Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study[1–3]

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ABSTRACT

Background: In a recent US cohort study, total coffee and tea consumption was inversely associated with risk of glioma, and experimental studies showed that caffeine can slow the invasive growth of glioblastoma.

Objective: The objective was to examine the relation between coffee and tea intake and the risk of glioma and meningioma in a large European cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC).

Design: Data on coffee and tea intake were collected from men and women recruited into the EPIC cohort study. Over an average of 8.5 y of follow-up, 343 cases of glioma and 245 cases of meningioma were newly diagnosed in 9 countries. We used Cox proportional hazards models to examine the relation between coffee and tea and brain tumors.

Results: We observed no associations between coffee, tea, or combined coffee and tea consumption and risk of either type of brain tumor when using quantiles based on country-specific distributions of intake. However, a significant inverse association was observed for glioma risk among those consuming ≥100 mL coffee and tea per day compared with those consuming <100 mL/d (hazard ratio: 0.66; 95% CI: 0.44, 0.97; $P = 0.03$). The association was slightly stronger in men (hazard ratio: 0.59; 95% CI: 0.34, 1.01) than in women (hazard ratio: 0.74; 95% CI: 0.42, 1.31), although neither was statistically significant.

Conclusions: In this large cohort study, we observed an inverse association between total coffee and tea consumption and risk of glioma that was consistent with the findings of a recent study. These findings, if further replicated in other studies, may provide new avenues of research on gliomas. *Am J Clin Nutr* 2010;92:1145–50.

INTRODUCTION

The etiology of brain tumors is poorly understood, and known risk factors, namely ionizing radiation and genetic predisposition, affect only a small proportion of the total population, which provides little opportunity for prevention. In Europe, the age-adjusted incidence rates for brain and nervous system tumors range between 4 and 6 per 100,000 person-years in women and between 6 and 8 per 100,000 person-years in men (1). Reported increases in incidence rates of brain tumors have been mostly attributed to improvements in diagnosis and classification (2).

A recent study in the United States with 335 incident cases of glioma from 3 large prospective cohorts reported a strong inverse association between total coffee and tea intake and risk of glioma (relative risk: 0.60; 95% CI: 0.41, 0.87 for ≥5 vs 0–1 cups/d; P for trend = 0.04) (3). An inverse association was also noted for caffeine intake, which was stronger in men than in women. Only 6 other epidemiologic studies, 1 cohort and 5 case-control studies, have measured the association between coffee, tea, or caffeinated beverages and glioma risk, and the results have been inconsistent (4–9). Caffeine has been inversely associated

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with many brain-related diseases, including Parkinson (10) and Alzheimer (11) diseases. In addition, coffee consumption has been reported to be inversely associated with liver cancer (12) and has been shown to reduce subclinical inflammation in a clinical trial (13).

Given the limited evidence suggesting that coffee and tea intake may reduce the risk of glioma, more studies are needed to address this hypothesis. Furthermore, the relation between coffee and tea intake and the risk of meningioma has not been examined to date. In this study, we examined the relation between coffee and tea intake and risk of glioma and meningioma in the prospective cohort study European Prospective Investigation into Cancer and Nutrition study (EPIC). This is the first study to examine coffee and tea intake and brain tumors in a European population.

SUBJECTS AND METHODS

EPIC is an ongoing prospective cohort study conducted in 10 European countries that was designed to investigate causes of cancer. The cohort consists of 521,448 male and female subjects, mostly aged 25–70 y, who were recruited between 1991 and 2000, usually from the general population residing within defined geographic areas (ie, towns or provinces), with some exceptions: women who were members of a health insurance scheme for state school employees (France), women attending breast cancer screening (Utrecht, the Netherlands and Naples, Italy), blood donors (some centers in Italy and Spain), and predominantly vegetarians (Oxford "health conscious" cohort). Eligible subjects were invited to participate in the study by mail or by personal contact. Those who decided to participate signed an informed consent form and were mailed a diet and lifestyle questionnaire, except for those at all of the centers in Spain, Greece, and Ragusa, where interviewer-administered questionnaires were used. In most countries, study subjects were invited to a center for blood collection and anthropometric measurements and to deliver the completed diet and lifestyle questionnaires. The questionnaires included questions on diet, smoking, alcohol drinking, education, occupation, history of previous illness and disorders or surgical operations, physical activity, and other lifestyle factors. Loss to follow-up (defined as unknown vital status at the last follow-up time) was <6% across centers. The study was approved by the Internal Review Board of the International Agency for Cancer Research on Cancer and the local ethics committees in the participating countries.

Cancer ascertainment

Cancer diagnoses are based on population cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. For France, Germany, and Greece, active follow-up was made by using a combination of different methods, including health insurance records and cancer and mortality registries. However, because of missing histology on cancer cases reported in the French cohort, France was excluded from the analysis. We included all first primary incident cases diagnosed through the end of follow-up (from January 2003 to November 2006 depending on center) using the *International Classification of Diseases–Oncology* [ICD-O] second edition (14) for glioma (9380-9460, 9505) and meningioma (9530-9537). A total of 343 glioma (165 men, 178 women) and 245 meningioma cases (54 men, 191 women) were available for these analyses.

Exposure assessment

Diet was measured over the 12 mo before recruitment by using food-frequency questionnaires specifically designed for each participating country; more details on the questionnaires can be found elsewhere (15). An interview-based dietary history method combining a questionnaire with a 7-d menu book was used in Malmö, Sweden. Participants reported consumption of coffee, tea, and herbal tea; questionnaires in some centers inquired about caffeinated and decaffeinated coffee consumption. The questionnaire for Norway did not include questions on tea intake. Participants recorded the number of cups of coffee or tea per month, week, or day; the exact structure of the questions varied

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[2] The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the Danish Cancer Society (Denmark); Ligue contre le Cancer, Société 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Medicale (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and the National Research Council (Italy); the Dutch Ministry of Public Health, Welfare and Sports (VWS); the Netherlands Cancer Registry (NKR); LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (the Netherlands); Statistics Netherlands; Norwegian Cancer Society (Norway); Health Research Fund (FIS), Regional Governments of Andalucía, Asturias, Basque Country, Murcia, and Navarra, ISCIII RETIC (RD06/0020) (Spain); the Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK; the Medical Research Council; Stroke Association; the British Heart Foundation; Department of Health, Food Standards Agency; and Wellcome Trust (United Kingdom).

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Received May 26, 2010. Accepted for publication August 6, 2010.

First published online September 15, 2010; doi: 10.3945/ajcn.2010.29876.

somewhat by country and questionnaire. Total consumption (in mL/d) was calculated for each center.

Data on tobacco use were obtained at baseline by means of questions on smoking status (current, past, or never smoker), type of tobacco (cigarettes, cigars, or pipe), number of cigarettes currently smoked, and the age when participants started and, if applicable, quit smoking. Height and weight were measured in all EPIC centers except for France, Norway, and Oxford (United Kingdom), for which self-reported height and weight were assessed via questionnaire (15). Education and occupation and other existing medical conditions were also recorded.

Statistical analyses

For this analysis, we excluded all prevalent cancers cases at baseline and individuals with incomplete follow-up (n = 27,082), those with missing dietary data (n = 6157), France because of missing histology (n = 69,427), and poorly completed questionnaires based on the ratio for energy intake compared with energy expenditure (excluding the top and bottom 1%; n = 8295). We further excluded brain cancer cases with missing histology or cases not classified as gliomas or meningiomas (n = 178). The final data set for the analysis included 410,309 participants with a mean follow-up time of 8.5 y. Person-time was calculated from the date of recruitment until the date of incident brain cancer diagnosis, death, date of last contact, or end of follow-up period, whichever came first. The hazard ratios (HRs) and their corresponding 95% CIs for brain tumors were estimated by using the Cox proportional hazards regression model, with age as the primary time variable. All models were stratified by EPIC-participating center, to account for center effects related to different recruitment and follow-up procedures, by sex, and by age at recruitment in 1-y categories and to reduce sensitivity to any violations of the proportional hazards assumption. Control for age in the models versus stratification resulted in the same associations for coffee and tea intake. For the main analyses, quantiles for the different beverages were created based on the distribution of intake within each country, given that coffee and tea vary substantially by country (especially volume and concentration of coffee). Our decision to present combined coffee and tea intake was based on the hypothesis that caffeine may play a role in risk of glioma (as described in the discussion) and because of the lack of an estimated "caffeine" variable in this data set; on average, coffee and tea intake combined are estimated to contribute 90% of all caffeine intake (3). We also conducted analyses in which categories were based on absolute volumes consumed rather than country distributions. There are no established risk factors for brain cancer in the general population, but we adjusted for BMI, smoking, and education in our final models because these variables are common cancer risk factors. However, the inclusion of these variables did not noticeably affect the coffee or tea estimates. Furthermore, among women, we examined whether menopausal status, hormone replacement therapy, and oral contraceptive (OC) use were confounding factors. Tests for trend across categories were calculated by assigning the median value to each quartile of intake and entering this variable as a continuous term in the Cox regression models. All statistical analyses were carried out with SAS 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Daily coffee and tea intake varied substantially across European countries participating in the EPIC cohort. The highest mean coffee consumption was reported in Denmark (798 mL/d) and the lowest in Italy (98 mL/d). For tea, the highest mean consumption was observed in the United Kingdom (532 mL/d) and the lowest in Spain (6.2 mL/d) (**Table 1**). Participants consuming higher volumes of coffee and tea tended to be slightly older, more educated, current smokers, and have a lower BMI (**Table 2**).

Given that the range of intakes varied substantially by country, we used the distribution of intake for each country to create quantiles of coffee, tea, and combined coffee and tea (**Table 3**). In these analyses, we observed no associations for coffee or tea in relation to either glioma or meningioma risk, and the associations were similar for men and women (data not shown). These results were similar when mutually adjusted for tea and coffee consumption in the same model (data not shown) or when controlled for hormone replacement therapy or OC use. All models with tea or coffee and tea combined excluded Norway because Norway did not have data on tea consumption.

TABLE 1
Distribution of coffee and tea intake in the data set for this analysis [EPIC (European Prospective Investigation into Cancer and Nutrition)], by country

		Coffee intake			Tea intake		
	Participants	Mean	Median	10th–90th Percentile	Mean	Median	10th–90th Percentile
			mL/d			*mL/d*	
Denmark	55,005	798	900	86–1600	302	85.7	0–900
Germany	49,478	428	392	48–864	129	21.4	0–398
Greece	25,615	181	140	11–354	9	0.5	0–11
Italy	44,507	98	90	6–180	39	5	0–150
Netherlands	36,288	552	500	125–1000	261	238	0–594
Norway[1]	35,217	416	360	60–780	—	—	—
Spain	40,003	118	93	0–275	6.2	0	0–0
Sweden	48,679	468	400	107–800	76	0	0–250
United Kingdom	75,517	378	339	4–856	532	475	2–1140

[1] No questions on tea in the dietary questionnaire.

TABLE 2
Distribution of baseline characteristics by coffee and tea intake in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort

	Coffee and tea intake combined (mL/d)			
Characteristic	<100	100–599	≥600	*P* value[1]
n	52,423	167,735	190,151	
Age at recruitment (y)	50.1 ± 10.2[2]	50.2 ± 10.1	51.9 ± 10.5	<0.001
Male (%)	32.7	33.4	36.6	<0.001
Smoking status (%)				<0.001
Never	59.4	48.8	42.9	
Former	21.7	26.6	30.7	
Current	18.9	24.6	26.4	
BMI (kg/m^2)	26.7 ± 4.6	26.0 ± 4.3	25.4 ± 4.0	<0.001
Education (%)				<0.001
None/primary	54.5	40.2	28.3	
Technical/professional	13.3	23.1	32.0	
Secondary	16.6	16.9	14.3	
University	15.6	19.8	25.4	

[1] Derived by chi-square and one-factor ANOVA or Kruskal-Wallis test.
[2] Mean ± SD (all such values).

We also examined the association with coffee and tea intake by using absolute cutoffs measured in volume (mL/d) (data not shown). No associations were observed for coffee and tea intake and risk of meningioma or glioma. However, for glioma, a suggestion of a threshold effect was observed at ≈100 mL/d. A comparison of those consuming ≥100 mL coffee and tea/d with those consuming <100 mL/d showed a statistically significant inverse association (HR: 0.66; 95% CI: 0.44, 0.97; $P = 0.03$). This inverse finding (hazard ratios: 0.21–0.81) was consistent across 6 of 7 countries, although individually the associations were not statistically significant (**Figure 1**); the Netherlands was excluded because there were no cases in the lowest category. The association was slightly stronger in men (HR: 0.59; 95% CI: 0.34, 1.01) than in women (HR: 0.74; 95% CI: 0.42, 1.31). Further control for menopausal status or OC use in women did not influence the estimates. Control for soft drinks (which

TABLE 3
Hazard ratios (HRs) and 95% CIs for coffee and tea intake and risk of glioma and meningioma in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort[1]

		Glioma		Meningioma	
	Person-years	Cases	HR[2] (95% CI)	Cases	HR[2] (95% CI)
Coffee					
Quintile					
1	682,062	57	1.0 (referent)	49	1.0 (referent)
2	737,184	83	1.21 (0.86, 1.71)	64	1.03 (0.71, 1.51)
3	706,526	77	1.15 (0.81, 1.63)	47	0.91 (0.60, 1.37)
4	644,138	62	1.27 (0.87, 1.84)	43	0.94 (0.61, 1.44)
5	723,334	64	0.98 (0.67, 1.41)	42	0.71 (0.46, 1.08)
P for trend			0.68		0.23
Tea[3]					
Quartile					
1	688,486	70	1.0 (referent)	41	1.0 (referent)
2	1,219,802	125	0.76 (0.52, 1.10)	74	0.95 (0.58, 1.55)
3	665,444	54	0.80 (0.55, 1.17)	35	0.85 (0.52, 1.37)
4	706,738	82	1.05 (0.75, 1.48)	52	1.02 (0.66, 1.60)
P for trend			0.59		0.83
Total coffee and tea[3]					
Quintile					
1	644,221	67	1.0 (referent)	49	1.0 (referent)
2	672,211	73	1.03 (0.73, 1.44)	39	0.72 (0.47, 1.10)
3	655,259	62	0.89 (0.63, 1.27)	33	0.61 (0.39, 0.95)
4	641,130	58	0.85 (0.60, 1.22)	39	0.73 (0.48, 1.12)
5	667,649	71	1.02 (0.72, 1.44)	42	0.71 (0.46, 1.10)
P for trend			0.85		0.38

[1] Quintile (or quartile for tea) cutoffs are based on the distribution of intake in each country.
[2] HRs are stratified by age, country, and sex and adjusted for smoking status, BMI, and education.
[3] Norway is excluded from these analyses (no data on tea).

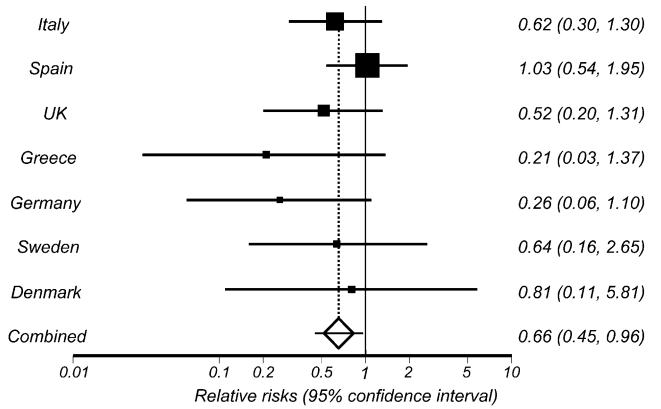

FIGURE 1. Hazard ratios and 95% CIs for glioma associated with coffee and tea intake (>100 mL/d compared with ≤100 mL/d) by country in the EPIC (European Prospective Investigation into Cancer and Nutrition) study. The Netherlands was excluded from this plot because of small numbers in the low coffee and tea group. Norway was excluded because no data were collected on tea intake.

may contain caffeine) did not modify the associations. No association was found for meningioma risk when the same cutoffs for coffee and tea intake combined (HR: 0.84; 95% CI: 0.50, 1.43) or when a higher cutoff of 200 mL/d (HR: 0.80; 95% CI: 0.50, 1.30) was used, given the suggested threshold in Table 3.

Most of the coffee consumed in this population was caffeinated because the consumption of decaffeinated coffee was very low (mean: 32 compared with 217 mL caffeinated coffee/d; based on data from Northern Italy, United Kingdom, the Netherlands, Greece, and Germany). We did not have a total caffeine variable, but we were able to examine caffeinated coffee consumption in a separate analysis; we observed no associations for this variable (data not shown). No associations were observed for herbal tea intake and risk of glioma or meningioma when examined in the centers that had this information (data not shown).

DISCUSSION

In this large EPIC cohort, daily coffee and tea consumption of ≥100 mL was associated with a lower risk of glioma. The slightly stronger inverse association in men was consistent with a recent prospective cohort analysis in the United States (3). No associations were noted for coffee and tea and risk of meningioma.

In a recent publication, 3 prospective cohorts from the United States were combined to examine coffee, tea, and caffeine intakes in relation to glioma risk (3). An inverse association was noted for combined coffee and tea consumption: ≥5 compared with 0–1 cups coffee and tea/d (HR: 0.60; 95% CI: 0.41, 0.87). A strong inverse association for caffeine intake was observed in men in a comparison of the top with the bottom quintile of total caffeine intake (HR: 0.46; 95% CI: 0.26, 0.81). Only 5 case-control studies have examined coffee or tea intake in relation to brain tumors, and the results have been inconsistent (5–9), although 2 of these studies reported inverse associations when estimating total caffeine consumption from beverages (7, 8).

Coffee and tea both contain caffeine and many other compounds, some of which have antioxidant properties. In fact, coffee has a greater total antioxidant capacity (ie, cumulative capacity of food components to scavenge free radicals) than any given fruit or vegetable (16). Given that we did not observe an association between coffee and tea consumption and meningioma risk, it is possible that the effect of coffee, if causal, is acting late in the process of carcinogenesis by preventing tumor growth. A recent study showed that caffeine can slow the invasive growth of glioblastoma in various in vitro assays by inhibiting inositol 1,4,5 triphosphate receptor subtype 3–mediated calcium release (17). Another potential mechanism that might be implicated involves the DNA repair protein *O*6-methylguanine-DNA methyltransferase (MGMT). The coffee components kahweol and cafestol have been reported to increase MGMT activity in rat liver (18). Similarly, the tea component polyphenol (−)-epigallocatechin-3-gallate reactivates methylation-silenced genes, including MGMT, in cancer cell lines (19). The higher activation state of MGMT is thought to have a protective effect against the development of several cancer types, including colon cancer (20) and glioma (21). Furthermore, the MGMT genetic polymorphism has been associated with glioma risk (22).

Coffee and tea consumption patterns vary substantially by country. The type of brewing method used for coffee can affect the concentration of coffee substantially. For example, espresso coffee, created by forcing hot pressurized water through ground coffee, is significantly more concentrated than is coffee that is gravity-brewed (eg, filtered coffee). For example, 1 fluid oz (29.6 mL) espresso contains 64 mg caffeine, whereas 8 oz (236.6 mL) gravity-brewed coffee contains 95 mg caffeine (23). Given these differences, the total volume consumed on a daily basis may not accurately reflect the actual consumption of caffeine or the concentration of other compounds contained in tea and coffee. Thus, differences in brewing methods by country will automatically result in some measurement error when it comes to estimating caffeine or coffee and tea compounds; this may explain why the results from the EPIC study were different from those reported in the US cohorts, in whom a lower risk of glioma was apparent at a higher intake (3). Nonetheless, given the large variability in coffee concentrations due to different brewing methods and inevitable measurement error, the consistency in the inverse associations found in these 2 studies is noteworthy and is unlikely to have been due to chance alone.

This was the first study to examine the relation between coffee and tea consumption and risk of meningioma and the second prospective study to examine these beverages in relation to glioma. By using a prospective design, we avoided many typical methodologic issues that arise in retrospective studies (eg, selection and recall bias) and others that often arise when dealing with brain tumors (eg, the need for use of proxy data for deceased cases and cognitive impairment in cases). In this study, we were able to examine coffee and tea consumption across different countries in Europe with a large range of intakes of both beverages, but we were unable to examine different brewing methods because these data were not systematically collected in all countries. Furthermore, as with other dietary studies, there was the potential for measurement error because food-frequency questionnaires measure average intake over a 1-y period and were only administered once in the EPIC study, and we were unable to examine lifetime exposure to coffee and tea intake or different time periods. Given the few known risk factors for brain tumors, any confounding would have been due to as yet nonestablished risk factors.

Overall, in this large prospective study, we reported a lower risk of glioma for men and women consuming ≥100 mL coffee

and tea per day. No associations were observed for coffee or tea consumption and risk of meningioma. More studies are needed to confirm these observations.

The authors' responsibilities were as follows—DSM: statistical analysis and writing of the manuscript; BS and BT: recruitment and follow-up of the Heidelberg cohort; HB and MS: recruitment and follow-up of the Potsdam cohort; AT and PL: recruitment and follow-up of the Greek cohort; CS, GM, RT, VK, and AM: recruitment and follow-up of the 5 Italian cohorts; HBB-d-M and MMR: recruitment and follow-up of the Bilthoven cohort; PHMP: recruitment and follow-up of the Utrecht cohort; MA, MJS, M-DC, EA, PJ, and MD: recruitment and follow-up of the 6 Spanish cohorts; K-TK and NW: recruitment and follow-up of the Cambridge cohort; NEA and TJK: recruitment and follow-up of the Oxford cohort; JM and EW: recruitment and follow-up of the Malmo cohort; GS and DE: recruitment and follow-up of the Norway cohort; BSM and LA: recruitment and follow-up of the Umea cohort; AJ and AO: recruitment and follow-up of the Copenhagen cohort; KO and CD: recruitment and follow-up of the Aarhus cohort; and ER: coordination of the entire EPIC collaboration. All authors contributed to the interpretation of the results and preparation and approval of the final manuscript. The sponsors were not influential in the study design, data collection or analysis, interpretation of results, or writing of the manuscript. None of the authors reported a conflict of interest.

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