



Clinical Study

The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors

Jimmy T. Efird¹, Gary D. Friedman^{2,3}, Stephen Sidney³, Arthur Klatsky³, Laurel A. Habel^{2,3}, Natalia V. Udaltsova³, Stephen Van Den Eeden^{2,3} and Lorene M. Nelson²

¹John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; ²Division of Epidemiology, Department of Health Research and Policy, Stanford School of Medicine, Stanford; ³Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA, USA

Key words: alcohol, cigarettes, coffee, gliomas, marijuana

Summary

Purpose: To determine the risk for malignant primary adult-onset glioma (MPAG) associated with cigarette smoking and other lifestyle behaviors in a large, multiethnic, managed-care cohort.

Methods: The study population included a cohort of 133,811 subscribers to the Kaiser Permanente Medical Care Program of Northern California who had received a multiphasic health checkup and questionnaire between 1977 and 1985, were at least 25 years old at their start of follow-up, and had no prior history of benign or malignant brain tumors. In this cohort, patients were followed for up to 21 years for the development of MPAG.

Results: Risk for MPAG among women increased with increasing packs of cigarettes smoked per day (p -for-trend = 0.04), adjusting for cigar and pipe smoking, patient age, sex, race, education, alcohol use and coffee consumption. A similar pattern was not observed for men. Individuals who smoked marijuana at least once a month, adjusting for cigarette smoking (packs smoked per day) and for the factors noted above, had a 2.8-fold (CI = 1.3–6.2) increased risk for MPAG. Relative risk for MPAG increased with increasing consumption of coffee (p -for-trend = 0.05).

Conclusions: Cigarette smoking was associated with an increased risk for MPAG among women but not among men. Individuals who smoked marijuana at least once a month had an increased risk for MPAG, although no dose-response relation was observed. Drinkers of >7 cups of coffee per day had a 70% increased risk for MPAG and smaller risk elevation for lower consumption. Alcohol usage was not associated with an increased risk for MPAG.

Abbreviations: CI – confidence interval; CBT – childhood brain tumors; ICD-9 – International Classification of Diseases, 9th revision; ICD-O – International Classification of Diseases for Oncology; KPMCP-NC – Kaiser Permanente Medical Care Program of Northern California; MHC – multiphasic health checkup and questionnaire; MPAG – malignant primary adult-onset glioma; NAT-2 – N-acetyltransferase 2; RR – relative risk; SAQ – supplemental alcohol questionnaire; SEER – surveillance, epidemiology and end results; SD – standard deviation; SSQ – supplemental smoking questionnaire.

Introduction

The estimated number of new brain and other nervous system cancer cases in the United States in 2003, based on data from the surveillance epidemiology and end results (SEER) program, was 18,300 [1], the majority being adult-onset gliomas. In the same year, ~13,100 patients died of these malignancies [1].

Established risk factors for primary malignant brain tumors include advancing age, male sex, caucasian race, and exposure to ionizing radiation [2]. Epidemiologic studies of lifestyle behaviors such as tobacco [3–18] and marijuana [19–27] smoking, alcohol consumption [3,5,6,8,12,14–16,28,29], and coffee drinking [8] either have not addressed brain tumors or have reported conflicting or negative results.

The purpose of this study was to determine the risk for malignant primary adult-onset glioma (MPAG) associated with cigarette smoking and other lifestyle behaviors in a large, multiethnic, managed-care cohort.

Study population and methods

The setting for this study was the Kaiser Permanente Medical Care Program of Northern California (KPMCP-NC). Approximately 30% of the general population in the areas served belongs to KPMCP-NC. The KPMCP-NC membership is ethnically and socio-economically diverse and reflects the overall population of the coverage area, except that it under-represents the very poor and wealthy, and its members are, on the average, more highly educated than the underlying population [30,31].

The initial cohort included 142,085 subscribers to the KPMCP who had received a multiphasic health checkup and questionnaire (MHC) between 1977 and 1985, were at least 25 years old at their start of follow-up (date of MHC), and had no prior history of benign or malignant brain tumors (International Classification of Diseases, 9th revision (ICD-9) [32]: 191.X, 192.1, 194.3, 194.4, 225.2, 227.3, 227.4, 237.0, 237.1, 237.5, 237.6). The MHC was a voluntary, comprehensive health evaluation used by members and their physicians for routine checkups. As part of this checkup, members completed a self-administered questionnaire soliciting information about a number of demographic and lifestyle factors including their sex, race, education, alcohol use, coffee consumption, and smoking habits. MHC participants were more likely to be of black race, better educated, and in better health than other subscribers [31,33]. Separate self-administered smoking and alcohol questionnaires, designed to collect more detailed information about type of cigarettes smoked, marijuana use, and alcohol habits were completed by a subset of the above subjects. Our analytic data set consisted of 133,811 (94%) patients with complete information on smoking history, age, sex, and race, of whom 105,005 (78%) and 108,019 (81%) also completed supplemental smoking (SSQ) and alcohol (SAQ) questionnaires. Information regarding former and current cigar and pipe smoking only was collected on the SSQ, but the number of MPAG events for these categories were too small for analysis in our multivariate models. In order to increase the number of events and sample size, information for cigar and pipe

smoking was obtained from the main MHC and was limited to 'ever *versus* never' responses.

Study follow-up began at the time of the subject's earliest MHC. Data from a later questionnaire, if available, was used when information was missing for smoking status, coffee consumption, alcohol usage, or race, with follow-up time calculated as if the exposure status were the same at baseline. Patient age was calculated using month and year of birth from membership files, and if missing there, from the MHC, SSQ or SAQ. Subjects were followed until the occurrence of a primary malignant glioma (International Classification of Diseases for Oncology (ICD-O) [34]: 938X/3-948X/3), death, December 31st of their last membership year, or March 31, 1999, whichever occurred first. Years with no membership before last contact were treated as continuous enrollment for computational purposes because evidence shows that very few cancers would have been missed [35]. The local KPMCP-NC tumor registry, which reports all cancers of members to the SEER program, was used to identify patients with malignant brain tumors during their follow-up period. Subjects with pre-study period brain tumors (see exclusion criteria) from 1971 forward were identified through computerized hospitalization records and cancer incidence files. Non-glial brain cancers were excluded in our analysis as their numbers are small, difficult to detect in some cases, and may have distinctly different risk factors than gliomas.

The Cox proportional hazards model was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) [36]. Primary multivariate models included a main effects variable (e.g., cigarettes or marijuana smoking) and were adjusted for age, sex, race, education, alcohol use, coffee consumption, cigar and pipe smoking, and packs of cigarettes currently or formerly smoked per day *versus* never (when cigarette smoking was not included as the main effect), based on baseline questionnaires. Risk for MPAG increased linearly with subject's age and was adjusted for in the model by starting the time axis at birth. This resulted in a more parsimonious model with fewer degrees of freedom.

Post-hoc analyses also were conducted by tumor site (frontal-parietal region (ICD-9: 191.1, 191.3), temporal-occipital region (ICD-9: 191.2, 191.4), and other combined locations (ICD-9: 191.0, 191.5, 191.6, 191.8, 191.9)) and histology (astrocytoma (ICD-O: 94003, 94103, 94113, 94203, 94213), glioblastoma (ICD-O: 94403), and other combined gliomas (ICD-O: 93803, 93823, 94423, 94503, 94513)). No other tumor locations (e.g., ICD-9: 191.7) or histologic categories

(e.g., ICD-O: 93813, 93831-93941, 94003-94013, 94223-94303, 94413, 94433, 94603-94813) were reported. Ordinal variables were assessed for linear dose-response effect using a likelihood ratio trend test (unknown categories excluded). All statistical tests were two-sided and considered significant at $P \leq 0.05$.

Results

The distributions of key study characteristics by current or former cigarette exposure (packs per day) are shown in Table 1. Smokers tended to be white, male, young (<65 years of age), and less educated, consistent with nationally published data [1].

The maximum follow-up time for the cohort was 21 years, with a mean of 13.2 ± 6.7 (standard deviation (SD)) years. A total of 130 subjects (≥ 25 years of age) were diagnosed with MPAG during the follow-up period. The mean age at diagnosis of the cases was 62.2 ± 13.5 (SD) years. Glioblastoma (57.7%) was the most common histologic type diagnosed, followed by astrocytoma (23.8%), malignant glioma (10.0%), and various other combined gliomas (8.5%). MPAG was most commonly found in the cerebrum (68.5%) and distributed almost equally between the frontal (27.7%) and temporal (26.9%) lobes.

The risk for MPAG was elevated in former and current smokers of cigarettes compared to never smokers of cigarettes (Table 2). With the exception of

Table 1. Key study characteristics by smoking status (packs per day)

Characteristic/ smoking exposure ¹	Never (%) (n = 65,544)	>0 to <1 packs (%) (n = 43,004)	1–2 packs (%) (n = 20,557)	>2 packs (%) (n = 4,706)	Total (%) (n = 133,811)
Sex					
Female	60.8	52.1	42.9	32.6	54.3
Male	39.2	47.9	57.1	67.4	45.7
Age (years)					
25–34	37.5	34.2	29.7	18.0	34.6
35–44	22.4	25.3	27.6	27.6	24.3
45–54	15.4	17.0	19.3	25.3	16.9
55–64	14.5	15.2	16.1	20.7	15.2
≥ 65	10.2	8.4	7.4	8.5	9.1
Race					
Non-white	42.5	45.6	28.4	17.0	40.5
Black	21.5	33.0	21.0	12.3	24.8
Asian	11.7	5.7	3.4	1.9	8.1
Other	9.4	7.0	4.0	2.9	7.6
White	57.5	54.4	71.6	83.0	59.5
Education (years college)					
None	31.3	36.2	37.6	38.8	34.1
1–2	22.8	28.2	29.5	29.3	25.8
>2	44.6	34.7	32.3	31.1	39.1
Unknown	1.3	0.9	0.7	0.8	1.0
Alcohol (current, drinks per day)					
None	24.5	10.4	9.5	11.9	17.2
1–2	68.4	78.3	71.2	60.1	71.1
3–5	2.7	6.6	12.7	15.6	6.0
≥ 6	0.5	1.4	3.3	8.5	1.5
Unknown	3.8	3.3	3.3	3.9	3.6
Coffee (past year, cups per day)²					
<1	41.6	28.1	19.0	16.4	32.9
1–3	42.8	50.2	42.3	34.0	44.8
4–6	9.6	15.1	25.2	25.9	14.3
≥ 7	2.1	4.0	11.0	20.7	4.7
Unknown	4.0	2.7	2.6	2.9	3.3

¹Packs of cigarettes currently or formerly smoked as of baseline questionnaire.

²Within the past year.

Table 2. Relative risk for malignant adult-onset glioma by smoking status ($N = 133,811$)

Smoking status level	No. of events	Univariate		Multivariate ¹	
		RR [95% CI]	<i>p</i> -Wald test	RR [95% CI]	<i>p</i> -Wald test
Tobacco					
Cigarettes					
Never	51	1.0	—	1.0	—
Ever	79	1.6 [1.1–2.3]	0.01	1.4 [1.0–2.1]	0.07
Former	45	1.6 [1.1–2.4]	0.02	1.3 [0.9–2.0]	0.19
Current	34	1.6 [1.1–2.5]	0.03	1.6 [1.0–2.5]	0.06
Packs per day					
>0 to <1	52	1.7 [1.1–2.5]	0.01	1.6 [1.1–2.4]	0.02
1–2	15	1.0 [0.6–1.9]	0.88	0.8 [0.5–1.5]	0.51
>2	12	3.2 [1.7–6.0]	<0.01	2.3 [1.2–4.5]	0.02
		<i>p</i> -for-trend 0.01 ³		<i>p</i> -for-trend 0.18 ³	
Type ²					
Filtered	32	1.6 [1.0–2.5]	0.05	1.4 [0.8–2.2]	0.20
Unfiltered	10	1.2 [0.6–2.4]	0.57	0.8 [0.3–1.7]	0.61
Regular (85 mm)	24	1.5 [1.0–2.5]	0.08	1.2 [0.7–2.0]	0.47
King-size (100 mm)	14	1.4 [0.8–2.6]	0.24	1.1 [0.6–2.1]	0.68
Long	4	1.2 [0.4–3.3]	0.75	1.1 [0.4–3.0]	0.91
Mentholated	8	1.2 [0.6–2.5]	0.63	1.2 [0.5–2.5]	0.71
Plain	34	1.5 [1.0–2.4]	0.05	1.2 [0.7–1.9]	0.49
Cigars (current)					
No	123	1.0	—	1.0	—
Yes	6	1.5 [0.7–3.4]	0.35	1.5 [0.6–3.5]	0.37
Unknown	1	0.3 [0.0–2.4]	0.27	0.9 [0.0–16.1]	0.93
Pipes (current)					
No	127	1.0	—	1.0	—
Yes	2	0.5 [0.1–2.1]	0.37	0.3 [0.1–1.4]	0.12
Unknown	1	0.3 [0.0–2.1]	0.22	0.4 [0.0–7.5]	0.54
Marijuana ²					
Never	60	1.0	—	1.0	—
Ever	9	2.2 [1.1–4.7]	0.03	1.9 [0.9–4.0]	0.10
Frequency					
Less than once a month	1	0.7 [0.1–5.2]	0.74	0.6 [0.1–4.4]	0.61
At least once a month	8	3.3 [1.5–7.3]	<0.01	2.8 [1.3–6.2]	0.01
Unknown	24	1.0 [0.7–1.7]	0.85	1.3 [0.8–2.2]	0.33
		<i>p</i> -for-trend 0.03 ³		<i>p</i> -for-trend 0.08 ³	

¹Multivariate models included a smoking status variable adjusting for cigars, pipes, sex, race, alcohol, education, and coffee, as of baseline questionnaire. When the main effect was not cigarette smoking, the cigarette smoking variable in multivariate analysis had the following four categories: never smokers (reference), and current or former smokers of >0 to <1, 1–2, and >2 packs per day. Age served as the time axis. Other variable levels are shown in column 1 of Table 1 and were controlled as dummy variables.

²Restricted to subjects who completed the subsample detailed smoking questionnaire ($n = 105,005$).

³Likelihood ratio trend test.

unfiltered cigarettes, a small positive risk was observed for each type of cigarette smoked (e.g., filtered, regular (85 mm), king-sized (100 mm), long, mentholated, plain), although all CIs included one. Ever smokers of marijuana had a 1.9-fold elevated risk for MPAG compared to never smokers of marijuana, adjusting for cigarette smoking (packs smoked per day). Individuals who smoked marijuana once a month or more frequently had a 2.8-fold increased risk compared to

never smokers of marijuana. Within this group, none of the subjects who reported daily smoking of marijuana ($n = 2,823$) had a brain tumor. However, there were four MPAG cases among subjects who reported smoking marijuana weekly ($n = 6,002$), yielding RR = 3.2 (CI = 1.1–9.2). Also, among subjects who reported smoking marijuana monthly ($n = 4,699$), four developed a brain tumor, yielding RR = 3.6 (CI = 1.3–10.2). Only one subject developed a brain

Table 3. Relative risk for malignant adult-onset glioma by other key study exposures ($N = 133, 811$)

Exposure level	No. of events	Univariate		Multivariate ¹	
		RR [95% CI]	<i>p</i> -Wald test	RR [95% CI]	<i>p</i> -Wald test
Sex					
Female	55	1.0	—	1.0	—
Male	75	1.7 [1.2–2.5]	<0.01	1.6 [1.1–2.3]	0.01
Race					
Non-white ²	28	1.0	—	1.0	—
White	102	1.8 [1.2–2.8]	<0.01	1.7 [1.1–2.6]	0.02
Education (years college)					
None	54	1.0	—	1.0	—
1–2	27	1.2 [0.7–1.9]	0.52	1.1 [0.7–1.8]	0.64
>2	48	1.6 [1.1–2.4]	0.02	1.5 [1.0–2.2]	0.05
Unknown	1	0.5 [0.1–3.8]	0.52	0.6 [0.1–4.3]	0.61
		<i>p</i> -for-trend 0.02 ³		<i>p</i> -for-trend 0.06 ³	
Coffee (past year, cups per day)					
<1	27	1.0	—	1.0	—
1–3	58	1.2 [0.7–1.9]	0.51	1.1 [0.7–1.8]	0.70
4–6	30	1.9 [1.1–3.2]	0.02	1.6 [0.9–2.8]	0.08
≥7	10	2.1 [1.0–4.4]	0.05	1.7 [0.8–3.6]	0.17
Unknown	5	1.2 [0.5–3.0]	0.75	1.4 [0.5–3.6]	0.54
		<i>p</i> -for-trend 0.01 ³		<i>p</i> -for-trend 0.05 ³	
Alcohol (current, drinks per day)					
None	26	1.0	—	1.0	—
1–2	89	1.2 [0.8–1.9]	0.39	0.9 [0.6–1.4]	0.60
3–5	10	1.5 [0.7–3.1]	0.29	0.9 [0.4–1.9]	0.70
≥6	1	0.7 [0.1–5.1]	0.72	0.4 [0.1–2.8]	0.35
Unknown	4	0.9 [0.3–2.6]	0.83	0.8 [0.3–2.2]	0.61
		<i>p</i> -for-trend 0.44 ³		<i>p</i> -for-trend 0.43 ³	
Beer (past year)⁴					
No	42	1.0	—	1.0	—
Yes	38	1.2 [0.8–1.9]	0.34	1.0 [0.6–1.6]	0.96
Unknown	21	1.0 [0.6–1.7]	0.95	0.8 [0.1–7.3]	0.84
Wine (past year)⁴					
No	23	1.0	—	1.0	—
Yes	57	1.2 [0.7–1.9]	0.54	0.8 [0.5–1.4]	0.48
Unknown	21	1.0 [0.6–1.9]	0.91	0.8 [0.1–7.0]	0.84
Liquor (past year)⁴					
No	22	1.0	—	1.0	—
Yes	58	1.5 [0.9–2.4]	0.13	1.3 [0.8–2.3]	0.27
Unknown	21	1.2 [0.7–2.2]	0.49	2.2 [0.2–19.4]	0.48

¹Multivariate models included the indicated exposure variable adjusting for cigarettes, cigars, pipes, sex, race, education, alcohol, and coffee. The cigarette variable in the multivariate analysis had the following four categories: never smokers (reference), and current or former smokers of >0 to <1, 1–2, and >2 packs per day. Age served as the time axis. Other variable levels are shown in column 1 of Table 1 and were controlled as dummy variables.

²Black, Asian, and Other.

³Likelihood ratio trend test (unknown category excluded).

⁴Restricted to subjects who completed the subsample detailed alcohol questionnaire ($N = 108,019$).

tumor among patients who reported smoking marijuana less frequently than once a month ($n = 5,768$).

Relative risk was elevated for men compared with women, and for whites compared with non-whites (Table 3). RR for MPAG increased with increasing

consumption of coffee (*p*-for-trend = 0.05). A slightly positive but non-statistically significant risk (RR = 1.3) for MPAG was observed among drinkers *versus* non-drinkers of hard liquor. However, risk was not elevated among drinkers of beer or wine.

Table 4. Multivariate RR for malignant adult-onset glioma by cigarette smoking status and indicated exposure level

Exposure level	Multivariate (packs per day) ¹				<i>p</i> -value ² (trend test)
	None	>0 to <1	1–2	>2	
	RR	RR [95% CI]	RR [95% CI]	RR [95% CI]	—
Age (years)					
<55 ³	1.0	1.8 [1.0–3.3]	1.0 [0.5–2.2]	1.8 [0.7–4.8]	0.42
≥55 ⁴	1.0	1.4 [0.8–2.5]	0.6 [0.2–1.6]	2.8 [1.1–7.1]	0.35
Sex					
Female	1.0	1.7 [0.9–3.1]	1.8 [0.8–4.1]	3.0 [0.9–10.6]	0.04
Male	1.0	1.4 [0.9–2.4]	0.4 [0.2–1.0]	1.9 [0.9–4.2]	0.93
Race					
Non-white ⁵	1.0	1.6 [0.7–3.7]	0.8 [0.2–3.6]	No events	—
White	1.0	1.6 [1.0–2.5]	0.8 [0.4–1.6]	2.6 [1.3–5.1]	0.14
Education (years college)					
None	1.0	1.0 [0.5–2.0]	0.9 [0.4–2.2]	3.8 [1.6–9.3]	0.09
1–2	1.0	4.0 [1.5–10.3]	0.7 [0.1–3.5]	1.1 [0.1–9.3]	0.97
>2	1.0	1.5 [0.8–2.9]	0.9 [0.4–2.3]	1.7 [0.5–5.9]	0.58
Alcohol (current)					
No	1.0	2.6 [1.0–6.6]	1.7 [0.5–6.7]	5.5 [1.3–23.1]	0.04
Yes	1.0	1.3 [0.8–2.0]	0.6 [0.3–1.2]	1.5 [0.7–3.3]	0.91
Coffee (past year, cups per day)					
Rarely or never (<1)	1.0	0.8 [0.3–2.2]	0.4 [0.0–2.9]	5.5 [1.7–17.7]	0.25
Daily (≥1)	1.0	1.9 [1.2–3.0]	1.0 [0.5–2.0]	1.9 [0.8–4.4]	0.24

¹Multivariate models were adjusted for cigarettes, cigars, pipes, sex, race, education, alcohol, and coffee. The cigarette variable in the multivariate analysis had the following four categories: never smokers (reference), and current or former smokers of >0 to <1, 1–2, and >2 packs per day. Age served as the time axis. Other variable levels are shown in column 1 of Table 1 and were controlled as dummy variables.

²Likelihood ratio trend test.

³Number of events = 63.

⁴Number of events = 67.

⁵Black, Asian, and other.

Increased risk for MPAG associated with increasing packs of cigarettes smoked per day was observed for women (Table 4). A similar pattern was not observed among men, although the risk for MPAG was elevated for smokers in the >0 to <1 and >2 packs per day group. A decreased risk was observed among male smokers of 1–2 packs per day; however, the CI for this RR included unity. Risk for MPAG among non-drinkers was elevated for all smoking levels. Except for subjects in the 1–2 years of college group, risk for MPAG was consistently elevated (RR ≥ 1.5) among smokers of >2 packs of cigarettes per day for all strata shown in Table 4.

There was no linear trend of increasing risk associated with increasing packs per day for any histologic type or any anatomic site, with the exception of the frontal–parietal region of the brain (Table 5). However, patients with frontal–parietal tumors in comparison to other sites were 1.9-fold (CI = 0.9–3.9) more likely to be women.

Discussion

The contribution of the current analysis differs from most other studies of adult-onset brain tumors in that we conducted a follow-up study of non-diseased persons, rather than retrospectively estimating risk in a case-control design. Our study represents the only cohort study to date of active cigarette smoking in a well-defined population that examined the risk for MPAG by age group, sex, race, education, alcohol consumption, and coffee drinking. Furthermore, no other published studies to our knowledge have addressed the relationship between marijuana smoking and MPAG. The results of our study suggest a modestly increased risk for MPAG among coffee drinkers, users of marijuana, and female smokers.

Several factors may have affected the results of this study and should be considered when interpreting these observations. All exposures in this study were defined according to information collected at cohort

Table 5. Multivariate RR for malignant adult-onset glioma by cigarette smoking status (packs per day), histology and site category

Category	No. of events	Multivariate (packs per day) ¹				<i>p</i> -value ² (trend test)
		None	>0 to <1	1–2	>2	
Histology						
Astrocytoma ²	31	1.0	1.7 [0.7–3.9]	1.1 [0.4–3.5]	2.6 [0.7–9.9]	0.31
Glioblastoma ³	75	1.0	1.6 [1.0–2.7]	0.5 [0.2–1.3]	2.2 [0.9–5.1]	0.57
Other glioma ⁴	24	1.0	1.3 [0.5–3.4]	1.6 [0.5–5.4]	1.7 [0.2–14.2]	0.38
Site						
Frontal–parietal ⁵	50	1.0	1.5 [0.8–2.9]	1.8 [0.8–4.0]	2.7 [0.9–8.3]	0.06
Temporal–occipital ⁶	39	1.0	2.5 [1.2–5.1]	0.6 [0.2–2.1]	1.9 [0.5–7.1]	0.74
Other location ⁷	41	1.0	1.1 [0.5–2.2]	0.3 [0.1–1.2]	2.3 [0.8–6.5]	1.0

¹Multivariate models were adjusted for cigarettes, cigars, pipes, sex, race, education, alcohol, and coffee. The cigarette variable in the multivariate analysis had the following four categories: never smokers (reference), and current or former smokers of >0 to <1, 1–2, and >2 packs per day. Age served as the time axis. Other variable levels are shown in column 1 of Table 1 and were controlled as dummy variables.

²ICD-O: 94003, 94013, 94113, 94203, 94213.

³ICD-O: 94403.

⁴ICD-O: 93803, 93823, 94423, 94503, 94513.

⁵ICD-9: 191.1, 191.3.

⁶ICD-9: 191.2, 191.4.

⁷ICD-9: 191.0, 191.5, 191.6, 191.8, 191.9.

entry, some of which may have changed over the study follow-up period (e.g., smoking history, education, alcohol use, and coffee consumption). Our inability to correct for the cessation or adoption of lifestyle behaviors that may have occurred more or less frequently among the exposed compared to unexposed after baseline could have resulted in an under- or over-estimation of the true association between MPAG and these behaviors. However, ascertainment of baseline exposures does not appear to have been influenced by disease status, as a 1-year lagged analysis did not substantively change our results. Smoking history was unknown for 4.7% of patients in our initial cohort. Patients who did not report their smoking histories were significantly older (mean age = 47.1 vs. 43.4, $p < 0.01$) and more frequently men (50.6% vs. 45.8%, $p < 0.01$) compared to responders. Non-response bias due to the relatively small amount of missing smoking data probably had little if any effect on our findings.

Some misclassification of disease status may have occurred due to the presence of undetected or under-reported cancer. Benign brain tumors occasionally can have a destructive clinical course indistinguishable from malignant tumors, and when not histologically confirmed, may have been incorrectly classified [37]. However, members of the KPMCP-NC have equal access to medical care including modern radiographic methods. A few cancers reported outside of the Kaiser

plan may have been missed in our study. However, surveillance for cancer by the Kaiser system is quite complete, with only 4.4% of cancers missed by not linking to SEER data [35].

The small number of outcome events for cigar and pipe smoking in our multivariate models may have resulted in some residual confounding with respect to cigarette and marijuana smoking. However, our multivariate models converged successfully and results appear stable when compared to univariate results. The possibility exists that our inclusion of missing data as a separate indicator variable in our models may have introduced some bias into the other RR estimates. However, all our models are based on the same questionnaire sample size and any underlying bias should be consistent across models.

While some individuals only had one MHC examination, others returned one or more times to the Kaiser health care plan following periods of non-membership. Follow-up time was calculated as the time from first enrollment to end of membership (e.g., periods of non-membership were not subtracted from follow-up time, but were treated as continuous enrollment). However, our study results likely were unaffected by this calculation, as the percentage of total years of follow-up that were missing was minimal and the missing data was almost evenly distributed among never (0.01%), former (0.01%), and current (0.02%) smokers. Further,

the percentage of the cohort that had years with no membership before last contact did not substantively vary by smoking status, with numbers ranging from the low to mid twenties for never (21%), former (22%), and current (25%) smokers.

The main strength of this study lies in its retrospective cohort design, multiethnic population, large size, and long follow-up time. Case-control studies of MPAG are subject to recall bias, as cases may be more or less likely to report accurately compared with controls.

The existence of a cancer registry increased the likelihood that diagnosed malignant glioma cases were identified and pathologically confirmed. Eighty-six percent of cases were biopsied and histologically typed. The remaining cases were classified using radiographic methods in conjunction with clinical history. Metastatic brain cancer usually is distinguishable from primary glioma because it typically presents as multifocal lesions within the brain parenchyma, with two-thirds of patients having a known underlying primary tumor, usually with metastatic disease at other sites [38]. Although none of the non-biopsied cases had a history of lung cancer either prior to or following their diagnosis of glioma, we can not rule out the possibility of lung metastases to the brain, which might increase the apparent risk for MPAG in cigarette smokers. However, reanalysis of our data with the non-biopsied cases removed did not materially change any of our conclusions. Additional review of the medical records of the 12 patients with glioma who had smoked two or more packs of cigarettes per day showed no evidence of lung cancer. Nine had a tissue diagnosis of primary glioma and three were diagnosed by imaging only.

Several plausible explanations may account for our result showing a negative association for MPAG among male smokers of 1–2 packs of cigarettes per day. Misclassification of smokers in the >2 packs per day group as non-smokers could yield a RR below unity for smokers in the 1–2 packs group. However, we have not observed a comparable effect for other smoking-related cancers in this data set. Neither, have we observed evidence of greater numbers of smokers of 1–2 packs per day ceasing to smoke after baseline due to efforts aimed at reducing smoking. A negative association, for the 1–2 pack subgroup, also was observed when current and former smokers (at baseline) were analyzed separately. This association does not appear to be related to a differential response of current *versus* former smokers, stratified by the number of packs of cigarettes smoked per day. The result could be due

to chance or data error, although the latter is unlikely given our careful validation of data collection, computer coding, and statistical analysis. A long induction period for MPAG could explain the observed effect if follow-up time was insufficient for subjects in the 1–2 packs group. However, follow-up time was similar among the different smoking groups.

The positive dose–response relationship between cigarette smoking and MPAG observed in our study for female smokers may be due to chance. However, a causal relationship is conceivable. For example, (a) cigarette smoke and condensate contain many carcinogenic compounds that can be absorbed in the lungs and transported throughout the body via the blood [39–46], (b) cigarette smoking has been positively associated with cancers of the lung, upper respiratory and digestive tracts, lower urinary tract, and pancreas [41], (c) smoking increases the levels of certain sex hormones and sex hormones have been shown to promote tumor progression in animal studies [47–48], (d) females are more susceptible to a variety of immunological disorders [49], which may be significant when considering that smoking affects immunological function and immunological factors impact on brain cancer [38,40,50–52], (e) the risk for smoking-related cancers of the esophagus, lung, and oral cavity have been observed in some studies to be higher in women compared to men [53–55], and (f) women have been reported to develop a relatively greater number of second primaries following smoking-related cancers of the esophagus, kidney, lung, and urinary bladder [56]. Furthermore, women may be more susceptible to tobacco smoke carcinogens than men in terms of a greater frequency for specific mutations in the p53 [57] and K-RAS [58] genes; an increased concentration of carcinogen adducts in smoking affected tissue [59]; an elevated expression of certain enzymes in the cytochrome p-450 family involved in the conversion of polycyclic hydrocarbons, nitrosamines, and aromatic amines to carcinogenic intermediates [60,61]; and a reduced capacity for DNA repair [62].

In a review of all studies known to us conducted over the past 30 years that examined the direct association between cigarette smoking and adult brain tumors, nine reported non-significant RRs less than or equal to 1.2 (range = 0.6–1.2) [3–11], and six reported non-significant RRs greater than 1.2 (range = 1.2–1.8) [12–17], with respect to never smokers. Only 2 [13,17] of 10 studies [6,8–14,16,17] that examined dose-response reported that risk increased with increasing amount smoked. Two studies that addressed

passive smoking among non-smoking women reported a positive association with brain tumors [11,14]. However, one of these studies [11] reported no association between active smoking and brain tumor risk. Among male smokers of unfiltered cigarettes, Lee et al. [16] observed that brain tumor patients had smoked this type of cigarette almost twice as long as controls ($p = 0.04$). Blowers et al. [11] reported an RR = 1.3 among smokers for ever having smoked unfiltered cigarettes.

Similar to results reported in the adult brain tumor literature, several studies have addressed the association between exposure to tobacco smoke and childhood brain tumors (CBT) and have reported negative or equivocal findings [63–70]. However, some studies have observed an elevated risk. For example, Cordier et al. [71] observed that childhood exposure to tobacco smoke was associated with a significant increase in risk for brain tumors (OR = 2.3, CI = 1.1–4.6) and that the risk to children who had *in utero* exposure to tobacco smoke was 50% higher compared to unexposed children, although the latter association was not statistically significant. Examining the role of maternal smoking prior to and during the index pregnancy, Gold et al. [72] observed a 5-fold greater risk for CBT compared with controls, although the number of subjects involved was small. A cohort study by Neutel and Buck [73] reported a increased risk for CBT (RR = 1.6, CI = 0.56–4.6) among children of mothers who smoked during pregnancy. Schuz et al. [74] in a German population-based case-control study, observed an increased risk (OR = 4.71, CI = 1.69–13.1) for ependymomas in children of mothers who smoked >10 cigarettes per day during pregnancy.

Regarding the exposure to passive smoking, John et al. [75] reported an elevated risk for CBT (OR = 1.9, CI = 0.9–4.2) among children whose father smoked during the year prior to their birth, in the absence of maternal smoking. A greater than 2-fold elevated risk for CBT (OR = 2.2, CI = 1.1–4.5) among children of a non-smoking mother exposed to passive smoke during pregnancy was reported in a case-control study by Filippini et al. [76]. Similarly, a statistically elevated risk for CBT among children of fathers who smoked during their gestation was observed in studies by McCredie et al. [77] (OR = 2.2, CI = 1.2–3.8) and Preston-Martin et al. [78] (OR = 1.5, one-sided $p = 0.03$). In a related study of early life exposure to paternal smoking, Sandler et al. [79] reported an elevated risk for adult brain tumors (RR = 2.3, CI = 0.9–6.0) among offspring whose

father smoked during their gestation or during their childhood.

To our knowledge the current study represents the first cohort analysis of the association between active cigarette smoking and incidence of MPAG in a general population. A cohort study of passive smoking reported a significant elevated risk for brain tumors among non-smoking women whose husbands smoked [18]. Another cohort study conducted among largely non-smoking and non-drinking Seventh-Day Adventists failed to find a positive association between cigarette smoking and the incidence of brain tumors [7]. A cohort study of mostly adult white male veterans followed for 16 years found no association between either current or former smoking history and deaths from cancer of the brain [80]. Interestingly, results of the latter study closely matched our results when we restricted our analysis to white men (never smoker: RR = 1.0; ever smoker: RR = 1.1, CI = 0.6–1.8; current smoker: RR = 1.2, CI = 0.6–2.3; former smoker: RR = 1.0, CI = 0.6–1.8).

A causal relationship between marijuana smoking and MPAG is also plausible. Marijuana smoke and tar, like tobacco, contain a variety of carcinogenic compounds including nitrosamines, vinyl chlorides, phenols, aldehydes, reactive oxygen species, and polycyclic aromatic hydrocarbons, some of which (e.g., benzo(a)pyrene and benz(a)anthracene) occur in concentrations up to 75% higher than in tobacco [81]. An equivalent weight marijuana joint deposits four times as much tar in the respiratory tract of an individual as a filtered tobacco cigarette in part to the higher smoking temperature (mainly due the loose manner in which marijuana is packed when rolled into a cigarette), the typical manner of smoking (e.g., deep inhalation, large puff volume, and long breathholding time), and the lack of a filter in the joint [19,81].

To our knowledge, no published studies have addressed the relationship between marijuana smoking and brain tumors. However, some epidemiologic studies of marijuana smoking have found an increased risk for other cancers including head and neck [19–21] and respiratory tract [22,23], while others have found no overall association with cancer incidence at any site [24]. An association between maternal marijuana use and childhood cancer has been reported in offspring for non-lymphoblastic leukemia [25], astrocytoma [26], and rhabdomyosarcoma [27]. Our result showing a positive association between marijuana smoking (at least once a month vs. never) and MPAG is subject to interpretation, given the small number of cases in

the ‘at least once a month’ group and the high percentage of cases (26%) that failed to report marijuana smoking status. While cases that did not report marijuana smoking status were approximately the same age at baseline (mean age = 52.9 vs. 51.9) as responders, non-responder cases were more frequently male (66.7% vs. 33.3%, $p < 0.01$). However, our multivariate model was adjusted for patient sex.

Under normal circumstances, the brain may not be vulnerable to carcinogens found in tobacco or marijuana smoke when delivered in the quantities or manner in which smoking exposure is imparted [82]. However, hypertension, viral and bacterial infection, ischemic lesions, physical trauma, changes in osmotic pressure of cerebral blood supply, and other disease states may reduce the efficiency of the blood–brain barrier in restricting these substances from entering the brain [83–85]. Tobacco and marijuana smoking-related carcinogens also may potentially enter the brain via the intranasal pathway, which bypasses the blood–brain barrier [86,87]. Furthermore, the carcinogenic effects of smoking may be due to immunologic or hormonal factors not influenced by the blood–brain barrier.

Our finding of a significant dose-response trend between increasing amounts of coffee consumption and MPAG has not been previously reported in the literature and requires confirmation. Only one [8] of 17 studies [3–18,28] in our review of primary adult-onset brain tumors reported results specifically for coffee drinking, and this study found no association ($RR < 1.3$) for all levels of consumption. Coffee contains various polycyclic aromatic hydrocarbons which are known carcinogens [88]. For example, benzo(a)pyrene, a compound produced in the coffee roasting process, may act as a co-carcinogen with carcinogens found in tobacco smoke [88,89]. Benzo(a)pyrene has been shown to induce brain tumors when directly injected in the brain of experimental animals [90], and animals exposed to benzo(a)pyrene manifest p53 mutations exhibiting G:C to T:A transversions, which have been linked to many smoking-related cancers [91]. Furthermore, the extracting agent trichloroethylene, known to be carcinogenic in animal studies [92–94], was once widely employed in decaffeination of coffee [95]. However, our study did not differentiate between drinkers of caffeinated *versus* decaffeinated coffee.

Our results are consistent with previously published studies that have found a null or inverse association between alcohol consumption and brain tumor risk [3,5,6,8,12,14–16,28], except for two case-control studies [5,13] reporting a positive association between

wine drinking and brain tumors, and one retrospective cohort study reporting a significantly elevated risk for brain tumor deaths among alcoholic *versus* non-alcoholic World War II veterans [29]. Our findings may be due to chance or imprecision given that risk did not significantly decrease with increasing alcohol usage and CIs included unity for all levels of alcohol usage. Further, we do not know of any established biologic mechanism that can explain an inverse association between alcohol usage and MPAG.

The interpretation of previous studies of cigarette smoking and the risk for brain tumors have been limited by the use of non-population based controls (e.g., hospital, friend, neighbor) [3,4,6,8,9,12,13,15,17] or proxy respondents [3,5,8,10,13–17]; small sample size [4,5,7,11,12]; potential recall, selection, or misclassification bias [3–6,8–17]; incomplete or missing information on smoking status, amount smoked, type of cigarette smoked, and time of smoking exposure [3–18]. In other cases, the use of restricted populations has prevented the generalization of results to the population at large [4,7,8,11,17,18]. We attempted to minimize the number and impact of the above issues by employing a multivariate, retrospective cohort design in a large, multiethnic, managed-care population and our results may better reflect the true association of smoking with risk for MPAG.

In conclusion, given the modest effects observed in the current study and our lack of understanding of how certain lifestyle factors such as cigarette and marijuana smoking, coffee consumption and alcohol usage might cause or prevent MPAG, we need further evidence on the consistency of an association in different populations and data on the reversibility of an effect. A simple association between lifestyle behaviors and MPAG is unlikely to emerge and future research will need to address these important issues. Notwithstanding such research, our study provides evidence of an elevated risk for MPAG among participants who smoked marijuana at least once a month and a dose-response association between MPAG and coffee consumption overall and for cigarette smoking among females.

Acknowledgements

This study was supported by grant #R35 CA49761 from the National Cancer Institute. We thank Harald Kipp (Division of Research, KPMCP-NC) for assistance in computer programming. Dr. Atsuko Shibata

(Division of Epidemiology, Stanford School of Medicine), Paige M. Bracci, Sarah Lopez (Department of Epidemiology and Biostatistics, UCSF School of Medicine), and Irene Tekawa (Division of Research, KPMCP-NC) offered valuable comments and suggestions during the writing of this manuscript and their knowledge and insight has been greatly appreciated. We also thank Howard A. Fine, M.D. (Chief, Neuro-Oncology Branch, NCI) and Griffith Harsh (Professor, Department of Neurosurgery, Stanford School of Medicine) for reviewing the manuscript.

References

1. Cancer Facts & Figures 2003/Cancer Prevention & Early Detection Facts & Figures 2003 (<http://www.cancer.org>). Atlanta, GA. 2003
2. Bondy M, Wrensch M: Epidemiology of primary malignant brain tumours. *Baillieres Clin Neurol* 5(2): 251–270, 1996
3. Choi N, Schuman L, Gullen W: Epidemiology of primary central nervous system neoplasms. II: case-control study. *Am J Epidemiol* 91: 467–485, 1970
4. Abramson Z, Kark J: Serum cholesterol and primary brain tumours: a case-control study. *Br J Cancer* 52: 93–98, 1985
5. Ahlbom A, Navier I, Norell S, Olin R, Spannare B: Non-occupational risk indicators for astrocytomas in adults. *Am J Epidemiol* 124: 334–337, 1986
6. Preston-Martin S, Mack W, Henderson B: Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res* 49: 6137–6143, 1989
7. Mills P, Preston-Martin S, Annegers J, Beeson L, Phillips R, Fraser G: Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. *Neuroepidemiology* 8: 266–275, 1989
8. Hochberg F, Toniolo P, Cole P: Nonoccupational risk indicators of glioblastoma in adults. *J Neuro-Oncol* 8: 55–60, 1990
9. Brownson R, Reif J, Chang J, Davis J: An analysis of occupational risks for brain cancer. *Am J Public Health* 80: 169–172, 1990
10. Schlehofer B, Kunze S, Sachsenheimer W, Blettner M, Niehoff D, Wahrendorf J: Occupational risk factors for brain tumors: results from a population-based case-control study in Germany. *Cancer Causes Control* 1: 209–215, 1990
11. Blowers L, Preston-Martin S, Mack W: Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* 8: 5–12, 1997
12. Musicco M, Filippini G, Bordo B, Melotto A, Morello G, Berrino F: Gliomas and occupational exposure to carcinogens: case-control study. *Am J Epidemiol* 116: 782–790, 1982
13. Burch J, Craib K, Choi B, Miller A, Risch H, Howe G: An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst* 78: 601–609, 1987
14. Ryan P, Lee M, North B, McMichael A: Risk factors for tumors of the brain and meninges: results from the Adelaide adult brain tumor study. *Int J Cancer* 51: 20–27, 1992
15. Zampieri P, Meneghini F, Grigoletto F, Gerosa M, Licata C, Casentini L, Longatti P, Padoan A, Mingrino S: Risk factors for cerebral glioma in adults: a case-control study in an Italian population. *J Neuro-Oncol* 19: 61–67, 1994
16. Lee M, Wrensch M, Mike R: Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). *Cancer Causes Control* 8: 12–24, 1997
17. Preston-Martin S, Paganini-Hill A, Henderson B, Pike M, Wood C: Case-control study of intracranial meningiomas in women in Los Angeles County, California. *J Natl Cancer Inst* 65: 67–73, 1980
18. Hirayama T: Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 13: 680–690, 1984
19. Zhang Z, Morgenstern H, Spitz M, Tashkin D, Yu G, Marshall J, Hsu T, Schantz S: Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev* 8: 1071–1078, 1999
20. Donald P: Marijuana smoking – possible cause of head and neck carcinoma in young patients. *Otolaryngol Head Neck Surg* 94: 517–520, 1986
21. Almadori G, Cerullo P, Ottaviani F, D’Alatri L: Marijuana smoking as a possible cause of tongue carcinoma in young patients. *J Laryngol Otol* 104: 896–899, 1990
22. Taylor F: Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. *South Med J* 81: 1213–1216, 1988
23. Sridhar K, Raub W, Weatherby N, Metsch L, Surratt H, Inciardi J, Duncan R, Anwyll R, McCoy C: Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *J Psychoactive Drugs* 26: 285–288, 1994
24. Sidney S, Quesenberry C, Friedman G, Tekawa I: Marijuana use and cancer incidence (California, United States). *Cancer Causes Control* 8: 722–728, 1997
25. Robison L, Buckley J, Daigle A, Wells R, Benjamin D, Arthur D, Hammond G: Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. *Cancer* 63: 1904–1911, 1989
26. Kuijten R, Bunin G, Nass C, Meadows A: Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res* 50: 2608–2612, 1990
27. Grufferman S, Schwartz A, Ruymann F, Maurer H: Parents’ use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. *Cancer Causes Control* 4: 217–224, 1993
28. Boeing H, Schlehofer B, Blettner M, Wahrendorf J: Dietary carcinogens and the risk for glioma and meningioma in Germany. *Int J Cancer* 53: 561–565, 1993
29. Robinette C, Hrubec Z, Fraumeni J: Chronic alcoholism and subsequent mortality in world war II veterans. *Am J Epidemiol* 109: 687–700, 1979
30. Krieger N: Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health* 82: 703–710, 1992

31. Hiatt R, Friedman G: The frequency of kidney and urinary tract diseases in a defined population. *Kidney Int* 22: 63–68, 1982
32. Karaffa M. ICD-9-CM: International classification of diseases, 9th revision, clinical modification. In: Karaffa MC (ed.) *Practice Management Information Corporation, United States*. 3rd edn., Vol 1–3. Health Care Financing Administration, Los Angeles, 1991
33. Friedman G: Effects of multiphasic health testing services (MHTS) on patients. In: Collen M (ed.) *Multiphasic Health Testing Services*. John Wiley & Sons, New York, 1978, pp 531–549
34. Percy C, Van Holten V, Muir C: *International Classification of Diseases for Oncology = ICD-O*. World Health Organization, Geneva, 1990
35. Friedman G, Habel L, Boles M, McFarland B: Kaiser Permanente Medical Care Program: Division of Research, Northern California, and Center for Health Research, Northwest Division. In: Strom B (ed.) *Pharmacoepidemiology*. 3rd edn., John Wiley & Sons, New York, 2000, pp 263–283
36. Crowder M, Kimber A, Smith R, Sweeting T: *Statistical Analysis of Reliability Data*. Chapman & Hall, London, 1991
37. Gurney J, Smith M, Bunin G: Chapter III: CNS and miscellaneous intracranial and intraspinal neoplasms. In: Ries L, Smith M, Gurney J, Linet M, Tamra T, Young J, Bunin G (eds) *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995*, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999, pp 51–63
38. Brada M, Thomas G: Tumours of the brain and spinal cord in adults. In: Peckham M, Pinedo H, Veronesi U (eds) *Oxford Textbook on Oncology*. Oxford University Press, New York, 15.2, 1995, p 2063
39. International Agency for Research on Cancer (IARC): *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Vol 38. Tobacco Smoking. Lyon, 1986, pp 199–375
40. Johnson J, Houchens, Kluwe W, Craig D, Fisher G: Effects of mainstream and environmental tobacco smoke on the immune system in animals and humans: a review. *Crit Rev Toxicol* 20: 369–395, 1990.
41. Winkelstein W: Smoking and cervical cancer – current status: a review. *Am J Epidemiol* 131: 945–957, 1990
42. Yamasaki E, Ames B: Concentration of mutagens from urine by adsorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. *Proc Natl Acad Sci USA* 74: 3555–3559, 1977
43. Petrakis N, Maack C, Lee R, Lyon M: Mutagenic activity in nipple aspirates of human breast fluid. *Cancer Res* 40: 188–189, 1980
44. Sasson I, Haley N, Hoffmann D, Wynder E, Hellberg D: Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. *N Engl J Med* 312: 315–316, 1985
45. Baron J, Rohan T: Tobacco. In: Schottenfeld D, Fraumeni J (eds) *Cancer Epidemiol Biomarkers Prev*. Oxford University Press, New York, 1996, pp 269–289
46. Hecht S, Hoffmann D: N-nitroso compounds and tobacco-induced cancers in man. In: O'Neill I, Chen J, Bartsch H (eds) *Relevance to Human Cancer of N-nitroso Compounds, Tobacco Smoke and Mycotoxins*. International Agency for Research on Cancer, Lyon, 1991, pp 54–61
47. Avtsyn A, Yablonovskaya L: Effects of disturbances in the hormonal status on experimental brain tumors. *Acta Unio Int Contra Cancrum* 20: 1519–1522, 1964
48. Law M, Hackshaw A, Allaway S, Hale A: Cigarette smoking, sex hormones and bone density in women. *Eur J Epidemiol* 13: 553–558, 1997
49. Rich R, Fleisher T, Shearer W, Kotzin B, Schroeder H (eds) *Clinical Immunology*, 2nd edn., Mosby International Limited, London, 2001
50. Hochberg F, Miller D: Primary central nervous system lymphoma. *J Neurosurg* 68: 835–853, 1998
51. Sawamura Y, de Tribolet N: Immunobiology of brain tumors and implications for immunotherapy. In: Kaye A, Laws E (eds) *Brain Tumors*. Churchill Livingstone, Edinburgh, 1995, pp 113–124
52. George J, Levy Y, Shoenfeld Y: Smoking and immunity: an additional player in the mosaic of autoimmunity. *Scand J Immunol* 45: 1–6, 1997
53. Ahsan H, Neugut A, Gammon M: Association of adenocarcinoma and squamous cell carcinoma of the esophagus with tobacco-related and other malignancies. *Cancer Epidemiol Biomarkers Prev* 6: 779–782, 1997
54. Zang E, Wynder E: Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst* 88: 183–192, 1996
55. Muscat J, Richie J, Thompson S, Wynder E: Gender differences in smoking and risk for oral cancer. *Cancer Res* 56: 5192–5197, 1996
56. Begg C, Zhang Z, Sun M, Herr H, Schantz S: Methodology for evaluating incidence of second primary cancers with application to smoking-related cancers from the surveillance epidemiology and end results (SEER) program. *Am J Epidemiol* 142: 653–665, 1995
57. Kure E, Ryberg D, Hewer A, Phillips D, Skaug V, Baera R, Haugen A: p53 mutations in lung tumours: relationship to gender and lung DNA adducts. *Carcinogenesis* 17: 2201–2205, 1996
58. Nelson H, Christiani D, Mark E, Wiencke J, Wain J, Kelsey K: Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. *J Natl Cancer Inst* 91: 2032–2038, 1999
59. Ryberg D, Hewer A, Phillips D: Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. *Cancer Res* 54: 5801–5803, 1994
60. Mollerup S, Ryberg D, Hewer A, Phillips D, Haugen A: Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients. *Cancer Res* 59: 3317–3320, 1999
61. Guengerich F, Shimada T: Activation of procarcinogens by human cytochrome P450 enzymes. *Mutat Res* 400: 201–213, 1998
62. Wei Q, Cheng L, Amos C, Wang L, Guo Z, Hong W, Spitz M: Repair of tobacco carcinogen-induced DNA adducts and

- lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst* 92: 1764–1772, 2000
63. Gold E, Leviton A, Lopez R, Gilles F, Hedley-Whyte T, Kolonel L, Lyon J, Swanson G, Weiss N, West D, Aschenbrener C, Austin D: Parental smoking and risk of childhood brain tumors. *Am J Epidemiol* 137: 620–628, 1993
 64. Filippini G, Maisonneuve P, McCredie M, Peris-Bonet R, Modan B, Preston-Martin S, Mueller B, Holly E, Cordier S, Choi N, Little J, Arslan A, Boyle P: Relationship of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. *Int J Cancer* 100: 206–213, 2002
 65. Norman M, Holly E, Ahn D, Preston-Martin S, Mueller B, Bracci P: Prenatal exposure to tobacco smoke and childhood brain tumors: results from the United States west coast childhood brain tumor study. *Cancer Epidemiol Biomarkers Prev* 5: 127–133, 1996
 66. Bunin G, Buckley J, Boesel C, Rorke L, Meadows A: Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the children's cancer group. *Cancer Epidemiol Biomarkers Prev* 3: 197–204, 1994
 67. Kuijten R, Bunin G, Nass C, Meadows A: Gestation and familial risk factors for children astrocytoma: results of a case-control study. *Cancer Res* 50: 2608–2612, 1990
 68. Howe G, Burch J, Chiarelli A, Risch H, Choi B: An exploratory case-control study of brain tumors in children. *Cancer Res* 49: 4349–4352, 1989
 69. Stjernfeldt M, Lindsten J, Berglund K, Ludvigsson J: Maternal smoking during pregnancy and risk of childhood cancer. *Lancet* 1: 1350–1352, 1986
 70. McKinney P, Stiller C: Maternal smoking during pregnancy and the risk of childhood cancer. *Lancet* 2: 519–520, 1986
 71. Cordier S, Iglesias M, Goaster C, Guyot M, Mandereau L, Hemon D: Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer* 59: 776–782, 1994
 72. Gold E, Gordis L, Tonascia J, Szklo M: Risk factors for brain tumors in children. *Am J Epidemiol* 109: 309–319, 1979
 73. Neutel C, Buck C: Effect of smoking during pregnancy on the risk of cancer in children. *J Natl Cancer Inst* 47: 59–63, 1971
 74. Schuz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J: Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol* 36: 274–282, 2001
 75. John E, Savitz D, Sandler D: Prenatal exposure to parents' smoking and childhood cancer. *Am J Epidemiol* 133: 123–132, 1991
 76. Filippini G, Farinotti M, Lovicu G, Maisonneuve P, Boyle P: Mothers' active and passive smoking during pregnancy and the risk of brain tumours in children. *Int J Cancer* 57: 769–774, 1994
 77. McCredie M, Maisonneuve P, Boyle P: Antenatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer* 56: 6–10, 1994
 78. Preston-Martin S, Yu M, Benton B, Henderson B: *N*-nitroso compounds and children brain tumors: a case-control study. *Cancer Res* 42: 5240–5245, 1982
 79. Sandler D, Everson R, Wilcox A, Browder J: Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health* 75: 487–492, 1985
 80. Rogot E, Murray J: Smoking and causes of death among US veterans: 16 years of observation. *Public Health Rep* 95: 213–222, 1980
 81. Roth M, Marques-Magallanes J, Yuan M, Sun W, Tashkin D, Hankinson O: Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta9-tetrahydrocannabinol. *Am J Respir Cell Mol Biol* 24: 339–344, 2001
 82. Hecht S: *N*-nitrosamines. In: *Environmental and Occupational Medicine*. 3rd edn., Lippincott-Raven Publishers, London, 1998, pp 1227–1238
 83. Shapiro W, Shapiro J, Walker R: Central nervous system. In: Abeloff M, Armitage J, Lichter A, Niederhuber J (eds) *Clinical Oncology*. 2nd edn., Churchill Livington, New York, 2000
 84. Roberts P: *Neuroanatomy*. 3rd edn., Springer-Verlag, New York, 1992
 85. Tuomanen E: Breaching the blood–brain barrier. *Sci Am* 268: 80–84, 1993
 86. Frey W: Bypassing the blood–brain barrier to deliver therapeutic agents to the brain and spinal cord. *Drug Deliv Technol* 2: 46–49, 2002
 87. Liu X, Fawcett J, Thorne R, DeFor T, Frey W: Intranasal administration of insulin-like growth factor-I bypasses the blood–brain barrier and protects against focal cerebral ischemic damage. *J Neurol Sci* 187: 91–97, 2001
 88. Kuratsune M, Hueper W: Polycyclic aromatic hydrocarbons in coffee soots. *J Natl Cancer Inst* 20: 37–51, 1958
 89. Challis B, Bartlett C: Possible cocarcinogenic effects of coffee constituents. *Nature* 254: 532–533, 1975
 90. Zimmerman H: Experimental brain tumors. In: Fields W, Sharkey P (eds) *The Biology and Treatment of Intracranial Tumors*. Charles C Thomas, Springfield, 1962, pp 49–74
 91. Davidson B, Hsu T, Schantz S: The genetics of tobacco-induced malignancy. *Arch Otolaryngol Head Neck Surg* 119: 1198–1205, 1993
 92. National Toxicology Program: NTP Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies). *Natl Toxicol Program Tech Rep Ser* 243: 1–174, 1990
 93. Waters E, Gerstner H, Huff J: Trichloroethylene. I. An overview. *J Toxicol Environ Health* 2: 671–707, 1977
 94. Agency for Toxic Substances and Disease Registry (ATSDR): Toxicological profile for trichloroethylene. US Department of Health and Human Services, Public Health Service, Atlanta, GA, 1997
 95. Peshin S, Lall S, Gupta S: Potential food contaminants and associated health risks. *Acta Pharmacol Sin* 23: 193–202, 2002

Address for offprints: Gary D. Friedman, M.D., M.S., Division of Research, Kaiser Permanente Medical Care Program of Northern California, 2000 Broadway, 3rd Floor, 031R16, Oakland, CA 94612-2304, USA; Tel.: 510-891-3542; Fax: 510-891-3606; E-mail: gdf@dor.kaiser.org