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Original Contribution

Coffee, Tea, and Fatal Oral/Pharyngeal Cancer in a Large Prospective US Cohort

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Epidemiologic studies suggest that coffee intake is associated with reduced risk of oral/pharyngeal cancer. The authors examined associations of caffeinated coffee, decaffeinated coffee, and tea intake with fatal oral/pharyngeal cancer in the Cancer Prevention Study II, a prospective US cohort study begun in 1982 by the American Cancer Society. Among 968,432 men and women who were cancer free at enrollment, 868 deaths due to oral/pharyngeal cancer occurred during 26 years of follow-up. Cox proportional hazards regression was used to estimate multivariable-adjusted relative risk. Intake of >4 cups/day of caffeinated coffee was associated with a 49% lower risk of oral/pharyngeal cancer death relative to no/occasional coffee intake (relative risk = 0.51, 95% confidence interval: 0.40, 0.64) (1 cup/day = 237 ml). A dose-related decline in relative risk was observed with each single cup/day consumed ($P_{trend} < 0.001$). The association was not modified by sex, smoking status, or alcohol use. An inverse association for >2 cups/day of decaffeinated coffee intake was suggested (relative risk = 0.61, 95% confidence interval: 0.37, 1.01). No association was found for tea drinking. In this large prospective study, caffeinated coffee intake was inversely associated with oral/pharyngeal cancer mortality. Research is needed to elucidate biologic mechanisms whereby coffee might help to protect against these often fatal cancers.

caffeine; coffee; cohort studies; head and neck cancer; mortality; oral cavity; pharynx; tea

Abbreviations: CI, confidence interval; HPV, human papillomavirus; RR, relative risk.

Oral/pharyngeal cancer is among the 10 most common cancers in the world, though less common in the United States where in 2012 an estimated 40,250 new cases and 7,850 deaths are expected to occur (1). Early stage disease is highly treatable with 82% 5-year survival. However, >60% of patients do not seek medical attention until their cancer has advanced to regional or distant stages; in these cases, long-term survival is poor at 56% and 34%, respectively (1, 2). Men are more than twice as likely as women to develop and die from cancer of the oral cavity or pharynx.

The strongest risk factors for oral/pharyngeal cancer are tobacco and alcohol use (1). Human papillomavirus (HPV), particularly HPV type 16, one of the strains which cause cervical cancer in women, is also associated with increased risk of oral/pharyngeal cancer (3). Limited evidence exists for a role of diet and nutrition in the etiology of cancers of the mouth and pharynx (4). Coffee, one of the most commonly consumed beverages worldwide, contains a variety of anitoxidants, polyphenols, and other biologically active compounds that may help to protect against development or progression of cancer (5, 6). Nine case-control and 1 prospective cohort study reported statistically significant inverse associations between coffee consumption and incident oral/pharyngeal cancer (7–16). A pooled analysis of unpublished, retrospectively collected data and a meta-analysis of published studies, mostly case-control, estimated between 35% and 40% lower relative risks for highest versus lowest daily intakes (17, 18). Two studies did not find any association between coffee drinking and oral/pharyngeal cancer (19, 20), though one, a US cohort study, did find a lower risk of pharyngeal cancer related to hot tea consumption (20).

Few studies have examined caffeinated and decaffeinated coffee separately, perhaps because of limited data on decaffeinated coffee, which is consumed less frequently and in smaller amounts than caffeinated coffee. However, a pooled analysis of both types reported an inverse association with caffeinated, but not decaffeinated, coffee intake (17). Because the decaffeination processes may alter the chemical constitution of coffee apart from caffeine extraction, it is possible that risks associated with caffeinated and decaffeinated coffee might differ. We undertook an analysis of caffeinated coffee, decaffeinated coffee, and tea intake as related to fatal oral/pharyngeal cancer in the American Cancer Society Cancer Prevention Study II, taking into account the potentially confounding effects of smoking, alcohol use, and other demographic, lifestyle, and dietary factors.

MATERIALS AND METHODS

Study population and ascertainment of oral/pharyngeal cancer deaths

The study population was selected from the 1,184,418 participants in the Cancer Prevention Study II, a prospective cohort study of mortality among men and women in the United States, begun in 1982 by the American Cancer Society (21). Participants were identified and enrolled by >77,000 volunteers in all 50 states, the District of Columbia, and Puerto Rico. The minimum age for enrollment was 45 years; younger members of the same household were enrolled if they were ≥30 years of age and at least 1 family member aged ≥45 years was enrolled. The average age of the Cancer Prevention Study II cohort at enrollment was 57 years. Participants completed a confidential, self-administered, mailed questionnaire in 1982, which included information on demographic characteristics, personal and family history of cancer and other diseases, and behavioral and dietary habits.

Participants were asked to give their current and previous daily intake amounts of several types of nonalcoholic beverages including caffeinated coffee, decaffeinated coffee, and tea. We excluded from the analysis all those who were missing beverage information ($n = 94,873$), as well as those who reported drinking excessive amounts of coffee (>20 cups) daily ($n = 1,175$) (1 cup = 237 ml). We also excluded those with prevalent cancer in 1982 ($n = 79,012$) and those with missing information on smoking status ($n = 35,286$) or alcohol use ($n = 5,391$).

Deaths occurring between enrollment and December 31, 2008, were identified through personal inquiries by American Cancer Society volunteers in September of 1984, 1986, and 1988 and automated linkage with the National Death Index thereafter (22). As of December 31, 2008, 46.0% of the participants (53.5% of the men, 40.3% of the women) had died, 53.8% were still living, and 0.2% had follow-up truncated on September 1, 1988, because of insufficient data for linkage with the National Death Index. Cause of death was ascertained for 99.3% of all known deaths.

Deaths from oral/pharyngeal cancer were defined as those who died during follow-up with cancer of the oral cavity, oropharynx, or hypopharynx (*International Classification of Diseases*, Ninth Revision, codes 141, 143–146, 148, and 149, and, beginning in 1999, Tenth Revision, codes C01–C06, C09, C10, and C12–C14) as the underlying cause of death. Deaths due to cancer of the lip, nasopharynx, and salivary glands were excluded ($n = 249$), as the clinical and etiologic features of these cancers differ from those of the cancers of interest. After all exclusions, a total of 968,432 men and women were eligible for analysis including 868 oral/pharyngeal cancer deaths.

Assessment of caffeinated coffee, decaffeinated coffee, and tea intake

At baseline, current daily intake, that is, cups/glasses/drinks per day, of caffeinated coffee, decaffeinated coffee, and tea was ascertained. Participants were also asked to report their previous amounts if their drinking habits of any of these beverages had changed in the last 10 years. For initial assessment of each beverage in relation to fatal oral/pharyngeal cancer, we defined exclusive groups of current caffeinated coffee only, caffeinated coffee plus some decaffeinated coffee or tea, tea only, decaffeinated coffee only, and tea and decaffeinated coffee with no caffeinated coffee. Daily intake of these beverages was categorized as <1 cup/day, 1–2 cups/day, 3–4 cups/day, >4 cups/day; the 2 higher intake categories of decaffeinated coffee only and tea only were collapsed because of the sparse number of deaths with >4 cups/day; intake of tea and decaffeinated coffee without caffeinated coffee was left as a single category.

Statistical analysis

Cox proportional hazards regression was used to estimate age/sex- and multivariable-adjusted hazard rate ratios with 95% confidence intervals for approximation of relative risk of death due to oral/pharyngeal cancer as related to daily intake of caffeinated coffee, decaffeinated coffee, and tea (23). Each beverage, categorized by intake, was first examined in 1 model where there was a single referent group of no tea or coffee intake of any kind. To better understand the association of caffeinated coffee with oral/pharyngeal cancer, we then examined intake of caffeinated coffee (no/occasional, 1–2 cups/day, 3–4 cups/day, >4 cups/day), while controlling for consumption of decaffeinated coffee and tea (yes/no); the no/occasional category comprised the referent group in these models. All models were stratified on single year of age at enrollment. The proportional hazards assumption for each exposure was evaluated with a likelihood ratio test comparing a model with cross-product terms for exposure and time (person-years) with a reduced model of main exposure terms and time only; both models were adjusted for covariates, and no violations of proportional hazards assumptions were found.

Covariates were chosen for their ability to confound the associations of interest as determined through univariate and stepwise models. Included in the final models were the following: sex (male/female); race (white/nonwhite); educational attainment (less than high school, high school graduate, some college or trade school, college graduate); body

mass index (weight (kg)/height (m)^2: 18.5–<25.0, 25.0–<30.0, ≥30, underweight, or missing); vegetable intake (tertiles); alcohol use (nondrinker, ≤1 drink/day (women) or ≤2 drinks/day (men), >1 drink/day (women) or >2 drinks/day (men)); and smoking status (lifetime nonsmoker and former smoker who quit ≥20 years ago, former smoker who quit >1–<10 years ago grouped by cigarettes/day (≤20/>20), former smoker who quit 10–<20 years ago by cigarettes per day (≤20/>20), current or recent smoker (i.e., quit ≤1 year ago) by cigarettes per day (≤20/>20), and smoker with incomplete data). Family history of oral/pharyngeal cancer, marital status, dietary fat, exercise, and consumption of milk and carbonated beverages were evaluated but not included in final models, as the influence of these variables on the associations of interest was found to be negligible (<2% change in relative risks). All relative risks reported in the text are multivariable adjusted.

To evaluate potential effect modification, we examined the associations by strata of sex, smoking status, and alcohol use; likelihood ratio tests for statistical interaction were conducted by comparing multivariable models with interaction terms with a multivariable model with main effects terms only. Tests for linear trend of oral/pharyngeal cancer mortality in relation to coffee and tea were conducted by modeling exposure as continuous cups/day and deriving the *P* value from the Wald chi-square statistic (24). All tests of statistical significance were 2 sided.

We evaluated the potential for misclassification bias due to changing coffee drinking habits by restricting the analysis to those who reported consistent coffee intake over the 10-year period preceding enrollment. To address the potential for reverse causation arising from modification or cessation of coffee drinking due to early symptoms of undiagnosed disease, we repeated the analysis excluding the first 3 years of follow-up.

RESULTS

Only 3.4% of the study population reported drinking no coffee or tea. Coffee drinkers comprised the majority with 25.3% of participants reporting consumption of caffeinated coffee only and an additional 41.7% reporting caffeinated coffee in addition to some decaffeinated coffee and/or tea. Drinkers of decaffeinated coffee only, tea only, and drinkers of decaffeinated coffee and tea (no caffeinated coffee) made up 10.1%, 9.2%, and 10.3% of the population, respectively.

Greater than 60% of the study participants reported daily consumption of at least 1 cup/day of caffeinated coffee; among these, the average amount consumed per day was 3 cups. Several risk factors for oral/pharyngeal cancer, particularly smoking status and alcohol use, varied according to caffeinated coffee intake (Table 1). Those who reported drinking >4 cups/day were much more likely to be current/recent smokers than those who reported lesser amounts of coffee. Heavy alcohol use was also positively associated with caffeinated coffee intake. Men were more likely than women to report higher (>4 cups/day) consumption, and college graduates comprised the greatest proportion of moderate coffee drinkers (1–4 cups/day). Consumption of decaffeinated coffee and tea was inversely associated with intake of caffeinated coffee.

As shown in Table 2, no associations between caffeinated coffee intake and oral/pharyngeal cancer mortality were evident in age/sex-adjusted models. However, after further adjustment for smoking, alcohol use, and other confounders, a strong inverse association emerged. The risk of death from this cancer was 42% lower among those who reported drinking >4 cups/day of caffeinated coffee only relative to no coffee or tea, and it was 55% lower among those who reported >4 cups/day of caffeinated coffee in addition to some decaffeinated coffee or tea. The relative risk for decaffeinated coffee intake was lower among those with daily intake of >2 cups/day, but the estimate was of marginal statistical significance (relative risk (RR) = 0.61, 95% confidence interval (CI): 0.37, 1.01). Relative risk estimates for tea were consistent with a null finding.

In models comparing daily caffeinated coffee intake with no/occasional caffeinated coffee and adjustment for all confounders including decaffeinated coffee and tea consumption, an approximately 50% lower relative risk of oral/pharyngeal cancer death associated with >4 cups/day was evident in both men and women separately (Table 3) and combined (RR = 0.51, 95% CI: 0.40, 0.64) (text only). When caffeinated coffee intake was modeled as continuous cups/day, a dose-related decline in risk of oral/pharyngeal cancer death was evident, with the lowest relative risk observed for men and women reporting intake of 5 cups/day (RR = 0.42) ($P_{trend} < 0.001$) (Figure 1).

There was little variation in the association between caffeinated coffee intake and oral/pharyngeal cancer mortality by smoking status or alcohol use, and there was no statistically significant interaction (Table 3). Reductions in oral/pharyngeal cancer mortality were observed in current/recent and former smokers who consumed >2 cups/day of caffeinated coffee compared with the no/occasional group, but the association was most pronounced among those who were nonsmokers for the past ≥20 years (RR = 0.36, 95% CI: 0.23, 0.58). Similar patterns of association were observed across strata of alcohol use. Among lifelong nonsmokers who did not drink alcohol, >2 cups/day of caffeinated coffee was associated with a relative risk = 0.51 (95% CI: 0.24, 1.09) on the basis of 10 oral/pharyngeal cancer deaths among this group (text only).

Approximately 17% of participants reported a decrease in caffeinated coffee intake during the 10 years preceding enrollment, whereas 6% reported an increase during that period. Exclusion of the 23% reporting any change in coffee habits over the preceding 10 years did not alter results. Relative risks were likewise unchanged when the first 3 years of follow-up time were excluded (for >4 cups/day compared with no/occasional intake of caffeinated coffee: RR = 0.51, 95% CI: 0.40, 0.66).

DISCUSSION

In this prospective cohort study, a strong, inverse linear association was found between caffeinated coffee intake and oral/pharyngeal cancer mortality after controlling for major risk factors. The risk of death from these cancers was

Table 1. Baseline Characteristics of the Study Population According to Cups/Day[a] of Caffeinated Coffee, Cancer Prevention Study II, 1982–2008

	Caffeinated Coffee Intake											
	No/Occasional			1–2 Cups/Day			3–4 Cups/Day			>4 Cups/Day		
	No.	%	Mean Age, Years	No.	%	Mean Age, Years	No.	%	Mean Age, Years	No.	%	Mean Age, Years
	376,382	39	57	272,086	28	57	194,727	20	55	125,237	13	54
	Age-adjusted %[b,c]											
	No/Occasional			1–2 Cups/Day			3–4 Cups/Day			>4 Cups/Day		
Sex												
Women	59.9			55.3			52.9			46.8		
Men	40.1			44.7			47.1			53.2		
Race												
White	92.2			93.8			96.5			96.7		
Nonwhite	7.4			5.8			3.1			2.9		
Educational attainment												
Less than high school	14.2			11.9			12.1			15.0		
High school graduate	26.6			24.6			25.2			25.9		
Some college/trade school	28.4			28.9			29.8			29.8		
College graduate	29.6			33.5			31.9			28.3		
Body mass index[d]												
18.5–<25.0	48.9			50.3			50.5			49.5		
25.0–<30.0	35.4			35.8			36.5			37.2		
≥30.0	11.7			10.2			9.3			9.4		
Alcohol use, drinks/day												
Nondrinker	60.4			51.1			47.4			49.5		
Women ≤1/day, men ≤2/day	29.7			35.7			37.1			33.9		
Women >1/day, men >2/day	9.8			13.3			15.6			16.6		
Smoking status												
Nonsmoker for past 20 years	58.0			53.0			42.5			31.1		
Former, quit >1–19 years ago	13.6			15.6			15.9			13.7		
Current or quit ≤1 year ago	17.1			18.3			27.2			39.7		
Smoker with incomplete data	11.3			13.1			14.4			15.5		
Vegetable intake, tertiles												
Low	31.7			28.8			28.4			31.1		
Medium	29.3			31.8			31.9			31.3		
High	30.5			31.5			31.9			30.0		
Decaffeinated coffee intake, yes	59.1			28.4			20.1			15.7		
Tea intake, yes	59.5			56.4			47.6			40.6		

[a] One cup = 237 ml.
[b] Adjusted to the age distribution of the Cancer Prevention Study II male/female population.
[c] Columns may not add to 100% because of missing data.
[d] Body mass index: weight (kg)/height $(m)^2$.

approximately 50% lower in men and women who consumed 4–6 cups/day relative to no/occasional caffeinated coffee consumption. Associations were not modified by sex, smoking status, or alcohol use. An inverse association with >2 cups/day of decaffeinated coffee intake was suggested, although of marginal statistical significance. Tea intake was not associated with oral/pharyngeal cancer in these data.

Table 2. Relative Risk of Death From Oral/Pharyngeal Cancer According to Coffee and Tea Intake, Cancer Prevention Study II, 1982–2008

	No. of Deaths	Person-Years	RR[a]	95% CI	RR[b]	95% CI
No coffee or tea	25	715,986	1.00	Referent	1.00	Referent
Caffeinated coffee only						
<1 cup/day[c]	15	260,908	1.46	0.77, 2.77	0.85	0.44, 1.61
1–2 cups/day	98	1,789,806	1.39	0.90, 2.16	0.80	0.51, 1.24
3–4 cups/day	91	1,792,247	1.40	0.90, 2.17	0.68	0.44, 1.07
>4 cups/day	73	1,393,090	1.52	0.96, 2.39	0.58	0.37–0.92
					$P_{trend} = 0.01$[d]	
Caffeinated coffee, decaffeinated coffee, and tea						
<1 cup/day	44	964,436	1.30	0.79, 2.12	0.95	0.58, 1.56
1–2 cups/day	125	4,042,281	0.85	0.55, 1.30	0.60	0.39, 0.92
3–4 cups/day	86	2,518,482	1.03	0.66, 1.60	0.59	0.38, 0.92
>4 cups/day	44	1,355,476	1.00	0.61, 1.63	0.45	0.28, 0.74
					$P_{trend} < 0.001$[d]	
Decaffeinated coffee only						
<1 cup/day	18	218,888	2.09	1.14, 3.83	1.47	0.80, 2.70
1–2 cups/day	50	906,141	1.33	0.82, 2.16	0.88	0.54, 1.42
>2 cups/day	38	845,038	1.16	0.70, 1.93	0.61	0.37, 1.01
					$P_{trend} = 0.24$[d]	
Tea only						
<1 cup/day	21	454,151	1.42	0.79, 2.53	1.17	0.65, 2.09
1–2 cups/day	39	860,832	1.38	0.84, 2.28	1.14	0.69, 1.88
>2 cups/day	21	628,666	1.11	0.62, 1.98	0.79	0.44, 1.42
					$P_{trend} = 0.99$[d]	
Tea and decaffeinated coffee	80	2,066,024	1.04	0.66, 1.64	0.74	0.47, 1.16
					$P_{trend} = 0.13$[d]	

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, race, education, body mass index, alcohol use, smoking, vegetable intake, and intake of the other beverages as shown.
[c] One cup = 237 ml.
[d] *P* value obtained from the Wald test for significance of trend.

The strong inverse association between fatal oral/pharyngeal cancer and caffeinated coffee observed in our study augments the epidemiologic literature on this topic. An analysis of pooled case-control data (17) and a meta-analysis (18) found inverse associations between coffee, particularly caffeinated coffee (17), and incident oral/pharyngeal cancer. The effect estimates were of similar magnitude (for >4 cups/day vs. nondrinkers: odds ratio = 0.61, 95% CI: 0.47, 0.80; for highest vs. lowest intake: RR = 0.64, 95% CI: 0.51, 0.80) in the pooled analysis and meta-analysis, respectively. In addition, a recent case-control study in Brazil found a strong inverse association between incident oral/pharyngeal cancer and cumulative lifetime coffee consumption (for highest vs. lowest intake: adjusted odds ratio = 0.39, 95% CI: 0.16, 0.94) (16). Of only 2 prospective studies to date on this topic, a Japanese cohort study found a strong inverse association between coffee consumption and risk of oral/pharyngeal cancer (for ≥1 cups/day vs. no consumption: RR = 0.35, 95% CI: 0.16, 0.77) (7), but a large US cohort study did not find coffee to be associated with oral or pharynx cancer (20). Reasons for the null findings in the latter study are unclear; residual confounding by smoking or alcohol seems unlikely, given that the results were finely adjusted for both factors.

Although only marginally significant, our data suggest that drinking decaffeinated coffee may also be inversely related to oral/pharyngeal cancer. A beneficial effect of drinking specifically decaffeinated coffee has not been previously reported. To our knowledge, 2 studies to date have examined caffeinated and decaffeinated coffee separately (10, 17). However both studies were limited by small numbers of decaffeinated coffee drinkers with intake of >1 cup/day and may have lacked power to detect an association. The nearly 40% lower relative risk estimated in our

Table 3. Relative Risk of Death From Oral/Pharyngeal Cancer According to Caffeinated Coffee Intake, Sex, Smoking Status, and Alcohol Use, Cancer Prevention Study II, 1982–2008

	No. of Deaths	Person-Years	RR[a]	95% CI	RR[b]	95% CI
Men						
No/occasional coffee	200	2,962,353	1.00	Referent	1.00	Referent
1–2 cups/day[c] of coffee	138	2,468,624	0.84	0.68, 1.05	0.68	0.55, 0.86
3–4 cups/day of coffee	120	1,917,978	1.03	0.82, 1.30	0.67	0.52. 0.85
>4 cups/day of coffee	85	1,383,962	1.09	0.85, 1.41	0.54	0.41, 0.71
Women						
No/occasional coffee	151	4,958,717	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	85	3,363,463	0.83	0.64, 1.08	0.67	0.51, 0.88
3–4 cups/day of coffee	57	2,392,751	0.87	0.64, 1.18	0.55	0.40, 0.75
>4 cups/day of coffee	32	1,364,605	0.93	0.63, 1.36	0.45	0.30, 0.67
				$P_{interaction}$ with sex = 0.68[d]		
Nonsmoker for the past ≥20 years						
No/occasional coffee	103	4,764,754	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	54	3,195,163	0.77	0.56, 1.08	0.68	0.49, 0.95
>2 cups/day of coffee	23	2,738,327	0.44	0.28, 0.68	0.36	0.23, 0.58
Former smoker (quit smoking >1–19 years ago)						
No/occasional coffee	42	1,061,240	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	23	909,163	0.63	0.38, 1.04	0.52	0.31, 0.87
>2 cups/day of coffee	32	1,097,115	0.78	0.49, 1.23	0.63	0.40, 1.01
Current or recent smoker (quit smoking ≤1 year ago)						
No/occasional coffee	136	1,262,883	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	96	1,003,099	0.85	0.66, 1.11	0.70	0.54, 0.92
>2 cups/day of coffee	179	2,244,432	0.78	0.62, 0.98	0.64	0.50, 0.81
Smoker with incomplete information						
No/occasional coffee	70	832,194	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	50	724,662	0.83	0.58, 1.19	0.72	0.49, 1.04
>2 cups/day of coffee	60	979,420	0.86	0.61, 1.21	0.70	0.49, 0.99
				$P_{interaction}$ with smoking = 0.22[d]		
No current alcohol use						
No/occasional coffee	145	4,776,958	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	81	2,949,815	0.89	0.68, 1.17	0.77	0.58, 1.01
>2 cups/day of coffee	109	3,303,268	1.18	0.92, 1.52	0.70	0.54. 0.92
Women ≤1 drink/day, Men ≤2 drinks/day						
No/occasional coffee	113	2,383,422	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	65	2,118,523	0.63	0.47, 0.86	0.57	0.42, 0.78
>2 cups/day of coffee	76	2,620,672	0.67	0.50, 0.90	0.45	0.33, 0.61
Women >1 drink/day, Men >2 drinks/day						
No/occasional coffee	93	760,691	1.00	Referent	1.00	Referent
1–2 cups/day of coffee	77	763,749	0.81	0.60, 1.09	0.68	0.49, 0.92
>2 cups/day of coffee	109	1,135,355	0.83	0.63, 1.09	0.56	0.42, 0.75
				$P_{interaction}$ with alcohol use = 0.24[d]		

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, race, education, body mass index, alcohol use, smoking, vegetable intake, tea consumption, and decaffeinated coffee consumption.

[c] One cup = 237 ml.

[d] *P* value obtained from the likelihood ratio test for significance of interaction.

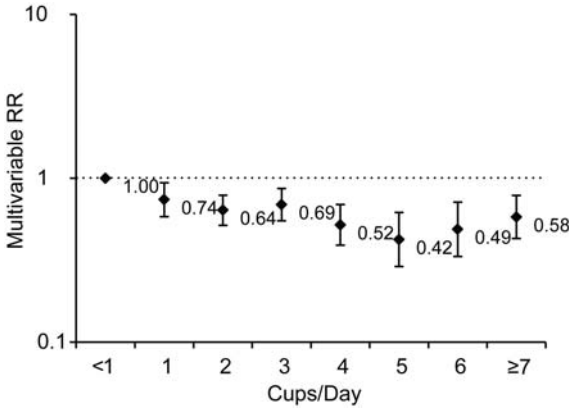

Figure 1. Multivariable relative risk (RR) of death from oral/pharyngeal cancer by single cup/day of caffeinated coffee, Cancer Prevention Study II, 1982–2008. Bars, confidence interval. P_{trend} < 0.001, obtained from the Wald test for significance of trend. One cup = 237 ml.

data for >2 cups/day of decaffeinated coffee intake warrants further investigation.

The relation between coffee intake and cancer of the oral cavity or pharynx is subject to confounding by tobacco and alcohol use; these risk factors are not only causally associated with the disease but also directly associated with coffee drinking. In our analysis, there was evidence of substantial confounding: Whereas no association between coffee and oral/pharyngeal cancer was apparent in age/sex-adjusted models, a strong inverse association emerged after further adjustment for smoking history, alcohol use, and other confounders. An observation of an inverse association of coffee with oral/pharyngeal cancer was also noted in lifelong nonsmokers who did not drink alcohol, where potential confounding by these factors is not an issue.

Strengths of this study include its prospective design, where self-reported coffee consumption is not likely to be influenced by recall bias of changes in dietary habits due to early symptoms of the cancer, especially in sensitivity analyses excluding the first few years of follow-up. The ability to control for detailed history of tobacco as well as alcohol use and other covariates is also a strength. Additionally, we were able to assess former, as well as current, baseline coffee and tea habits. Although measurement error cannot be ruled out, self-reported coffee-drinking habits using frequency questionnaires have been shown to be highly reproducible and consistent (25–27). Furthermore, the coffee consumption patterns of participants in our cohort were fairly stable in the 10 years preceding enrollment.

There are several important limitations to this study. Information on oral HPV status was not available in our cohort. However, examination of the relative risks restricted to cancers of the pharynx, the site of cancers most likely to be HPV associated, did not reveal any variation in the pattern of associations with coffee intake. Our study participants were predominantly white, middle aged or elderly, and well educated; therefore, results may not be generalizable to populations with different characteristics. Finally, the lower oral/pharyngeal cancer mortality associated with caffeinated coffee in our cohort is not directly comparable to the lower relative risks found in studies of incident cancer. Mortality rates are derived from incidence and survival. Thus, the outcome in this study reflects both risk and survival after diagnosis of oral/pharyngeal cancer in the population. It is important to note that all study participants were cancer free at enrollment. Therefore, our finding of a lower relative risk of death from oral/pharyngeal cancer, due in part to incidence of the disease, strengthens the evidence of a possible protective effect of caffeinated coffee in the etiology and/or progression of cancers of the mouth and pharynx. Whether coffee consumption is related to better prognosis after oral/pharyngeal cancer diagnosis has not, to our knowledge, been studied. This may be of considerable interest and should be investigated in survivors.

Coffee contains multiple biologically active compounds that may help to lower the risk of developing and/or dying from cancer. In addition to caffeine, the polyphenol caffeic acid and 2 coffee-specific diterpenes, cafestol and kahweol, have been studied and found in vitro and in animals to protect against oxidative DNA damage, promote apoptosis, or have antiproliferative activity (28–36). In animal/cell cultures, no single anticancer mechanism has been identified, but rather many pathways appear to be involved, depending upon the specific compound and anatomic site. Epidemiologic evidence supports probable protective associations of coffee with cancers of the liver (37) and endometrium (38), as well as a possible protective association with colorectal cancer (39–41). Although in vitro studies have been conducted in normal and malignant cells from these and several other sites, experimental and clinical studies are needed to confirm and understand the potential chemopreventive and/or antiproliferative effects of coffee in human oral cavity and pharynx tissue.

As one of the most widely consumed beverages in the world, coffee and its effects on human health are of considerable interest. Although some health conditions will preclude the consumption of any caffeinated beverages on a regular basis, our results contribute to the body of research suggesting that there may be beneficial effects to coffee, particularly caffeinated coffee, and its daily enjoyment.

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