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Analgesic Use and the Risk of Primary Adult Brain Tumor

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Abstract

Glioma and meningioma are uncommon tumors of the brain with few known risk factors. Regular use of aspirin has been linked to a lower risk of gastrointestinal and other cancers, though evidence for an association with brain tumors is mixed. We examined the association of aspirin and other analgesics with the risk of glioma and meningioma in a large US case-control study. Cases were persons recently diagnosed with glioma or meningioma and treated at medical centers in the southeastern US. Controls were persons sampled from the same communities as the cases combined with friends and other associates of the cases. Information on past use of analgesics (aspirin, other anti-inflammatory agents, and acetaminophen) was collected in structured interviews. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for analgesic use adjusted for potential confounders. All associations were considered according to indication for use. A total of 1123 glioma cases, 310 meningioma cases and 1296 controls were included in the analysis. For indications other than headache, glioma cases were less likely than controls to report regular use of aspirin (OR: 0.69; CI: 0.56, 0.87), in a dose-dependent manner (p trend < 0.001). No significant associations were observed with other

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analgesics for glioma, or any class of pain reliever for meningioma. Results suggest that regular aspirin use may reduce incidence of glioma.

Keywords

glioma; glioblastoma; risk; prevention; aspirin; nonsteroidal anti-inflammatory agents; case-control study; epidemiology

Introduction

Brain tumors are relatively uncommon with an estimated 23,130 adults diagnosed with malignant brain or nervous system cancers in 2013 and an estimated 14,080 brain tumor related deaths [1], in addition to the far larger number of primary benign brain tumors (meningiomas) diagnosed annually in the US [2]. Glioma remains one of the most aggressive human tumors with a median survival of only 12–15 months among persons with high grade tumors [3]. Glioma is more common in Caucasians and among males [4] and geographical variation has been reported within the US [5]. Meningiomas are more common in persons of African descent and with an excess risk among females [2]. Genetic susceptibility has also been documented in glioma [6, 7] and meningioma [8]. With the exception of ionizing irradiation [9], environmental and lifestyle risk factors for brain tumors remain largely unknown. Whether aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) reduce incidence of these tumors as observed in gastrointestinal and some other cancers [10] has not been determined.

Experimental and *in vivo* evidence are consistent with a possible preventive role for aspirin/NSAIDs in glioma. Aspirin/NSAIDs have been proposed to reduce cancer through inhibition of COX-2, the key enzyme for the synthesis of prostaglandin E2 (PGE2) that has been implicated in tumorigenesis [11, 12]. COX-2 is constitutively expressed in the brain and overexpression is observed in the majority of high-grade gliomas [13–17], and is associated with a clinically more aggressive phenotype [13, 14, 16–18]. Furthermore, PGE2 levels are significantly higher in glioma samples compared to control brain samples [19] while surgical removal of malignant brain tumors has been shown to decrease PGE2 levels [20]. Mechanistically, PGE2 contributes to the immune suppressive state in the CNS [21], and may promote tumor angiogenesis [22]. NSAIDs may also suppress glioma growth through COX-2–independent mechanisms [23–26].

A secondary analysis of cardiovascular trials has provided evidence in support of a possible chemopreventive role for daily aspirin use in glioma [27]. In a meta-analysis of 3 trials comprising 10,500 subjects with long-term follow up, Rothwell et al. [27] found a significantly reduced mortality from brain tumors (primarily glioma) during the first 10-years of post-trial follow up. No benefit was observed beyond 10 years though the mean time from randomization to death remained significantly longer in the aspirin group 20 years post randomization. In contrast, a regimen of alternate day, low-dose aspirin (100 mg) for 10 years did not reduce incidence of invasive brain tumors (glioma and meningioma) in the Women's Health Study trial [28].

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Epidemiologic studies evaluating the influence of aspirin/NSAIDs on glioma risk have yielded conflicting results. A reduced risk with regular aspirin/NSAID use has been demonstrated in several case-control studies [29–32] whereas cohort studies [33–35] and studies based on record linkages to prescription databases [36, 37] have suggested no benefit. All previous studies lacked information on indication for analgesic use; thus, findings were subject to reverse causation bias e.g. use of analgesics to alleviate brain tumor symptoms in the cases, a phenomena that may account for the *positive* associations observed with current NSAID use in a number of studies [33, 35, 38].

To our knowledge, only one study has examined the possible relation of aspirin/NSAIDs in the development of meningioma, a generally slow growing tumor arising from meningothelial cells in the arachnoid villi. In a case-control study based on the UK Clinical Practice Research Datalink [37], a statistically significant positive association with meningioma was observed with the prescription of nonaspirin NSAIDs only, whereas no association was observed for aspirin.

Given lack of preventive measures for primary brain tumors, the potential for chemoprevention with aspirin use warrants further examination. To shed further light on the association of aspirin and other analgesics on the risk of brain tumors including glioma and meningioma, we examined data from a large case-control study conducted at centers in the southeastern US. Data were collected on ever regular use, duration and indication for use of prescription and over-the-counter analgesics including aspirin, other NSAID analgesics, COX-2 inhibitors and acetaminophen.

Subjects and Methods

Study Population

Subjects in the analysis were enrolled in a clinic-based case-control study examining risk factors for glioma and meningioma. All individuals in the present analysis were aged 18 or older and had a recent (within 3 months) diagnosis of primary (e.g. nonrecurrent) glioma, including astrocytoma (ICD-0 codes 9400, 9401, 9410, 9411, 9420, 9421, 9424, 9425, 9440, 9441), oligodendroglioma (ICD-0 codes 9450, 9451) and oligoastrocytoma (ICD-0 code 9382) or meningioma (ICD-0 codes 9530-9534, 9537-9539). Brain tumor cases were identified in neurosurgery and neuro-oncology clinics in the Southeastern US including Vanderbilt University Medical Center (Nashville, TN); Moffitt Cancer Center (Tampa, FL); University of Alabama at Birmingham (Birmingham, AL); Emory University (Atlanta, GA); and the Kentuckiana Cancer Institute (Louisville, KY). Cases were enrolled between December 2004 and June 2012. Eighty-seven percent of eligible brain tumor patients were enrolled in the study and completed the study interview, a median of 1.5 months following diagnosis of the brain tumor (interquartile range: 3 weeks – 2.8 months). Controls were comprised of persons identified from telephone white page listings (n=1128) supplemented with friends and other associates of the cases (n=168) as previously described [39]. In the case of community controls, for each brain tumor case, a commercial survey firm provided a list of ~20 residential phone numbers of persons residing in the same general neighborhood as the case based on census track and with a presumed household member of the same age, race, and gender as the index case. A screening interview was used to confirm presence of an

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eligible person in the household and to elicit participation. An estimated 50% of contacted eligible households yielded a participating control. Investigational Review Boards from each participating institution approved the study and written informed consent was obtained from all participants.

Data Collection

Information on demographics and on known and suspected brain tumor risk factors were collected in structured interviews. For analgesics use, subjects were asked to report past use of acetaminophen, aspirin, COX-2 inhibitors and other nonaspirin NSAID pain medications in a series of questions, beginning with the question "Have you ever taken [analgesic] on a regular basis? By regular, I mean at least twice a week for 12 consecutive months". Embedded in each question, examples were given of common over-the-counter and prescribed medications including Anacin, Bayer, Bufferin, or Excedrin for aspirin, Vioxx, Celebrex, Bextra and Arcoxia for COX-2 inhibitors, Advil, Motrin, Aleve or Ibuprofen, for nonaspirin NSAIDs and Tylenol, for acetaminophen. Those answering the screening question affirmatively were asked to report age at first regular use, total years of regular use, and indication(s) for regular use. For indication of use, subjects were provided a list of response options including 'arthritis', 'back pain', "to prevent heart attack", 'headache', or 'another reason' with a write-in option. (Dental pain, menstrual symptoms, injury-related pain, and 'as a sleep aid' were the most frequently cited reasons).

Statistical Analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) relating medication use with risk of glioma and meningioma. Multivariate models included terms for age at interview (5-year categories), state of residence, race (Caucasian/non-Caucasian), gender, and education (high school or less, some college, college graduate, graduate education). We evaluated risk associated with regular use of each class of medication (i.e. acetaminophen, aspirin, nonaspirin NSAIDs, and COX-2 inhibitors) against a referent group of no regular use of any analgesic. To consider potential confounding by indication, we examined risk according to reported indication for analgesic use including headache, body pain, cardioprevention, and a combined category of other reported indications. To evaluate dose response, an ordinal term for duration of analgesic use was included in multivariate models. Statistical analysis was performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). A P-value <0.05 was considered statistically significant and all statistical tests were two-sided.

Results

Characteristics of the study population are shown in Table 1. A total of 1123 glioma cases, 310 meningioma cases and 1296 controls were included in the analysis. The median age at enrollment was 53 years (range: 18–92) for glioma cases, 56 years (range: 19–90) for meningioma cases, and 57 years (range: 18–90) for controls. Consistent with population incidence rates [3], glioma cases were comprised of an excess of males (58%) and meningioma cases of females (74%). A majority of subjects were Caucasian in meningioma (91%) and glioma cases (94%), and in controls (96%). Somewhat fewer brain cases than

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controls graduated college or attained a graduate degree. A total of fifteen case interviews (1.3%) were conducted with a proxy respondent.

Results according to regular use of each analgesic are shown in Table 2. Glioma risk was unrelated to the use of acetaminophen (OR: 1.20; 95% CI: 0.93, 1.54) and nonaspirin NSAIDs (OR: 0.95; 95% CI: 0.75, 1.19), with borderline inverse associations for aspirin (OR: 0.83; 95% CI: 0.67, 1.02) and COX-2 inhibitors (OR: 0.72; 95% CI: 0.53, 1.00). In contrast, meningioma cases were significantly more likely than controls to report regular use of acetaminophen (OR: 1.85; 95% CI: 1.29, 2.65) and aspirin (OR: 1.41; 95% CI: 1.02, 1.95), with a suggestive positive association also observed for nonaspirin NSAIDs (OR: 1.31; 95% CI: 0.93, 1.85), whereas no association was demonstrated for COX-2-inhibitors (OR: 0.95; 95% CI: 0.60, 1.50).

Associations with acetaminophen, aspirin and nonaspirin NSAIDs according to reported indication for use are shown in Table 3. Persons with glioma were more likely than controls to report analgesic use for headache with a significant positive association observed for acetaminophen (OR: 1.49; 95% CI: 1.09, 2.04) and aspirin (OR: 1.89; 95% CI: 1.24, 2.88), and a nonsignificant positive association observed for nonaspirin NSAIDs (OR: 1.38; 95% CI: 0.98, 1.95). Similarly, each class of analgesic was more often reported by meningioma cases than controls for the alleviation of headache (OR: 2.35, 2.86, and 1.98, for acetaminophen, aspirin, and nonaspirin NSAIDs, respectively). Results according to other indications (body pain, cardioprevention and miscellaneous reasons) varied by brain tumor type and class of analgesic. When considering glioma, an inverse association was observed with aspirin use for all indications combined excluding headache (OR: 0.69; 95% CI: 0.56, 0.87), and for body pain (OR: 0.41; 95% CI: 0.20, 0.85), cardioprevention (OR: 0.72; 95% CI: 0.57, 0.91), and miscellaneous other indications (OR: 0.71; 95% CI: 0.47, 1.07), individually, though, the latter result was nonsignificant. Nonaspirin NSAIDs taken for all indications other than headache was also associated with a reduced risk of glioma (OR: 0.75; 95% CI: 0.57, 0.99), with a significant inverse association observed for body pain (OR: 0.73; 95% CI: 0.54, 0.98) though not other indications combined (OR: 0.84; 95% CI: 0.60, 1.19). Acetaminophen use was unrelated to glioma risk when taken for any reason other than headache (OR: 0.86; 95% CI: 0.60, 1.24), with null results observed for body pain (OR: 0.94; 95% CI: 0.64, 1.39) and other indications (OR: 0.71; 95% CI: 0.45, 1.13). All results were similar in glioblastoma and lower grade tumors combined (not shown). For COX-2 inhibitors (not shown), a nonsignificant inverse association was observed for all indications other than headache (OR: 0.71; 95% CI: 0.50, 1.02) ((56 glioma cases (5.0%) and 96 controls (7.4%)). For meningioma, no class of analgesic was associated with risk regardless of whether the medication was taken for body pain, cardioprevention (aspirin only) or other indications excluding headache.

We considered associations for glioma according to mutually exclusive categories of analgesic use after excluding subjects reporting analgesic use for headache (202 glioma cases (18%), 83 meningioma cases (27%) and 172 controls (13%)) (not shown). Regular aspirin use was consistently reported more often by controls than glioma cases whether taken alone (OR: 0.73; 95% CI: 0.56, 0.95), or in combination with another analgesic (OR: 0.50; 95% CI: 0.35, 0.72). Nonaspirin NSAIDs were not significantly related to glioma risk

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when taken as a single agent (OR: 0.86; 95% CI: 0.57, 1.29) or when taken with another analgesic, excluding aspirin, including COX2 inhibitor (OR: 0.98; 95% CI: 0.43, 2.24) or acetaminophen (OR: 1.88; 95% CI: 0.68, 5.21), though data in individual exposure categories were sparse. Exclusive use of COX-2 inhibitors had a nonsignificant inverse association with risk (OR: 0.60; 95% CI: 0.31, 1.14) though results were based on few exposed subjects (15 cases and 30 controls). A nonsignificant positive association was observed with acetaminophen when used alone (OR: 1.51; 95% CI: 0.79, 2.87) or with another analgesic excluding aspirin (OR: 1.82; 95% CI: 0.84, 3.98).

We further evaluated associations for glioma according to duration of aspirin use for indications other than headache, overall, and separately for glioblastoma and lower grade tumors (Table 4). A longer duration of aspirin use was associated with a reduced risk of glioma in a dose-dependent manner ($P < 0.001$). Persons reporting 10 or more years of use had an approximately 50% reduction in risk when compared to persons reporting no use of any analgesic (OR: 0.45; 95% CI: 0.32, 0.63). Similar results were observed for high grade glioblastomas (ICD-0 codes 9440–9441; n=682, 61%) (OR: 0.45; 95% CI: 0.31, 0.65) and for all lower grade gliomas combined (n=441, 39%) (OR: 0.38; 95% CI: 0.20, 0.74).

We investigated evidence of latency for effects of aspirin use on glioma risk based on reported age at commencement of regular aspirin use. When compared to no analgesic use, a nonsignificant positive association for aspirin use *related to headache* was observed for use beginning less than 5 years (OR: 2.25; 95% CI: 0.66, 7.70) and 5 to 10 years (OR: 1.89; 95% CI: 0.57, 6.21) prior to interview, with an attenuated though still positive association noted for use beginning greater than 10 years (OR: 1.38; 95% CI: 0.81, 2.35) prior to the interview. When considering aspirin use for all *other indications*, a statistically significant inverse association was observed for commencement of use more than 10 years (OR: 0.52; 95% CI: 0.38, 0.72) and 5 to 10 years (OR: 0.64; 95% CI: 0.44, 0.92), but not less than 5 years (OR: 0.84; 95% CI: 0.60, 1.17) prior to interview.

Discussion

In this large case-control study, we observed evidence of confounding by indication for associations with analgesic use. For both brain tumors (glioma and meningioma), strong positive associations were observed in association with all classes of analgesics when taken for headache. In contrast, in glioma only, inverse associations were noted for aspirin taken for all other indications excluding headache. As headache is a major presenting symptom in brain tumor patients, noted positive associations with analgesic use for headache are likely to reflect reverse causation or ‘protopathic bias’ [40]. Regular aspirin use for indications other than head ache was associated with an approximately 30% reduction in glioma risk. Furthermore, longer-term use of aspirin conferred greater protection. The association was consistent regardless of glioma subtype (glioblastoma and lower grade tumors) and was observed across major indications excluding headache. No similar inverse association was identified for meningioma though statistical power for these analyses was more limited. We also observed an inverse association with COX-2 inhibitors for glioma, whereas other analgesics, including nonaspirin NSAIDs and acetaminophen, taken for reasons other than headache, had no appreciable association with the risk of either brain tumor. All classes of

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pain relievers (excluding COX-2 inhibitors) used for alleviation of headache were reported more often in glioma and meningioma cases, and the inverse association with aspirin use in glioma was observed only after excluding subjects using aspirin for headache. Taken together these results suggest that regular aspirin may reduce incidence of glioma but confers little benefit in reducing the occurrence of meningioma.

Aspirin has been definitely linked to a reduced incidence of gastrointestinal cancers [27, 41, 42] with some evidence also supporting a benefit for nonGI cancers [27]. In glioma, case-control studies [29–32] had consistently inverse associations for aspirin/NSAIDs, whereas prospective [33–35] and pharmacy database [36, 37] studies had either null findings [34, 36, 37] or suggestive positive associations [33, 35]. A potential bias in studies to date is that results may have reflected analgesic use by the cases for symptoms related to the preclinical brain tumor. In line with this, two prospective studies showed *positive* associations with 'recent' aspirin use (during the preceding one or 6 months) prior to the baseline survey. To avoid this bias, pharmacy-based studies [36, 37] disregarded analgesics dispensed in the year prior to the index date, whereas one prospective study [34] enforced a lag time of several years between the baseline survey and the beginning of observation. However, these measures may not have entirely avoided protopathic bias [40] given evidence that some gliomas have an extended preclinical phase lasting a decade or more [41]. It is notable that a *positive* though nonsignificant association for regular aspirin use persisted in the NIH-AARP study [34, 37] with a lag time of more than 5 years consistent with lingering protopathic bias. Studies to date generally lacked power to evaluate associations when accounting for latency to isolate aspirin use predating onset of the brain tumor. In one study based on the Danish National Prescription Registry that considered both recency and duration of NSAID prescription [36], no overall association of aspirin with glioma was demonstrated; however, results were consistent with a protective association for long-term use of low dose aspirin (generally used for cardiopreventive measures rather than headache or pain relief) a minimum of 3 years prior to the index date (OR: 0.47, 95% CI: 0.14, 1.55).

In line with the current results, a preventive role of aspirin in glioma was demonstrated in a secondary analysis of cardioprevention trials of daily aspirin [27]. Among 10,502 patients with scheduled duration of trial treatment ≥5 years, deaths from primary brain tumors (presumably all gliomas) were reduced in the aspirin arm during the first 10-years of follow-up (HR: 0.31; 95% CI: 0.11–0.89, p=0.03). No benefit was observed beyond 10 years though the mean time from randomization to death remained significantly longer in the aspirin group at 20-years. No association with 'invasive brain tumor' incidence was observed in the Women's Health Initiative (WHI) trial which tested efficacy of alternate day, low-dose aspirin (100 mg) for 10 years [28]. It is not clear why results from the WHI differ from those of the cardioprevention trials of daily aspirin. The WHI analysis could have included malignant meningiomas, a tumor which is seldom fatal. Biologic effects of aspirin could be sex-dependent [42]. In the present study, the inverse association with regular aspirin taken for reasons other than headache was stronger in men (OR: 0.64; 95% CI: 0.48, 0.85) than in women (OR: 0.80; 95% CI: 0.55, 1.15) though differences by gender were nonsignificant (p for interaction = 0.22). Clinical trial results were based on small numbers of incident brain tumors (17 and 31 events, respectively) and findings from both studies were compatible with chance.

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Aspirin has well established effects on platelet function [43, 44], inhibition of COX-2 [45, 46], and apoptosis [47–50] that may contribute to chemopreventive effects in cancer. The present data suggests that aspirin may specifically be beneficial in glioma as nonaspirin NSAIDs appeared to confer no benefit when taken as a single agent (e.g. without aspirin). If not due to chance, the present observations are consistent with a mechanism specific to platelet function given that platelets are known to release substances that promote cancer incidence and progression, and platelets are more potently inhibited by aspirin than other anti-inflammatory agents [10]. However, it should be noted that our question on 'other analgesics' was open-ended and reporting of other types of analgesics would have diluted associations for nonaspirin NSAIDs.

The study had a number of strengths for examining the present hypothesis but also several limitations. Our series of glioma and meningioma cases well represent the documented incidence patterns of these tumors by sex, age, and race in the US population [1, 2]. A large proportion of eligible cases (~87%) were enrolled in the study and few case interviews (<2%) were completed by a proxy respondent. Furthermore, the study interview included questions on indication for analgesic use which enabled us to consider (and attempt to avoid the influence of) protopathic bias on the results. Moreover, the study was conducted in the period after the introduction of COX-2 inhibitors permitting us to examine for the first time whether use of these agents influences brain tumor risk. However, several limitations must be noted. First, the power of subgroup analyses and for analyses focused on meningioma was limited, in particular, after deleting analgesic-using headache sufferers from analysis (with a total of 921 gliomas, 227 meningiomas and 1124 controls remaining). Second, we lacked information on dose and frequency of pill use and could not evaluate the consistency or frequency of exposure over the years of reported analgesic use. Third, response rates in controls were suboptimal and selection bias is a concern if participation in the study by controls was conditional on analgesic use. While we cannot rule out such bias, we note that the consistency of results regardless of indication (body pain, cardioprevention, other indications) argues against (though does not rule out) selection bias in the data. Moreover, inverse associations of aspirin use with glioma were observed both in college educated- and lesser educated subjects (not shown) suggesting that results are not due to selection bias on SES. Demonstration of inverse associations for glioma but not for meningioma also argues against strong selection bias in the data. Recall or reporting bias was also possible. However, that findings were specific to aspirin (and possibly COX-2 inhibitors) argues against systematic underreporting of medications among the glioma cases. Furthermore, all results were essentially unchanged after excluding glioma cases with tumors affecting the temporal lobe, the seat of long-term memory in the brain (not shown).

In summary, the present results suggest that regular use of anti-inflammatory drugs, specifically aspirin, reduce the incidence of glioma. In view of the absence of prevention strategies for glioma, a devastating tumor of the CNS, these results merit further investigation. A pooled analysis combining prospective studies in which long-term follow up to avoid protopathic bias is the next step to confirm or rule out a benefit of aspirin in the chemoprevention of glioma.

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Table 1

Descriptive characteristics of brain tumor cases and controls

Variable	Glioma Cases (N=1123)	Meningioma Cases (N=310)	Community Controls (N=1296)
Age			
Mean (SD)	53.0 (15.4)	56.2 (13.5)	55.3 (14.5)
Median (range)	54 (18–92)	55 (19–90)	57 (18–90)
Gender, N (%)			
Male	654 (58.2)	80 (25.8)	644 (49.7)
Female	469 (41.8)	230 (74.2)	652 (50.3)
Race, N (%)			
Caucasian	1057 (94.1)	282 (91.0)	1239 (95.6)
Other	66 (5.88)	28 (9.03)	57 (4.40)
Education, N (%)			
High School or Less	409 (36.4)	104 (33.5)	348 (26.9)
Some College	308 (27.4)	99 (31.9)	358 (27.6)
College Degree	238 (21.2)	71 (22.9)	359 (27.7)
Graduate Degree	168 (15.0)	36 (11.6)	231 (17.8)
State, N (%)			
FL	455 (40.5)	96 (31.0)	422 (32.6)
TN	217 (19.3)	113 (36.5)	380 (29.3)
AL	215 (19.1)	13 (4.19)	164 (12.7)
GA	117 (10.4)	51 (16.5)	137 (10.6)
KY	70 (6.23)	24 (7.74)	118 (9.10)
Other	49 (4.36)	13 (4.19)	75 (5.79)

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Table 2

Regular use of analgesics and risk of primary brain tumor

	Glioma Cases	Meningioma Cases	Controls	Glioma		Meningioma	
	N (%)	N (%)	N (%)	OR	95% CI	OR	95% CI
Tylenol	182 (24.4)	72 (37.7)	179 (22.7)	1.20	(0.93, 1.54)	**1.85**	**(1.29, 2.65)**
Aspirin	317 (36.0)	110 (48.0)	432 (41.5)	0.83	(0.67, 1.02)	**1.41**	**(1.02, 1.95)**
nonaspirin NSAIDs	206 (26.8)	73 (38.0)	264 (30.3)	0.95	(0.75, 1.19)	1.31	(0.93, 1.85)
COX2-inhibitors	69 (6.14)	28 (9.03)	117 (9.03)	0.72	(0.53, 1.00)	0.95	(0.60, 1.50)

Number (N) and percent (%) of persons reporting use of specified analgesic. Percentages are calculated as ((number of users)/ (number of users plus nonanalgesic users) * 100). OR= odds ratio; CI = confidence interval. ORs/CIs are adjusted for age, gender, race, education and state of residence. Reference group comprised of persons reporting no regular analgesic use (564 glioma cases, 119 meningioma cases, 608 controls). Statistically significant results (P<0.05) are bolded.

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Table 3

Risk of brain tumor associated with ever regular use of analgesics according to indication for use.

	Gliomas	Meningiomas	Controls	Glioma		Meningioma	
	N (%)	N (%)	N (%)	OR	95% CI	OR	95% CI
Headache							
Tylenol	116 (17.1)	48 (28.7)	93 (13.3)	**1.49**	**(1.09, 2.04)**	**2.35**	**(1.53, 3.61)**
Aspirin	65 (10.3)	26 (17.9)	44 (6.75)	**1.89**	**(1.24, 2.88)**	**2.86**	**(1.63, 5.01)**
Other NSAIDs	91 (13.9)	33 (21.7)	81 (11.8)	1.38	(0.98, 1.95)	**1.98**	**(1.22, 3.20)**
All Other Indications							
Tylenol	66 (10.5)	24 (16.8)	86 (12.4)	0.86	(0.60, 1.24)	1.26	(0.74, 2.14)
Aspirin	252 (30.9)	84 (41.4)	388 (39.0)	**0.69**	**(0.56, 0.87)**	1.16	(0.82, 1.64)
Other NSAIDs	115 (16.9)	40 (25.2)	183 (23.1)	**0.75**	**(0.57, 0.99)**	1.03	(0.68, 1.57)
Body Pain							
Tylenol	59 (9.47)	20 (14.4)	70 (10.3)	0.94	(0.64, 1.39)	1.27	(0.72, 2.26)
Aspirin	12 (2.08)	8 (6.30)	29 (4.55)	**0.41**	**(0.20, 0.85)**	1.21	(0.51, 2.87)
Other NSAIDs	94 (14.3)	32 (21.2)	153 (20.1)	**0.73**	**(0.54, 0.98)**	1.00	(0.63, 1.57)
Cardioprevention							
Aspirin	223 (28.3)	70 (37.0)	330 (35.2)	**0.72**	**(0.57, 0.91)**	1.14	(0.78, 1.65)
Other Indications							
Tylenol	36 (6.00)	11 (8.46)	56 (8.43)	0.71	(0.45, 1.13)	0.91	(0.45, 1.86)
Aspirin	48 (7.84)	15 (11.2)	74 (10.9)	0.71	(0.47, 1.07)	0.97	(0.52, 1.82)
Other NSAIDs	70 (11.0)	18 (13.1)	99 (14.0)	0.84	(0.60, 1.19)	0.87	(0.49, 1.53)

Number (N) and percent (%) of persons reporting use of specified analgesic. Percentages are calculated as ((number of users)/ (number of users plus nonanalgesic users) * 100). OR = Odds Ratio; CI = Confidence Interval. Multivariate ORs/ CIs are adjusted for age, gender, race, education and state of residence. Reference group comprised of persons reporting no analgesic use (564 glioma cases, 119 meningioma cases, 608 controls). Results for headache include persons also reporting other indications for use. Results for other indications (body pain, cardioprevention and 'other') exclude persons reporting headache as an indication. Statistically significant results (P<0.05) are bolded.

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Table 4

Glioma risk according to years of regular aspirin use for reasons other than headache

	Gliomas N (%)	GBM N (%)	LGG N (%)	Controls N (%)	All Gliomas OR (95% CI)	GBM OR (95% CI)	LGG OR (95% CI)
never	564 (72.3)	321 (65.5)	243 (83.8)	608 (62.8)	referent	referent	referent
<3	80 (10.3)	62 (12.7)	18 (6.21)	107 (11.1)	0.83 (0.59, 1.16)	0.85 (0.59, 1.23)	0.67 (0.38, 1.16)
4–9	69 (8.85)	52 (10.6)	17 (5.86)	109 (11.3)	**0.63 (0.44, 0.89)**	**0.61 (0.41, 0.89)**	0.63 (0.36, 1.13)
10 or more	67 (8.59)	55 (11.2)	12 (4.14)	144 (14.9)	**0.45 (0.32, 0.63)**	**0.45 (0.31, 0.65)**	**0.38 (0.20, 0.74)**
p-trend					<0.001	<0.001	0.002

Number (N) and percent (%) of persons reporting use of specified analgesic. Percentages are calculated as ((number of users)/ (number of users plus nonanalgesic users) * 100). GBM = Glioblastoma multiforme; LGG = Lower Grade Glioma; OR = Odds Ratio; CI = Confidence Interval. Multivariate ORs/CIs are adjusted for age, gender, race, education and state of residence. Reference group includes persons that reported no regular analgesics use. Cases and controls reporting use of any analgesic for headache were excluded from analysis. Information on duration of aspirin use is missing for 36 gliomas, 19 GBM, 17 LGG and 28 controls. Statistically significant results (P<0.05) are bolded.