Coffee, Tea, Caffeine Intake, and Risk of Adult Glioma in Three Prospective Cohort Studies

Crystal N. Holick[1], Scott G. Smith[2], Edward Giovannucci[1,2,3], and Dominique S. Michaud[1,4]

Abstract

Current data suggest that caffeinated beverages may be associated with lower risk of glioma. Caffeine has different effects on the brain, some of which could play a role in brain carcinogenesis, and coffee has been consistently associated with reduced risk of liver cancer, thus suggesting a potential anticarcinogenic effect. A total of 335 incident cases of gliomas (men, 133; women, 202) were available from three independent cohort studies. Dietary intake was assessed by food frequency questionnaires obtained at baseline and during follow-up. Cox proportional hazard models were used to estimate incidence rate ratios (RR) and 95% confidence intervals (CI) between consumption of coffee, tea, carbonated beverages, caffeine, and glioma risk adjusting for age and total caloric intake. Estimates from each cohort were pooled using a random-effects model. Consumption of five or more cups of coffee and tea daily compared with no consumption was associated with a decrease risk of glioma (RR, 0.60; 95% CI, 0.41-0.87; P_{trend} = 0.04). Inverse, although weaker, associations were also observed between coffee, caffeinated coffee, tea, and carbonated beverages and glioma risk. No association was observed between decaffeinated coffee and glioma risk. Among men, a statistically significant inverse association was observed between caffeine consumption and risk of glioma (RR, 0.46; 95% CI, 0.26-0.81; P_{trend} = 0.03); the association was weaker among women. Our findings suggest that consumption of caffeinated beverages, including coffee and tea, may reduce the risk of adult glioma, but further research is warranted to confirm these findings in other populations. *Cancer Epidemiol Biomarkers Prev; 19(1); 39–47. ©2010 AACR.*

Introduction

Coffee and tea, the most frequently consumed beverages in the world, contain high levels of caffeine and polyphenols. Caffeine is a complex compound that has many different properties, some of which are mutagenic, and others are anticarcinogenic, depending on experimental conditions (1). Caffeine is well known to be a stimulant of the central nervous system and has many physiologic effects on the brain, including decreasing cerebral blood flow (2, 3). Although the *in vivo* effects of caffeine on brain tumors are not known, decreased cerebral blood flow could potentially affect angiogenesis by reducing access to nutrients and oxygen. Polyphenol compounds, which have antioxidant properties (4), may also influence carcinogenesis and are present in both beverages, although the types of polyphenol differ in coffee and tea; coffee is rich in phenolic acids, whereas tea is rich in flavonoids (5). Furthermore, coffee has been consistently associated with a lower risk of liver cancer (6).

To date, only three epidemiologic studies have examined coffee intake and glioma risk (7-10); the associations for coffee intake were null in these studies. The only study to examine tea intake alone found no association with glioma risk [rate ratio (RR) = 1.26; 95% confidence interval (CI), 0.70-2.25, for high intake compared with never used regularly; ref. 9]. In contrast, inverse associations were observed in two case-control studies that combined coffee, tea, and cola drinks into "caffeinated beverages" [RR, 0.3; 95% CI, 0.1-1.2, for top versus bottom quartile, P_{trend} = 0.03 (ref. 11); RR, 0.55; 95% CI, 0.30-1.02, for top versus bottom tertile among females, but no association was noted for males (ref. 12)].

Taken together, these findings suggest that caffeinated beverages may be related to the risk of glioma. To examine whether the consumption of coffee, tea, carbonated beverages, and caffeine is associated with the risk of glioma, we conducted an analysis using data from three large prospective studies of men and women with detailed and updated dietary information and up to 24 years of follow-up.

Materials and Methods

Study Populations

The Nurses' Health Study (NHS I) was initiated in 1976, when 121,700 registered U.S. female nurses, ages 30 to 55 y returned a mailed questionnaire that assessed

Authors' Affiliations: Departments of [1]Epidemiology and [2]Nutrition, Harvard School of Public Health; and [3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and [4]Department of Epidemiology and Public Health, Faculty of Medicine, Imperial College London, London, United Kingdom

Corresponding Author: Dominique S. Michaud, Imperial College London, St Mary's Campus, Norfolk Place, London, W2 1PG, United Kingdom. Phone: 0-20-75943426; Fax: 0-20-72621034. E-mail: d.michaud@imperial.ac.uk

information on life-style factors, medical, and smoking histories (13, 14). Similarly, the Health Professionals Follow-Up Study (HPFS) is a cohort of 51,529 U.S. male physicians, dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who were 40 to 75 y of age at enrollment in 1986. The study design and methods of dietary assessment and follow-up for the NHS II are very similar to NHS. In 1989, 116,686 women ages 25 to 42 y and living in 14 U.S. states were enrolled into the NHS II. Follow-up questionnaires are mailed biennially to all cohort members to update information on life-style factors, diet, and newly diagnosed medical conditions. The questionnaire response rate over the period of follow-up was 95% among women in the NHS I diet cohort (1980-2002) and 92% among men in the HPFS (1986-2002). The follow-up rate for the cohorts for incidence of cancer was >95% of the total possible person-years. This study was approved by the Human Research Committee of the Brigham and Women's Hospital.

Dietary Assessment

To assess dietary intake, food frequency questionnaires (FFQ) were initially collected in 1986 for 49,935 men (HPFS), in 1980 for 92,468 women (NHS I), and in 1991 for 95,391 women (NHS II), and diet was generally updated every 4 y. For the NHS I, we used a 61-item semi-quantitative FFQ at baseline in 1980 (15), which was expanded to ~130 food and beverage items in 1984, 1986, and every 4 y thereafter. For the HPFS and NHS II cohorts, baseline dietary intake was assessed using a 131-item FFQ (16). For each item, participants were asked to report their average use over the preceding year for a specified serving size of each food and beverage. Nine prespecified frequency responses were possible, ranging from never or almost never, to six or more times per day. Individual nutrient intakes were calculated by multiplying the frequency of each food or beverage consumed by the nutrient content of the specified portion size and then by summing the contributions from all foods and beverages.

We assessed intake of caffeinated coffee, decaffeinated coffee, coffee (caffeinated and decaffeinated combined), tea (caffeinated, decaffeinated, and herbal combined), and a combination of coffee and tea. Because decaffeinated and herbal tea intake was first reported on the 1998 FFQ in the cohorts, we were unable to assess decaffeinated/herbal tea intake as an independent variable in the analysis due to the lack of sufficient data. We also assessed caffeinated carbonated beverages (diet and regular) and decaffeinated carbonated beverages. Beverages whose description on the FFQ contained the word or phrase caffeine, with caffeine, or caffeinated were classified as caffeinated carbonated beverages, whereas beverages whose description on the FFQ contained the word or phrase decaffeinated, without caffeine, or caffeine-free were classified as decaffeinated carbonated beverages. When caffeine or one of it derivatives did not appear in the beverage description on the FFQ, assessment was classified as follows. Beverages listed as "colas" on the FFQ were classified as caffeinated carbonated beverages, whereas "other" carbonated beverages (e.g., lemon-lime, orange, grape, root beer, and ginger ale sodas) were classified as decaffeinated carbonated beverages. For both the HPFS and NHS cohorts, total caffeine intake was calculated by summing the amount of caffeine in coffee (77% of total caffeine intake), tea (13%), soda (6.6%), decaffeinated coffee (3%), chocolate (0.3%), and candies (0.1%) consumed by the study participants.

The reproducibility and validity of food and beverage intake have been described previously for the HPFS (16, 17) and the NHS I (15, 18, 19). Pearson correlations between the average intake, assessed by two 1-wk diet records completed 6 mo apart, and the baseline FFQ were 0.93 and 0.77 for coffee and tea, respectively, in the HPFS (17) and 0.78 and 0.93 for coffee and tea, respectively, in the NHS I (19).

Case Ascertainment

On each biennial questionnaire, participants were asked whether they had been diagnosed with any cancer, heart disease, or other medical conditions during the previous 2 y. When permission was received from the cases (or next of kin for decedents), medical records and pathology reports were obtained from hospitals and reviewed by study investigators who were blinded to questionnaire exposure information. Nonrespondents were called by phone in an attempt to confirm the initial cancer report and date of diagnosis. Medical records and pathology reports were requested for reported and deceased glioma cases; ~88% of glioma diagnoses were confirmed by medical, pathology, or death records. When we were unable to obtain records, we attempted to corroborate diagnoses of glioma with additional information from the participant, next of kin, or by cross-linking with cancer registries. We only included glioma cases for which a medical, pathology, or death record or other confirmation of the cancer was obtained. We included all glioma brain tumors; these included astrocytoma, glioblastoma, oligodendroglioma, ependymoma, and mixed glioma subtypes. Vital status was ascertained through next of kin and the National Death Index; both methods identify at least 98% of deaths in the cohorts (20).

We identified 133 newly diagnosed gliomas between 1986 and 2002 among men, 182 gliomas among women in the NHS I between 1980 and 2002, and 20 gliomas among women in the NHS II between 1991 and 2003.

Statistical Analysis

Person-time of follow-up was calculated from the date for return of the baseline FFQ (1980 for NHS I, 1986 for HPFS, 1991 for NHS II) until the date of glioma diagnosis, date of death from any cause, or the end of follow-up (December 31, 2004 for HPFS, May 31, 2004 for NHS I. and May 31, 2005 for NHS II), whichever came first. After excluding participants who reported a history of cancer other than nonmelanoma skin cancer or those with missing information on diet at baseline, the cohorts for analyses included 47,897 (96%) men in the HPFS followed for

up to 18 y (775,826 person-years of follow-up), 88,795 (96%) women in the NHS I who were followed for up to 24 y, and 93,963 (99%) women in the NHS II who were followed for up to 14 y (3,329,090 total person-years of follow-up among women). Over the period of follow-up, missing dietary data were carried forward form the previous follow-up cycle from which a participant had an available FFQ.

We estimated the power to detect trends across quartiles for specified incidence RRs in a comparison of the highest with the lowest quartiles, assuming a linear relation and fixing the two-tailed $\alpha = 0.05$ (21). We found a 72% power to detect a RR of 1.5 between the highest and lowest quartiles, a 91% power to detect a RR of 1.7 between the highest and lowest quartiles, and a >99% power to detect a RR of 2.0 between the highest and lowest quartiles.

Baseline dietary intakes were determined by the 1986 FFQ for men in the HPFS, the 1980 FFQ for women in NHS I, and the 1991 FFQ for women in NHS II. Cox proportional hazards models for failure time data were used to estimate the incidence RR and 95% CIs for glioma risk and to simultaneously adjust for age (5-y age groups) and total caloric intake, which minimizes extraneous variation introduced by underreporting or overreporting in the FFQ (22). Additional adjustment for potential risk factors, including processed meat intake (consists of processed meats, bacon, and hot dogs, quintiles), alcohol intake (0, 0.1-1.4, 1.5-4.9, 5.0-29.9, ≥30.0 g/d), pack-years of cigarette smoking history (<10, 10-24, 25-44, ≥45 pack-years), current smoking, and reproductive factors (status and age at menopause: premenopausal; postmenopausal, age <45 y; postmenopausal, age 45-49 y; postmenopausal, age 50-55 y; postmenopausal, age >55 y), and fruits and vegetables (quintiles) did not change the associations of beverage consumption with glioma risk.

The main analyses were based on the cumulative average intake of coffee, tea, carbonated beverages, and caffeine based on available dietary questionnaires in each cohort (1984, 1986, 1990, 1994, 1998, and 2002 in NHS I; 1990, 1994, 1998, and 2002 in HPFS; 1995, 1999, and 2003 in NHS II). The use of cumulative averages reduces within-person subject variation and better represents long-term average intake. For example, in the HPFS, dietary data from the 1986, FFQ was used for follow-up from 1986 to 1990; dietary data from the 1990 FFQ was used for follow-up from 1990 to 1994; data from the 1994 FFQ was used for follow-up from 1994 to 1998; data from the 1998 FFQ was used for follow-up from 1998 to 2002; and data from the 2002 FFQ was used for follow-up from 2002 to 2004. We also examined the relationship between recent intake of coffee, tea, carbonated beverages, caffeine, and the risk of glioma by updating diet with the most recent dietary questionnaire. Details of these methods are described elsewhere (22, 23). To minimize the possibility that baseline intake may have been altered because of preclinical disease, or for other reasons, an analysis excluding the first 2 years of follow-up was done

using baseline coffee, tea, carbonated beverages, or caffeine intake.

Additional analyses were restricted by tumor histology (astrocytoma: ICD-O: 94003, 94013, 94113, 94103, 94203, 94213; or glioblastoma: ICD-O: 94403, 94413, 94423). Tests of linear trend for increasing categories of coffee, tea, carbonated beverages, and caffeine intake were conducted by assigning the median values for each and treating those as a single continuous variable, using Cox proportional hazards regression. We nonparametrically examined, with restricted cubic splines, the possibly nonlinear relation between coffee plus tea and caffeine intake, and the RR of glioma (24). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Because of the small number of glioma cases observed in the NHS II, the NHS I and NHS II cohorts were combined; the results in the women reflect the pooled estimates of the two cohorts. Before pooling with the use of meta-analysis, tests of heterogeneity of the main exposures by cohort were done using the Q statistic, and data were pooled by using a random-effects model for the log of the RR (25); no statistically significant heterogeneity was observed unless noted otherwise. All reported P values are two tailed.

Results

The histologic distributions of the cases are provided in Table 1. Cases from the NHSII cohort had a slightly different distribution because of the age distribution; the mean age of glioma cases was 66.9 years for men, and 62.6 years and 43.7 years for women in the NHS I and NHS II, respectively. Data on histology was available for 77% of the cases. For both men (83%) and women in NHS I (70%), glioblastoma was the most common histologic type (similar to Central Brain Tumor Registry of the United States data; ref. 26); astrocytomas accounted for 14% of tumors in men and 24% of tumors in NHS I.

At baseline, men and women who had a high intake of coffee and tea (five or more cups per day) when compared with those drinking none to one cup of coffee and tea were more likely to be past or current smokers and consumed more alcohol (Table 2). Men and women with higher intakes of coffee and tea had lower intakes of vitamins C and E, and folate and lower multivitamin use than those consuming less coffee and tea. Height, body mass index, total meats, and processed meats did not vary appreciably across categories of coffee and tea consumption. Coffee and tea intake was highly correlated with caffeine consumption (Pearson correlation coefficients: NHS I, 0.87; NHS II, 0.78; HPFS, 0.73).

We observed a statistically significantly lower risk of glioma among men and women who consumed five or more cups of coffee and tea daily compared with one or less cups per day, after adjusting for age and total

Table 1. Distribution of glioma histology subtypes by cohort study

Histology	HPFS	NHSI	NHSII
Glioblastoma	70 (83%)	104 (70%)	8 (50%)
Astrocytoma	12 (14%)	35 (24%)	3 (19%)
Oligodendroglioma	0	5 (3%)	0
Ependymoma	1 (1%)	1 (1%)	2 (12%)
Mixed glioma	1 (1%)	3 (2%)	3 (19%)
Missing medical record (or subtype not specified)	49	34	4
Total glioma cases	133	182	20

caloric intake (Table 3). The cohorts were pooled in Table 3 as the associations were similar in men and women; RRs for highest versus lowest quintile for coffee and tea intake were 0.51 (95% CI, 0.27-0.95) in the HPFS, 0.67 (95% CI, 0.41-1.08) in the NHS I, and 0.37 (95% CI, 0.04-3.25) in the NHS II. After further adjustment for caffeine consumption, the inverse association between coffee and tea consumption and glioma risk was weaker and no longer statistically significant (RR, 0.68; 95% CI, 0.38-1.22). In an alternative analyses, we removed women (NHS I only)

Table 2. Age-standardized baseline characteristics by combined coffee and tea consumption among men in the HPFS (1986) and women in the NHS I (1980) and NHS II (1991)

Characteristic	Men, HPFS			Women, NHS I			Women, NHS II		
	Coffee and tea (cups/d)			Coffee and tea (cups/d)			Coffee and tea (cups/d)		
	0-1	3	≥5	0-1	3	≥5	0-1	3	≥5
No. of individuals	15,718	11,632	9,275	19,992	22,781	30,163	34,039	23,960	16,418
Age (y)	54.0	54.7	53.6	46.5	46.7	46.7	35.5	37.1	37.9
Height (inches)	70.1	70.0	70.2	64.4	64.4	64.5	64.9	64.9	65.0
Body mass index (kg/m^2)	25.3	25.7	25.9	25.0	24.4	24.4	25.1	24.3	24.8
Past smokers, %	33.8	48.4	51.3	26.5	29.3	26.2	15.6	27.1	25.3
Current smokers, %	5.7	10.8	19.1	21.0	26.7	40.4	6.9	13.5	25.8
Pack-years of cigarettes*	22.1	25.6	30.7	43.2	40.6	39.6	11.0	11.4	14.4
Daily dietary consumption									
Tea (cups)	0.1	0.4	0.9	0.2	0.7	1.5	0.2	0.7	1.7
Coffee (cups)	0.2	1.6	3.2	0.2	1.9	4.3	0.1	1.6	3.3
Carbonated beverages† (cups)	0.4	0.4	0.4	0.8	0.6	0.6	0.9	0.7	0.8
Caffeine (mg)	55	282	540	71	333	708	70	295	557
Alcohol‡ (g)	8.0	13.8	13.9	5.0	7.3	6.7	1.9	4.1	3.9
Total meat§ (servings)	1.2	1.3	1.5	1.4	1.4	1.5	1.2	1.2	1.3
Processed meat‖ (servings)	0.3	0.4	0.4	0.3	0.4	0.4	0.2	0.2	0.3
Fruits and vegetables (servings)	6.0	5.6	5.6	4.2	3.9	4.0	4.9	5.1	5.2
Vitamin C¶ (mg)	484	400	369	358	297	277	268	254	238
Vitamin Eb (mg)	57.0	48.2	43.7	43.5	34.0	31.0	26.7	24.8	24.4
Folateb (μg)	507	468	445	395	360	346	492	468	446
Multivitamin use, %	63.9	61.3	58.8	37.3	33.8	31.9	45.3	43.0	40.4

NOTE: Means or proportions.
*Pack-years are calculated for current and past smokers.
†Carbonated beverages consists of caffeinated sodas (low calorie and regular).
‡Alcohol consists of beer, wine, and liquor.
§Total meat consists of processed meats; bacon; hot dogs; hamburger; beef, pork, or lamb as a sandwich or mixed dish; beef, pork, or lamb as a main dish; chicken with skin; and chicken without skin.
‖Processed meat consists of processed meats, bacon, and hot dogs.
¶Energy-adjusted nutrient intake from diet and vitamin supplement.

who reported on the baseline (1980) FFQ having changed their coffee or tea intake substantially in the previous decade (this question was not asked in the HPFS or NHS II). We observed a similar inverse association between glioma risk and cumulative updated coffee and tea intake compared with one or less cups per day (RR, 0.70; 95% CI, 0.41-1.20); however, 95% CIs were wide because we had fewer cases in this analysis ($n = 140$).

Among coffee drinkers, which included caffeinated and decaffeinated coffee consumption, greater than three cups of coffee daily was associated with a lower although not statistically significant risk of glioma; no significant

Table 3. Cumulative updated intake of tea, coffee, carbonated beverages, and the risk of glioma among men in the HPFS (1986-2004) and women in the NHS I (1980-2004) and NHS II (1991-2005)

Beverage	Quantity of intake					Trend test *P*
Coffee and tea (cups/d)	0-1	2	3	4	≥5	
Cases/person-years	78/886,659	53/680,134	91/1,015,354	56/609,832	57/912,937	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.75 (0.44-1.26)	0.89 (0.65-1.22)	1.04[‡] (0.51-2.13)	0.60 (0.41-0.87)	0.04
Coffee (cups/d)	None	1	2	3	≥4	
Cases/person-years	47/681,953	72/858,800	54/635,722	86/1,008,541	76/919,900	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.82 (0.56-1.19)	0.71 (0.35-1.45)	0.85 (0.59-1.23)	0.80 (0.54-1.17)	0.51
Coffee, caffeinated (cups/d)	None	1	2	≥3		
Cases/person-years	79/925,585	81/871,674	121/1,635,311	54/672,346		
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.79 (0.58-1.09)	0.71 (0.53-0.95)	0.80 (0.55-1.15)		0.27
Coffee, decaffeinated (cups/d)	None	1	2	≥3		
Cases/person-years	75/1,268,472	133/1,439,836	72/830,723	55/565,885		
Pooled MV RR (95% CI)*,†	1.00 (Reference)	1.06 (0.78-1.43)	1.05 (0.68-1.62)	1.06[§] (0.71-1.58)		0.77
Tea (cups/wk)	None	1	2-3	4-7	≥8	
Cases/person-years	85/898,988	73/752,946	88/983,530	41/633,214	48/836,238	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.96 (0.70-1.32)	0.92 (0.67-1.25)	0.72 (0.42-1.23)	0.71 (0.45-1.12)	0.24
Carbonated beverages, caffeinated (cups/wk)	None	1	2	3-4	≥5	
Cases/person-years	82/734,585	91/960,836	79/859,941	40/562,424	43/987,130	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.88 (0.65-1.20)	0.94 (0.68-1.31)	0.87 (0.59-1.29)	0.75 (0.51-1.11)	0.13
Carbonated beverages, decaffeinated (cups/wk)	None	1	2	3	≥4	
Cases/person-years	83/969,370	104/1,205,497	64/657,686	53/575,895	31/696,468	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.97 (0.72-1.32)	1.11 (0.79-1.55)	1.23 (0.67-2.27)	0.75 (0.49-1.17)	0.31

NOTE: Glioma risk was assessed with relation to the cumulative average of dietary intakes, which was calculated from all dietary questionnaires (see Materials and Methods).

*Multivariate (MV) RR and 95% CI adjusted for age and total caloric intake.

†Results were obtained from pooling the β-coefficient and SEM estimates for the men and women by using the DerSimonian and Laird random-effects model. No evidence of heterogeneity by cohort was observed, except where noted by footnote ‡.

‡The DerSimonian and Laird random-effects model Test of Heterogeneity was significant ($P = 0.04$). The individual cohort multivariate RR and 95% CI adjusted for age and total caloric intake are as follows: HPFS, 1.31 (0.80-2.16); NHS I, 0.58 (0.34-0.99); NHS II, 2.10 (0.54-8.16). The number of cases/person-years associated with the individual cohorts is as follows: HPFS, 26/96,707; NHS I, 26/359,560; NHS II, 4/153,565.

§This value represents the pooled results of NHS I and HPFS only. NHS II data were collapsed into the level below due to the fact that no cases existed in the higher level.

trend of lower glioma risk was observed with increasing coffee intake. Caffeinated coffee consumption was associated with a similar lower risk of glioma compared with no consumption; however, intake of decaffeinated coffee was not related to the risk of glioma. We observed no association with the type of brewing method (i.e., filtered, instant, or espresso; asked on the 1990 questionnaire in the HPFS and NHS I) and glioma risk, controlling for the amount of coffee consumed (data not shown).

To further explore specific nutrients in tea, we examined the association between glioma risk and flavonoid intake (baseline in 1990); no association was observed between intake of total flavonoid, myricetin, kaempferol, quercetin, and glioma risk; however, fewer cases were available for those analyses (data not shown).

Intake of sugared or artificially sweetened caffeinated carbonated beverages (diet and regular) was associated with a lower although not statistically significant risk of glioma; no significant trend of lower glioma risk was observed with increasing intakes. Results for decaffeinated carbonated beverages were similar to those reported for caffeinated carbonated beverages.

Among men, there was a statistically significant inverse association between caffeine consumption and risk of glioma (Table 4). Compared with the bottom quintile of intake, the top quintile (median, 528 mg/d) was associated with a 54% lower risk of glioma; the trend was linear ($P = 0.03$; Fig. 1A). Among women, the relation between caffeine consumption and glioma risk was weaker and statistically nonsignificant (Fig. 1B). In a quintile analysis, the lowest risk was observed among women with a median intake of 378 mg/day (or the

fourth quintile of caffeine consumption) compared with women with no caffeine consumption (Table 3). Given that the brain tumor cases in NHS II differ somewhat in histologic distribution, we conducted a subanalysis to examine the results after removing this cohort study. The results for NHS I were similar for the top quintile of caffeine intake (RR, 0.94; 95% CI, 0.60-1.46, comparing highest to lowest quintile intake), but the fourth quintile was significantly inverse (RR, 0.54; 95% CI, 0.33-0.90, for the second highest compared with the lowest quintile). A similar dip in the association was observed for cumulative updated intake of coffee and tea in the NHS I (RR, 0.58; 95% CI, 0.34-0.99, fourth versus first quintile; RR, 0.67; 95% CI, 0.41-1.08, for fifth versus first quintile).

As a U-shaped association had been previously observed in the NHS cohort for caffeine and Parkinson's disease (27), and later explained with effect modification by postmenopausal hormones (28, 29), we explored the possibility of effect modification by hormone use in women. The association with caffeine among never Postmenopausal Hormone (PMH) users was slightly stronger (RR, 0.62; 95% CI, 0.24-1.60, for the top versus bottom quintile of caffeine intake) than among past PMH users (RR, 0.83; 95% CI, 0.44-1.59, for the same comparison); however, unlike with Parkinson's disease, no effect modification was observed.

In addition to the cumulative updated analyses for the intake of coffee, tea, carbonated beverages, and caffeine, we examined early (baseline diet) and recent (simple updated) intake. The analyses using cumulative updated intake produced similar although somewhat stronger results to those using baseline or simple updated intake (data not shown).

Table 4. Cumulative updated intake of caffeine, and the risk of glioma among men in the HPFS (1986-2004) and women in the NHS I (1980-2004) and NHS II (1991-2005)

	Quantity of intake					Trend test P
Men						
Caffeine (quintile)	1	2	3	4	5	
Median (mg/d)	14	73	166	307	538	
Cases/person-years	39/150,161	28/155,220	21/155,113	27/158,247	18/157,086	
MV RR (95% CI)*	1.00 (Reference)	0.66 (0.40-1.07)	0.52 (0.31-0.90)	0.67 (0.41-1.11)	0.46 (0.26-0.81)	0.03
Women						
Caffeine (quintile)	1	2	3	4	5	
Median (mg/d)	40	145	251	378	606	
Cases/person-years	44/637,951	46/671,576	39/676,961	30/675,919	43/666,682	
Pooled MV RR (95% CI)*,†	1.00 (Reference)	0.96 (0.64-1.46)	0.80 (0.52-1.23)	0.75 (0.30-1.87)	0.91 (0.60-1.40)	0.43

NOTE: Glioma risk was assessed with relation to the cumulative average of dietary intakes, which was calculated from all dietary questionnaires (see Materials and Methods).
*Multivariate RR and 95% CI adjusted for age and total caloric intake.
†Results were obtained from pooling the β-coefficient and SEM estimates for the women by using the DerSimonian and Laird random-effects model. No significant evidence of heterogeneity by cohort was observed (α = 0.05).
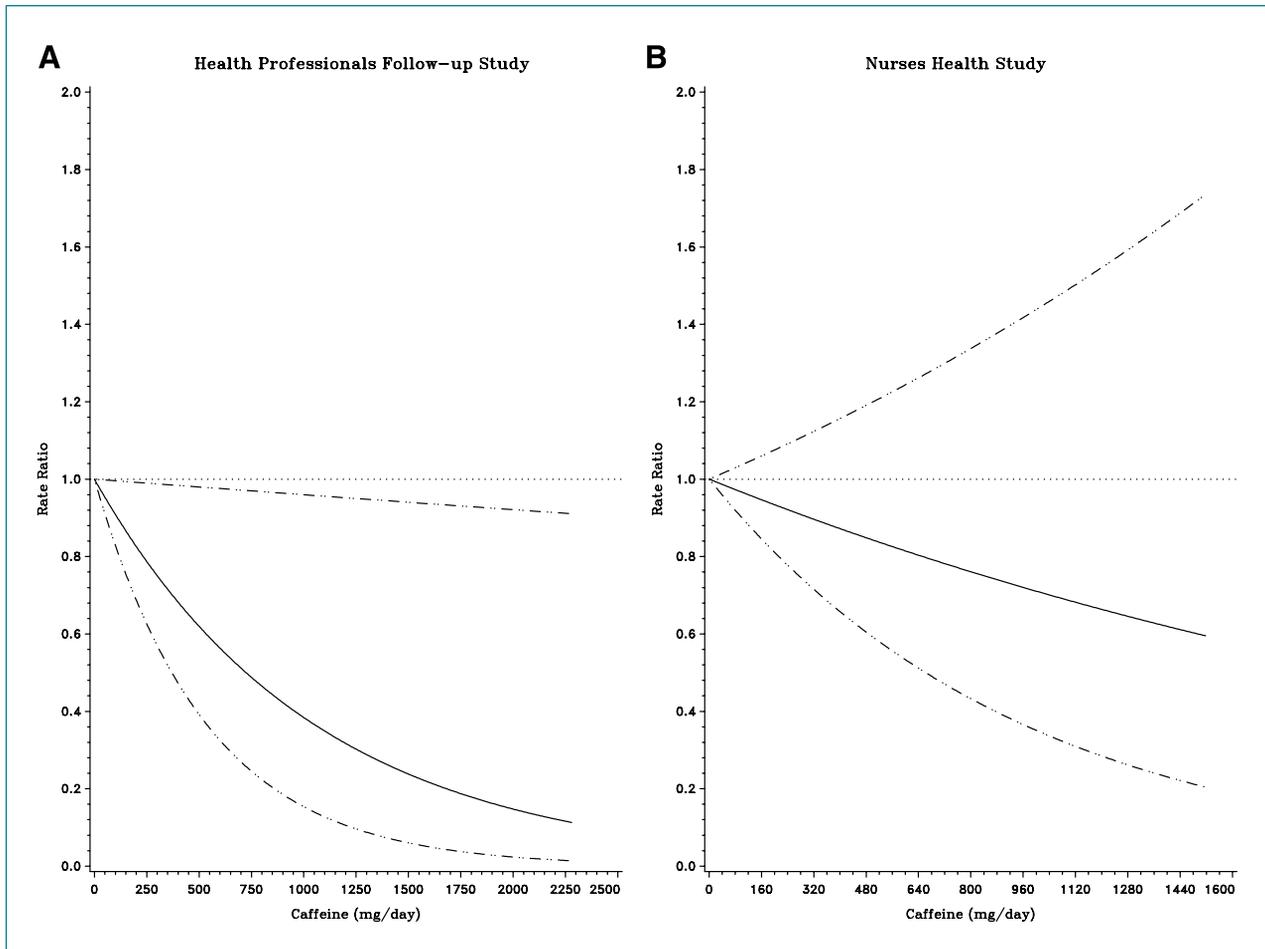
Figure 1. RR and 95% CI for cumulative updated intake of caffeine and the risk of glioma (**A**) among men in the HPFS (1986-2004) and (**B**) women in the NHS I (1980-2004), using restricted cubic splines. RR and 95% CI are adjusted for age and total caloric intake. Glioma risk was assessed in relation to the cumulative average of dietary intakes, which was calculated from all dietary questionnaires (see Materials and Methods.

Because individuals may have altered their diet due to preclinical manifestations of disease, we repeated our analyses (using baseline diet; 1980 for NHS I, 1986 for HPFS, and 1991 for NHS II) after excluding the first 2 years of follow-up. Such analyses, compared with cumulative updated analyses, did not lead to substantially different findings for any of the beverages (data not shown).

Results restricted to cases with a diagnosis of astrocytoma or glioblastoma, or cases confirmed by pathology records were similar to analyses that considered all cases. The relative risk for the highest versus lowest intake of coffee and tea for risk of glioblastoma was 0.50 (95% CI, 0.21-1.18).

Discussion

Using data from three prospective cohort studies, we observed a consistent inverse association for a combined intake of coffee and tea and risk of glioma. Caffeine in-take was inversely related to risk in men, but the association was less apparent in women.

Few observational studies have examined the association between tea, coffee, and other caffeinated drinks; caffeine intake; and glioma risk (7-12); interpretation of the literature is difficult given that these studies report on only one or a combination of these beverages in relation to glioma risk, and most had limited data on intake. For example, in one study, no association was reported for high average weekly consumption of "other drinks" defined as regular nondiet soft drinks, diet soft drinks, caffeinated coffee, decaffeinated coffee, tea, lemon in tea, milk or cream in coffee or tea, and sugar in coffee or tea, compared with low intake (10). Inverse associations were observed among women in two studies where results were provided for combined caffeinated beverages (defined as cola, coffee, or tea). In one study of women, a decreased glioma risk was observed with increasing intake (P_{trend} = 0.03; ref. 11). In a second study, an inverse association was observed among women

[odds ratio (OR) 0.55; 95% CI, 0.30-1.02, top versus bottom tertile of caffeinated beverages], but no consistent trend was observed among men (12).

Regular intake of tea was not associated with glioma risk (OR, 1.26; 95% CI, 0.70-2.25, for high intake, ≥41,000 6-ounce lifetime cups, compared with never used regularly) in the only case-control study to report on tea (9). In the same study, no association was observed for coffee consumption (RR, 1.40; 95% CI, 0.76-2.58, for ≥38,000 6-ounce lifetime cups versus, never used regularly; ref. 9), and similarly, no association was observed for coffee intake in another case-control study (8). In a cohort of over 133,000 subscribers to the Kaiser Permanente Medical Care Program, 130 glioma cases were identified over an average of 13 years of follow-up (7). This study reported a suggestive positive association between coffee consumption and glioma risk ($P_{trend} = 0.05$; RR 1.7; 95% CI, 0.8-3.6 for more than or equal to seven cups of coffee per day in the past year compared with less than one cup per day).

Results for cola drinks are inconsistent; in one case-control study, intake of cola drinks was inversely associated with glioma risk among men (OR, 0.37; 95% CI, 0.19-0.70) and women (OR, 0.39; 95% CI, 0.17-0.91; ref. 12), whereas in a second study, no association between regular intake of soft drinks and glioma risk was observed (9).

Polyphenols, including phenolics acids and flavonoids, are abundant in coffee and tea, respectively (5). These dietary constituents are known for their antioxidative activities, modulation of xenobiotic metabolite enzymes, and inhibition of tumor promotion (30), and have shown to possibly protect against cancer (31, 32). Coffee and tea are also a dietary source of caffeine; on average, the levels of caffeine in tea are lower than those in coffee (33). Caffeine has been studied extensively, and it has been found to both increase and decrease malignant cell development by altering cell cycle checkpoint function, several mechanisms of DNA repair, apoptosis, and key regulatory proteins, including the tumor suppressor protein, p53, as well as carcinogen metabolism (34). In addition, caffeine has substantial influence on the central nervous system, including decreasing cerebral blood flow (2), which could influence brain carcinogenesis; the exact mechanism, however, if a causal association exists, will have to be elucidated.

In the current study, we collected information on tea, caffeinated and decaffeinated coffee, caffeinated soda, total caffeine intake (calculated from all caffeinated beverages and foods), and also on the brewing method typically used for brewing coffee, which may be important as specific methods (e.g., filtered, instant) may affect the concentration of certain compounds found in coffee, including caffeine. We observed a suggestive decrease in glioma risk for high daily consumption of tea, and although flavonoid intake was not associated with glioma risk, we were unable to examine the most abundant flavonoids found in tea. Furthermore, we were unable to distinguish between caffeinated, decaffeinated, or herbal teas.

The strengths of our study include its large number of brain cancer cases ($n = 355$), the prospective design, long follow-up, and detailed and updated information on tea, caffeinated and decaffeinated coffee, and caffeine intake. The prospective design precludes recall bias, and selection bias is minimized by the very high rate of follow-up over a long period of time. No proxies were needed as information on diet was obtained before the occurrence of disease. The availability of repeated dietary measures in the cohorts permits a consideration of early (baseline), most recent (simple update), and long-term (cumulative updated and restricted analyses) dietary intake. We cannot exclude measurement error due to self-reported diet as a contributor to the lack of associations in the current study; however, we have previously shown the accuracy of self-reported beverage intake in these cohorts, and the repeated assessment of dietary intake may reduce within-person subject variation and better represent long-term average intake. However, we cannot exclude the possibility that these results are due to chance.

Overall, our findings suggest that a high intake of coffee and tea reduces the risk of glioma in both men and women. The results for total caffeine intake, derived from drinks and food, were less consistent across men and women, and suggest that the association may be more complex in women. Our findings are especially noteworthy, considering that there are no modifiable risk factors for brain tumors at this time, but because this is the first study to examine these beverages in detail, they need to be confirmed in other populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Grant Support

References

1. Nehlig A, Debry G. Potential genotoxic, mutagenic and antimuta-genic effects of coffee: a review. Mutat Res 1994;317:145–62.
2. Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res Brain Res Rev 1992;17:139–70.
3. Lunt MJ, Ragab S, Birch AA, Schley D, Jenkinson DF. Comparison of caffeine-induced changes in cerebral blood flow and middle cerebral artery blood velocity shows that caffeine reduces middle cerebral artery diameter. Physiol Meas 2004;25:467–74.
4. Croft KD. The chemistry and biological effects of flavonoids and phenolic acids. Ann N Y Acad Sci 1998;854:435–42.
5. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000;130:2073–85S.
6. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. Gastroenterology 2007;132:1740–5.
7. Efird JT, Friedman GD, Sidney S, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. J Neurooncol 2004;68:57–69.
8. Hochberg F, Toniolo P, Cole P, Salcman M. Nonoccupational risk indicators of glioblastoma in adults. J Neurooncol 1990;8:55–60.
9. Burch JD, Craib KJ, Choi BC, et al. An exploratory case-control study of brain tumors in adults. J Natl Cancer Inst 1987;78:601–9.
10. Lee M, Wrensch M, Miike R. Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). Cancer Causes Control 1997;8:13–24.
11. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). Cancer Causes Control 1997;8:5–12.
12. Giles GG, McNeil JJ, Donnan G, et al. Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. Int J Cancer 1994;59:357–62.
13. Belanger CF, Hennekens CH, Rosner B, Speizer FE. The Nurses' Health Study. Am J Nurs 1978;78:1039–40.
14. Colditz G. The Nurses' Health Study: findings during 10 years of follow-up of a cohort of U.S. women. Curr Prob in Obstet Gynecol Fertil 1990;13:130–74.
15. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
16. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of a expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
17. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
18. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99.
19. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
20. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
21. Chapman D, Nam J. Asymptotic power of χ^2 tests for linear trends in proportions. Biometrics 1968;24:315–27.
22. Willett WC. Nutritional Epidemiology. 2nd ed. New York: Oxford University Press; 1998.
23. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.
24. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–61.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
26. CBTRUS. Statistical Report: Primary Brain Tumors in the United States, 1998-2002: Central Brain Tumor Registry of the United States. 2005.
27. Ascherio A, Zhang SM, Hernan MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol 2001;50:56–63.
28. Ascherio A, Chen H, Schwarzschild MA, et al. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology 2003;60:790–5.
29. Ascherio A, Weisskopf MG, O'Reilly EJ, et al. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. Am J Epidemiol 2004;160:977–84.
30. Frei B, Higdon JV. Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. J Nutr 2003;133:3275–84S.
31. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. Annu Rev Pharmacol Toxicol 2002;42:25–54.
32. Ju J, Lu G, Lambert JD, Yang CS. Inhibition of carcinogenesis by tea constituents. Semin Cancer Biol 2007;17:395–402.
33. Barone JJ, Roberts HR. Caffeine consumption. Food Chem Toxicol 1996;34:119–29.
34. Bode AM, Dong Z. The enigmatic effects of caffeine in cell cycle and cancer. Cancer Lett 2007;247:26–39.