the idea that use of antiinflammatory compounds, in general, is inversely associated with glioblastoma multiforme.

One last limitation of the present study is that although it was based on a relatively large group of incident glioblastoma multiforme cases, the numbers of persons in specific exposure categories were small when subjects were stratified by reporting status (self vs. proxy) and type of analgesic. In spite of small numbers, we found statistically significant reductions among self-reported cases in the risk of glioblastoma multiforme for users of aspirin, ibuprofen, and naproxen/other NSAIDs.

Given the potential limitations noted above, more epidemiologic research is needed to confirm findings and to further investigate issues of dose response, specificity, and timing of exposure. The possibility that NSAID use may be a marker for diseases or physiologic states (e.g., arthritis) inversely associated with glioblastoma multiforme also requires investigation. In addition, laboratory-based research efforts are indicated for elucidation of the possible roles of cyclooxygenase-2 expression and eicosanoid biosynthesis in glioblastoma multiforme carcinogenesis. If our results are confirmed in subsequent studies, NSAIDs might be evaluated as possible agents for inhibiting the development or progression of this fatal tumor.

ACKNOWLEDGMENTS

This work was supported by grant RO1-52689 from the US National Cancer Institute and in part by grant 2001-2906 from the Swedish Council for Working Life and Social Research.

REFERENCES


