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Research Article

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Coffee and Tea Intake and Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium

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Abstract

Background: Only a few studies have explored the relation between coffee and tea intake and head and neck cancers, with inconsistent results.

Methods: We pooled individual-level data from nine case-control studies of head and neck cancers, including 5,139 cases and 9,028 controls. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI), adjusting for potential confounders.

Results: Caffeinated coffee intake was inversely related with the risk of cancer of the oral cavity and pharynx: the ORs were 0.96 (95% CI, 0.94–0.98) for an increment of 1 cup per day and 0.61 (95% CI, 0.47–0.80) in drinkers of >4 cups per day versus nondrinkers. This latter estimate was consistent for different anatomic sites (OR, 0.46; 95% CI, 0.30–0.71 for oral cavity; OR, 0.58; 95% CI, 0.41–0.82 for oropharynx/hypopharynx; and OR, 0.61; 95% CI, 0.37–1.01 for oral cavity/pharynx not otherwise specified) and across strata of selected covariates. No association of caffeinated coffee drinking was found with laryngeal cancer (OR, 0.96; 95% CI, 0.64–1.45 in drinkers of >4 cups per day versus nondrinkers). Data on decaffeinated coffee were too sparse for detailed analysis, but indicated no increased risk. Tea intake was not associated with head and neck cancer risk (OR, 0.99; 95% CI, 0.89–1.11 for drinkers versus nondrinkers).

Conclusions: This pooled analysis of case-control studies supports the hypothesis of an inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx.

Impact: Given widespread use of coffee and the relatively high incidence and low survival of head and neck cancers, the observed inverse association may have appreciable public health relevance. *Cancer Epidemiol Biomarkers Prev; 19(7); 1723–36. ©2010 AACR.*

Introduction

Tobacco smoking and alcohol drinking are the major risk factors for cancers of the oral cavity and pharynx and of the larynx (head and neck cancers), and together are responsible of ~75% of cases diagnosed in North America and Europe (1, 2); however, other dietary and lifestyle factors, including other types of beverages, such as matè (3), may also play a role (4). Tea and coffee are the most common hot beverages in the world (5). In 1990, the International Agency for Research on Cancer evaluated the evidence of an association between coffee intake and head and neck cancers to be inadequate to reach a conclusion, based on results of six case-control studies (5). Since then, a possible association between coffee intake and risk of cancer of the oral cavity and pharynx was examined in at least two other prospective studies (6, 7) and several case-control studies (8-21).

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Table 1. Characteristics of individual studies of the INHANCE consortium pooled analysis, including information on caffeinated coffee, decaffeinated coffee, or tea drinking

Study reference*	Study location	Recruitment period	Source (cases/controls)	Information on		
				Caffeinated coffee	Decaffeinated coffee	Tea
Europe						
(32)	Italy (Milan)	1984–1989	Hospital/hospital	Yes	Yes	Yes
(33)	France	1987–1992	Hospital/hospital	Yes	No	Yes
(34, 40)	Italy multicenter (Aviano, Milan, Latina)	1990–2005	Hospital/hospital	Yes	Yes	Yes
(35)	Switzerland (Lausanne)	1991–1997	Hospital/hospital	Yes	Yes	Yes
North America						
(36)	United States (Los Angeles)	1999–2004	Cancer registry/neighborhood	Yes	Yes	Yes
(37)	United States (Boston)	1999–2003	Hospital/residential records	Yes	Yes	Yes
(1)	U.S. multicenter (Atlanta, Los Angeles, San Francisco, New Jersey)	1983–1984	Cancer registry/random digit dialing-healthcare financing	Yes	No	Yes
(38)	Memorial Sloan-Kettering Cancer Center New York	1992–1994	Hospital/hospital	Yes	Yes	Yes
Central America						
(39)	Puerto Rico	1992–1995	Cancer registry/ residential records	Yes	No	Yes
	Total subjects					

(*Continued on the following page*)

Two cohort (6, 7) and three case-control (10, 12, 19) studies reported some inverse relation, but most investigations reported inconsistent results, partly due to the limited number of cases included in each study and the different grouping of various head and neck cancers. One cohort study (22) and five case-control studies considered the association between coffee intake and laryngeal cancer risk (14, 23-26), and overall showed no relation. At least two studies considered upper aerodigestive tract cancers all together, including cancer of the esophagus besides head and neck—a multicenter case-control study, conducted in several European countries (Alcohol-Related Cancers and Genetic Susceptibility in Europe, ARCAGE; ref. 27), and a prospective study among Hawaii Japanese men (28); both found no consistent association with coffee drinking.

With reference to decaffeinated coffee, only one study considered head and neck cancers and found no consistent association (19).

Likewise, one prospective (29) and several case-control studies (9, 13-15, 19, 21, 24) found no material association between tea intake and head and neck cancer risk, whereas a prospective study among Hawaii Japanese men (28) and the ARCAGE study (27) found an inverse relation.

Given the persistent uncertainties on the issue, we considered the relationship between caffeinated, decaffeinated coffee, and tea drinking and the risk of head and neck cancers using data from a pooled analysis of studies collected by the International Head and Neck Cancer Epidemiology (INHANCE) consortium (30).

Materials and Methods

The INHANCE consortium includes 33 epidemiologic studies providing data on 24,571 cases of head and neck cancers and 33,013 controls from many countries and regions, including carcinomas of the oral cavity/pharynx and larynx, and excluding lymphomas and sarcomas, and cancers of the nasopharynx and salivary glands (30). Among the 33 studies, 23 had no information on coffee nor tea drinking and thus could not be included in this investigation. Another study was excluded because data on caffeinated coffee and tea amount were missing for 46% and 67% of cases and 28% and 51% of controls, respectively (31). Therefore, nine studies reporting information on caffeinated coffee, decaffeinated coffee, or tea drinking were included. All nine case-control studies included cancer of the oral cavity and pharynx and seven studies also included laryngeal cancer. The characteristics of the studies are reported in Table 1.

Cases were subdivided in the following sites: (*a*) oral cavity (including lip, tongue, gum, floor of mouth, and hard palate); (*b*) oropharynx (including base of tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx); (*c*) hypopharynx (including pyriform sinus); (*d*) oral cavity, pharynx unspecified or overlapping (not

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Table 1. Characteristics of individual studies of the INHANCE consortium pooled analysis, including information on caffeinated coffee, decaffeinated coffee, or tea drinking (Cont'd)

Participation rate of cases and controls (%)	Age eligibility (y)	Cancer of total oral cavity/pharynx			Cancer of larynx	Controls[†]
		Oral cavity	Oropharynx/ hypopharynx	Oral cavity/ pharynx NOS		
95[‡]–95[‡]	<80	48	61	65	242	1,531
95[‡]–95[‡]	Not reported	49	102	18	154	234
>95[‡]–95	18–80	209	502	90	460	2,716
95[‡]–95[‡]	<80	138	247	7	124	883
49–67.5	18–65	53	173	112	90	1,040
88.7–87.3	≥18	139	291	43	111	659
75–76	18–79	386	510	218	—	1,268
95[‡]–95[‡]	>20	75	26	2	43	176
71–83	21–79	94	200	521	—	521
		1,191	2,112	612	1,224	9,028

*Representative publications in which study methods are available.
[†]The total number of controls for the analyses on laryngeal cancer was 7,239, as two studies were not included (1, 39).
[‡]Participation rate was not formally assessed.

otherwise specified, NOS); (*e*) larynx (including glottis, supraglottis, and subglottis); (*f*) head and neck cancers unspecified (including overlapping lesions not listed above).

This pooled analysis is based on a total of 3,915 cases of cancer of the oral cavity and pharynx (1,191 of the oral cavity, 2,112 of oropharynx/hypopharynx, and 612 of oral cavity and pharynx NOS) and 9,028 controls from nine studies (1, 32-39), and 1,224 cases of cancer of the larynx and 7,239 controls from seven studies (32-38).

Controls were patients in hospital for acute, nonneoplastic diseases, not related to tobacco smoking and alcohol drinking, in five studies (32-35, 38), and were population-based in the other studies (1, 36, 37, 39). Two studies were multicenter themselves (refs. 1, 34; Table 1). In the present report, the Italian multicentric study also includes the most recent data from Milan (40). Results on coffee drinking from four studies included in this analysis have already been published separately (1, 32, 34, 35).

Face-to-face interviews were conducted in all studies. Informed consent was obtained from all study subjects, and the investigations were approved by relevant ethic committees according to the rules of each country and time period. Blank questionnaires were collected from all the individual studies to assess the comparability of all data collected and of the wording of the interview questions among the studies. Data from individual studies were checked for inconsistencies and pooled in a standardized way into a common database, including a range of sociodemographic, behavioral, lifestyle, and health information (30).

Questions about caffeinated coffee, decaffeinated coffee, and tea drinking were similar across studies, although the exact wording differed. Information was collected as cups of caffeinated coffee, decaffeinated coffee, or tea per day in four studies (32, 33, 37, 39), per week in two studies (34, 35) and per month in one study (38), and as open questions for two studies (1, 36). Information across studies was then converted into the variables "cups of caffeinated coffee per day," "cups of decaffeinated coffee per day," and "cups of tea per day."

Statistical analysis

The association between head and neck cancers and caffeinated coffee, decaffeinated coffee, or tea intake was assessed by estimating the odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) using unconditional logistic regression models. All models included terms for study center, age (quinquennia, categorically), sex, education level (no formal education, less than junior high school, some high school, high school graduate, vocational/some college, college graduate/postgraduate), race/ethnicity (non-Hispanic white, black, Hispanic/Latino, other), cigarette smoking (never, 1–10, 11–20, 21–30, 31–40, 41–50, >50 pack-years,

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Table 2. Distribution of cases of head and neck cancers and controls according to selected variables

	Cancer of total oral cavity/pharynx (*n* = 3,915)		Controls (*n* = 9,028)		Cancer of the larynx (*n* = 1,224)		Controls (*n* = 7,239)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Age (y)								
<40	157	(4.0)	581	(6.4)	26	(2.1)	495	(6.8)
40–44	182	(4.7)	597	(6.6)	39	(3.2)	538	(7.4)
45–49	397	(10.1)	948	(10.5)	121	(9.9)	825	(11.4)
50–54	609	(15.6)	1,457	(16.1)	180	(14.7)	1,245	(17.2)
55–59	754	(19.3)	1,604	(17.8)	262	(21.4)	1,351	(18.7)
60–64	624	(15.9)	1,320	(14.6)	247	(20.2)	1,010	(14.0)
65–69	583	(14.9)	1,253	(13.9)	211	(17.2)	925	(12.8)
70–74	410	(10.5)	927	(10.3)	112	(9.1)	692	(9.6)
≥75	199	(5.0)	339	(3.8)	26	(2.2)	156	(2.1)
Missing	0		2		0		2	
P (χ^2 test, two-sided)		<0.001				<0.001		
Sex								
Men	2,970	(76.0)	6,343	(70.3)	1,105	(90.3)	5,089	(70.4)
Women	940	(24.0)	2,680	(29.7)	118	(9.7)	2,145	(29.6)
Missing	5		5		1		5	
P (χ^2 test, two-sided)		<0.001				<0.001		
Race/ethnicity								
Non-Hispanic white	3,354	(86.0)	8,116	(90.3)	1,157	(95.0)	6,753	(93.8)
Black	293	(7.5)	378	(4.2)	27	(2.2)	134	(1.9)
Hispanic/Latino	122	(3.1)	308	(3.4)	24	(2.0)	222	(3.1)
Other*	133	(3.4)	190	(2.1)	10	(0.8)	94	(1.2)
Missing	13		36		6		3	
P (χ^2 test, two-sided)		<0.001				0.06		
Education								
No formal	13	(0.3)	31	(0.3)	9	(0.7)	31	(0.4)
Less than junior high school	1,173	(30.1)	3,635	(40.5)	675	(55.5)	3,409	(47.4)
Some high school	835	(21.4)	1,221	(13.6)	136	(11.2)	742	(10.3)
High school graduate	426	(10.9)	823	(9.2)	140	(11.5)	722	(10.0)
Vocational school, some college	1,021	(26.2)	1,987	(22.1)	147	(12.1)	1,060	(14.7)
College graduate/postgraduate	430	(11.1)	1,289	(14.3)	110	(9.0)	1,233	(17.2)
Missing	220		250		168		249	
P (χ^2 test, two-sided)		<0.001				<0.001		
Cigarette smoking (pack-years)								
Never smokers	570	(14.8)	3,571	(40.1)	58	(4.8)	2,907	(40.8)
1–10	261	(6.8)	1,477	(16.6)	71	(5.9)	1,234	(17.3)
11–20	340	(8.8)	1,039	(11.7)	130	(10.7)	881	(12.4)
21–30	452	(11.7)	873	(9.8)	191	(15.8)	707	(9.9)
31–40	540	(14.0)	696	(7.8)	230	(19.0)	552	(7.8)
41–50	448	(11.6)	452	(5.1)	187	(15.5)	336	(4.7)
>50	1,240	(32.3)	789	(8.9)	343	(28.3)	504	(7.1)
Missing	64		131		14		118	
P (χ^2 test, two-sided)		<0.001				<0.001		
Mean ± SD	3.67 ± 2.18		1.79 ± 2.00		3.98 ± 1.78		1.69 ± 1.92	
P (*t* test, two-sided)		<0.001				<0.001		
Duration of cigar smoking (y)								
Mean ± SD	1.76 ± 7.69		0.81 ± 4.96		0.96 ± 5.99		0.54 ± 3.92	
P (*t* test, two-sided)		<0.001				0.0019		

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Table 2. Distribution of cases of head and neck cancers and controls according to selected variables (Cont'd)

	Cancer of total oral cavity/pharynx (*n* = 3,915)	Controls (*n* = 9,028)	Cancer of the larynx (*n* = 1,224)	Controls (*n* = 7,239)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Duration of pipe smoking (y)				
Mean ± SD	1.27 ± 6.25	0.79 ± 4.62	0.66 ± 4.98	0.60 ± 4.03
P (*t* test, two-sided)	<0.001		0.676	
Alcohol intake (mL/d)				
Nondrinkers	356 (9.4)	1,894 (21.5)	113 (9.6)	1,618 (22.9)
>0–1	94 (2.5)	280 (3.2)	6 (0.5)	65 (0.9)
>1–3	138 (3.6)	570 (6.5)	21 (1.8)	376 (5.3)
>3–8	206 (5.4)	784 (8.9)	35 (3.0)	509 (7.2)
>8–18	398 (10.5)	1,230 (14.0)	73 (6.2)	942 (13.3)
>18–40	565 (14.9)	1,603 (18.2)	146 (12.4)	1,365 (19.3)
>40–75	640 (16.9)	1,358 (15.4)	248 (21.0)	1,245 (17.6)
>75–115	453 (11.9)	573 (6.5)	219 (18.4)	513 (7.3)
>115–155	381 (10.0)	330 (3.7)	201 (17.0)	295 (4.3)
>155	566 (14.9)	184 (2.1)	119 (10.1)	134 (1.9)
Missing	118	222	43	177
P (χ^2 test, two-sided)	<0.001		<0.001	
Mean ± SD	85.80 ± 148.65	33.17 ± 52.65	80.01 ± 70.87	35.14 ± 47.93
P (*t* test, two-sided)	<0.001		<0.001	

*Includes Brazilian, Asian and Pacific islanders, and other races.

categorically), duration of cigar smoking (continuously), duration of pipe smoking (continuously), alcohol drinking (nondrinkers, >0–1, >1–3, >3–8, >8–18, >18–40, >40–75, >75–115, >115–155, >155 mL per day, categorically), body weight (quartiles, categorically), and vegetable and fruit consumption (quartiles of intake, categorically). For subjects with missing education level (388 cases and 250 controls), we applied multiple imputations (five imputations) with the PROC MI procedure in SAS. To calculate summary estimates, the study-specific estimates were included in a two-stage random-effects logistic regression model with the maximum likelihood estimator. Pooled ORs were also estimated with a fixed-effects logistic regression model. We tested for heterogeneity among the study ORs using a likelihood ratio test comparing a model that included the product terms between each study (other than the reference study) with the variable of interest and a model without a product term, for the risk of head and neck cancers combined and of each anatomic subsite. The likelihood ratio test was assessed on the category of intake. We used the random-effects (41) estimates when heterogeneity was detected ($P < 0.05$), and the fixed-effects estimates otherwise. We also conducted an influence analysis, in which each study was excluded one at time to ensure that the statistical significance and magnitude of the overall estimates were not dependent on any one study.

The OR for consumption of more than 4 cups per day of caffeinated coffee was also calculated in strata of age, sex, geographic region, education, tobacco consumption, alcohol consumption, and vegetable and fruit intake. In stratified analyses, light tobacco users were smokers of ≤20 pack-year equivalent (combination of pack-years of cigarettes and equivalent amount of cigars or pipe). Heavy tobacco users were smokers of >20 pack-year equivalent. Light alcohol drinkers were drinkers of <3 drinks per day, and heavy alcohol drinkers were those drinking ≥3 drinks per day.

Results

Table 1 presents the characteristics of the nine case-control studies included in the pooled analysis. Of them, five were hospital based and four were population based. Four studies were conducted in Europe, four in North America, and one in Central America. The North American multicenter study (1) and the Central American study (39) did not include laryngeal cancer.

The distribution of cases at various organs within head and neck and controls according to age, sex, and other selected covariates is shown in Table 2. Males were 76% of oral cavity and pharynx and 90% of laryngeal cancer cases, and non-Hispanic whites were 86% and 95%,

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Table 3. Distribution of cases of head and neck cancers by anatomic site and of controls, and corresponding ORs and 95% CI according to caffeinated coffee, decaffeinated coffee, and tea drinking

	Oral cavity/pharynx									Larynx		
	Total			Oral cavity		Oropharynx/ hypopharynx		NOS				
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Caffeinated coffee*												
Nondrinkers	1,435	542	1†	177	1†	284	1†	81	1†	1,293	144	1†
Drinkers	7,496	3,203	0.84 (0.60–1.18)	953	0.62 (0.40–0.99)	1,739	0.82 (0.55–1.23)	511	0.76 (0.52–1.11)	5,855	1,034	1.04 (0.80–1.36)
Cups/d												
>0 to <3	4,637	1,827	0.88 (0.62–1.25)	538	0.65 (0.42–1.02)	986	0.89 (0.60–1.31)	303	0.82 (0.59–1.15)	3,796	568	1.08 (0.82–1.42)
3 to 4	2,029	851	0.78 (0.49–1.24)	259	0.52 (0.27–0.98)	465	0.73 (0.41–1.31)	127	0.70 (0.45–1.09)	1,527	335	1.12 (0.81–1.55)
>4	830	525	0.61 (0.47–0.80)	156	0.46 (0.30–0.71)	288	0.58 (0.41–0.82)	81	0.61 (0.37–1.01)	532	131	0.96 (0.64–1.45)
Missing	97	170		61		89		20		91	46	
Total	9,028	3,915		1,191		2,112		612		7,239	1,224	
P for trend			0.01		<0.01		0.02		<0.01			0.82
P for heterogeneity between studies			<0.01		<0.01		0.02		0.4			0.11
For an increment of 1 cup/d			0.96 (0.94–0.98)		0.96 (0.92–0.99)		0.95 (0.93–0.98)		0.96 (0.91–1.00)			0.99 (0.95–1.04)
Decaffeinated coffee‡												
Nondrinkers	6,102	1,845	1†	512	1†	1,076	1†	257	1†	6,102	945	1†
Drinkers	806	270	1.05 (0.85–1.29)	89	1.17 (0.81–1.69)	137	0.94 (0.72–1.23)	44	1.40 (0.93–2.12)	806	78	0.96 (0.41–2.22)
Cups/d												
>0 to <1	404	135	1.03 (0.78–1.34)	37	1.18 (0.67–2.08)	73	0.96 (0.68–1.35)	25	1.59 (0.93–2.71)	404	38	1.60 (0.37–6.85)
≥1	402	135	1.09 (0.83–1.44)	52	1.51 (0.97–2.35)	64	0.94 (0.64–1.37)	19	1.36 (0.77–2.42)	402	40	0.84 (0.34–2.06)
Missing	97	166		61		87		18		97	47	
Total	7,005	2,281		662		1,300		319		7,005	1,070	
P for trend		0.57	0.09	0.78	0.17		0.75					
P for heterogeneity between studies		0.33	0.08	0.13	0.67		0.04					
For an increment of 1 cup/d			1.03 (0.92–1.15)		1.04 (0.87–1.23)		1.04 (0.91–1.19)		0.91 (0.75–1.11)			0.91 (0.75–1.09)
Type of coffee‡												
Nondrinkers	1,004	314	1†	96	1†	180	1†	38	1†	1,004	105	1†
Only caffeinated coffee drinkers	5,093	1,530	0.92 (0.57–1.47)	416	0.77 (0.55–1.09)	895	0.92 (0.52–1.54)	219	1.08 (0.69–1.69)	5,093	839	1.15 (0.76–1.75)
Only decaffeinated coffee drinkers	271	93	1.05 (0.64–1.71)	30	1.02 (0.52–2.01)	40	0.87 (0.44–1.73)	23	1.84 (0.95–3.55)	271	33	1.86 (0.80–4.35)

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Table 3. Distribution of cases of head and neck cancers by anatomic site and of controls, and corresponding ORs and 95% CI according to caffeinated coffee, decaffeinated coffee, and tea drinking (Cont'd)

	Oral cavity/pharynx								Larynx		
	Total			Oral cavity		Oropharynx/ hypopharynx		NOS			
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Drinkers of both types	531	171	0.79 (0.51–1.21)	55	0.72 (0.39–1.33)	96	0.80 (0.46–1.38)	20	1.11 (0.54–2.29)	531	44	0.92 (0.34–2.53)
Missing	106	173		65		89		19		106	49	
Total	7,005	2,281		662		1,300		319		7,005	1,070	
P for heterogeneity between studies			<0.01		0.14		<0.01		0.25			0.02
Tea*												
Nondrinkers	4,850	2,096	1†	604	1†	1,182	1†	310	1†	3,991	779	1†
Drinkers	4,076	1,648	0.99 (0.89–1.11)	523	1.06 (0.88–1.27)	841	0.93 (0.81–1.06)	284	1.10 (0.88–1.39)	3,155	399	0.97 (0.80–1.18)
Cups/d												
≤1	3,398	1,362	1.00 (0.89–1.13)	433	1.10 (0.92–1.33)	696	0.93 (0.80–1.07)	233	1.10 (0.87–1.40)	2,670	322	0.90 (0.73–1.10)
>1	678	286	0.94 (0.77–1.16)	90	0.94 (0.68–1.29)	145	0.92 (0.71–1.18)	51	1.12 (0.74–1.69)	485	77	1.48 (1.03–2.14)
Missing	102	171		64		89		18		93	46	
Total	9,028	3,915		1,191		2,112		612		7,239	1,224	
P for trend			0.72		0.90		0.36		0.43			0.40
P for heterogeneity between studies			0.30		0.45		0.23		0.95			0.08
For an increment of 1 cup/d			0.99 (0.94–1.04)		0.98 (0.91–1.06)		0.98 (0.92–1.05)		1.02 (0.93–1.12)			1.06 (0.97–1.16)

NOTE: Random-effects estimates were used when heterogeneity was detected, and fixed-effects estimates were used otherwise. Adjusted for age, sex, race/ethnicity, education, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake, weight, and vegetable and fruit intake.

*Includes nine studies for cancer of the oral cavity and pharynx (1, 32-39) and seven studies for laryngeal cancer (32-38).

†Reference category.

‡Includes six studies for both oral cavity and pharynx and laryngeal cancers (32, 34-38).

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respectively. Cases were less educated than controls, more often smokers and heavy alcohol drinkers.

The ORs of head and neck cancer for consumption of caffeinated coffee, decaffeinated coffee, and tea are reported in Table 3. Compared with nondrinkers, the ORs of cancer of the oral cavity and pharynx combined were 0.88 (95% CI, 0.62–1.25) for <3 cups of caffeinated coffee per day, 0.78 (95% CI, 0.49–1.24) for 3 to 4 cups per day, and 0.61 (95% CI, 0.47–0.80) for >4 cups per day (*P* value of test for linear trend <0.01). The ORs among caffeinated coffee drinkers of >4 cups per day, based on nine studies, were 0.46 (95% CI, 0.30–0.71) for oral, 0.58 (95% CI, 0.41–0.82) for oropharyngeal/hypopharyngeal, and 0.61 (95% CI, 0.37–1.01) for cancer of the oral cavity and pharynx NOS (*P* value of tests for linear trend <0.01, 0.02, and <0.01). The corresponding OR for laryngeal cancer, based on seven studies was 0.96 (95% CI, 0.64–1.45). The ORs for an increment of one cup per day were 0.96 (95% CI, 0.94–0.98) for cancer of the oral cavity and pharynx [0.96 (95% CI, 0.92–0.99) for cancer of the oral cavity, 0.95 (95% CI, 0.93–0.98) for cancer of the oropharynx/hypopharynx, and 0.96 (95% CI, 0.91–1.00) for cancer of the oral cavity and pharynx NOS] and 0.99 (95% CI, 0.95–1.04) for laryngeal cancer. Further adjustment for former smoking did not materially change the results.

Information on decaffeinated coffee derived from six studies for either oral cavity and pharynx or laryngeal cancers. Decaffeinated coffee was consumed by 11% to 15% of cases of cancer of the oral cavity and pharynx and by 12% of controls, with corresponding ORs of 1.05 (95% CI, 0.85–1.29) for cancer of the oral cavity and pharynx, 1.17 (95% CI, 0.81–1.69) for oral cavity, 0.94 (95% CI, 0.72–1.23) for oropharyngeal/hypopharyngeal, and 1.40 (95% CI, 0.93–2.12) for cancer of the oral cavity and pharynx NOS. Eight percent of cases of laryngeal cancer consumed decaffeinated coffee. The corresponding OR for laryngeal cancer was 0.96 (95% CI, 0.41–2.22). The estimates were not different for consumption of <1 cup and ≥1 cup per day. When we combined information on types of coffee consumed, 73% of cases of cancer of the oral cavity and pharynx and 74% of controls were drinkers of caffeinated coffee alone, 4% of both cases and controls were drinkers of decaffeinated coffee alone, and 8% of cases and controls drank both caffeinated and decaffeinated coffee. As compared with nondrinkers of any type of coffee, the ORs for drinkers of both types of coffee were 0.79 (95% CI, 0.51–1.21) for cancer of the oral cavity and pharynx, 0.72 (95% CI, 0.39–1.33) for oral cavity, 0.80 (95% CI, 0.46–1.38) for oropharyngeal/hypopharyngeal cancer, and 1.11 (95% CI, 0.54–2.29) for cancer of the oral cavity and pharynx NOS. The corresponding OR for laryngeal cancer was 0.92 (95% CI, 0.34–2.53).

Compared with tea nondrinkers, the ORs for tea drinkers were 0.99 (95% CI, 0.89–1.11) for cancer of the oral cavity and pharynx, 1.06 for oral (95% CI, 0.88–1.27), 0.93 (95% CI, 0.81–1.06) for oropharyngeal/hypopharyngeal, 1.10 (95% CI, 0.88–1.39) for oral cavity and pharynx NOS (based on nine studies), and 0.97 (95% CI, 0.80–1.18) for laryngeal cancer (based on seven studies).

Figure 1 shows the study-specific estimates for the relation between amount of caffeinated coffee consumption and cancer of the oral cavity and pharynx. Panel A gives the ORs for >0 to <3 cups per day, panel B gives the ORs for ≥3 to ≤4 cups per day, and panel C gives the ORs for >4 cups per day, versus nondrinkers of caffeinated coffee. For an intake of >4 cups per day of caffeinated coffee, the ORs of cancer of the oral cavity and pharynx were below unity in seven studies (significant in two studies) and above unity in two studies (nonsignificant), resulting in a summary OR of 0.61 (95% CI, 0.49–0.77) with a *P* value for heterogeneity equal to 0.57.

Figure 2 shows the study-specific estimates for the relation between levels of caffeinated coffee consumption and laryngeal cancer. Panel A gives the ORs for >0 to <3 cups per day, panel B gives the ORs for ≥3 to ≤4 cups per day, and panel C gives the ORs for >4 cups per day, versus nondrinkers of caffeinated coffee. For an intake of >4 cups per day, the ORs of laryngeal cancer were close to unity in two studies, above unity in one study (nonsignificant), and below unity in three studies (significant in one), resulting in a summary OR of 0.94 (95% CI, 0.62–1.42) with *P* value for heterogeneity equal to 0.07. In sensitivity analysis, summary ORs were calculated after exclusion of one study at a time. These analyses did not reveal any notable change in the estimates, with ORs for cancer of the oral cavity and pharynx varying between 0.58 and 0.68.

Table 4 reports the ORs of cancer of the oral cavity and pharynx for caffeinated coffee intake of >4 cups per day in strata of selected covariates. There was no heterogeneity across strata of age, sex, geographic region, education, tobacco smoking, alcohol drinking, vegetable and fruit intake, and type of controls. However, the numbers of cases were small among never and light tobacco smokers.

Discussion

In this pooled analysis of case-control studies, caffeinated coffee was inversely related with the risk of cancer of the oral cavity and pharynx. The protection was similar across the oral cavity and pharyngeal sites, with a substantial amount of heterogeneity between studies. No association of caffeinated coffee drinking was found with cancer of the larynx. Data on decaffeinated coffee and tea indicated a lack of material association. However, for decaffeinated coffee, data were limited, as both the prevalence of consumption and the amount consumed by drinkers were low.

Risk estimates of cancer of the oral cavity and pharynx for caffeinated coffee drinking were heterogeneous between studies. Chemical composition of coffee beverages varies according to variety of the plant (Arabica or Robusta) and preparation; however, most studies had inadequate information on these issues. Another source

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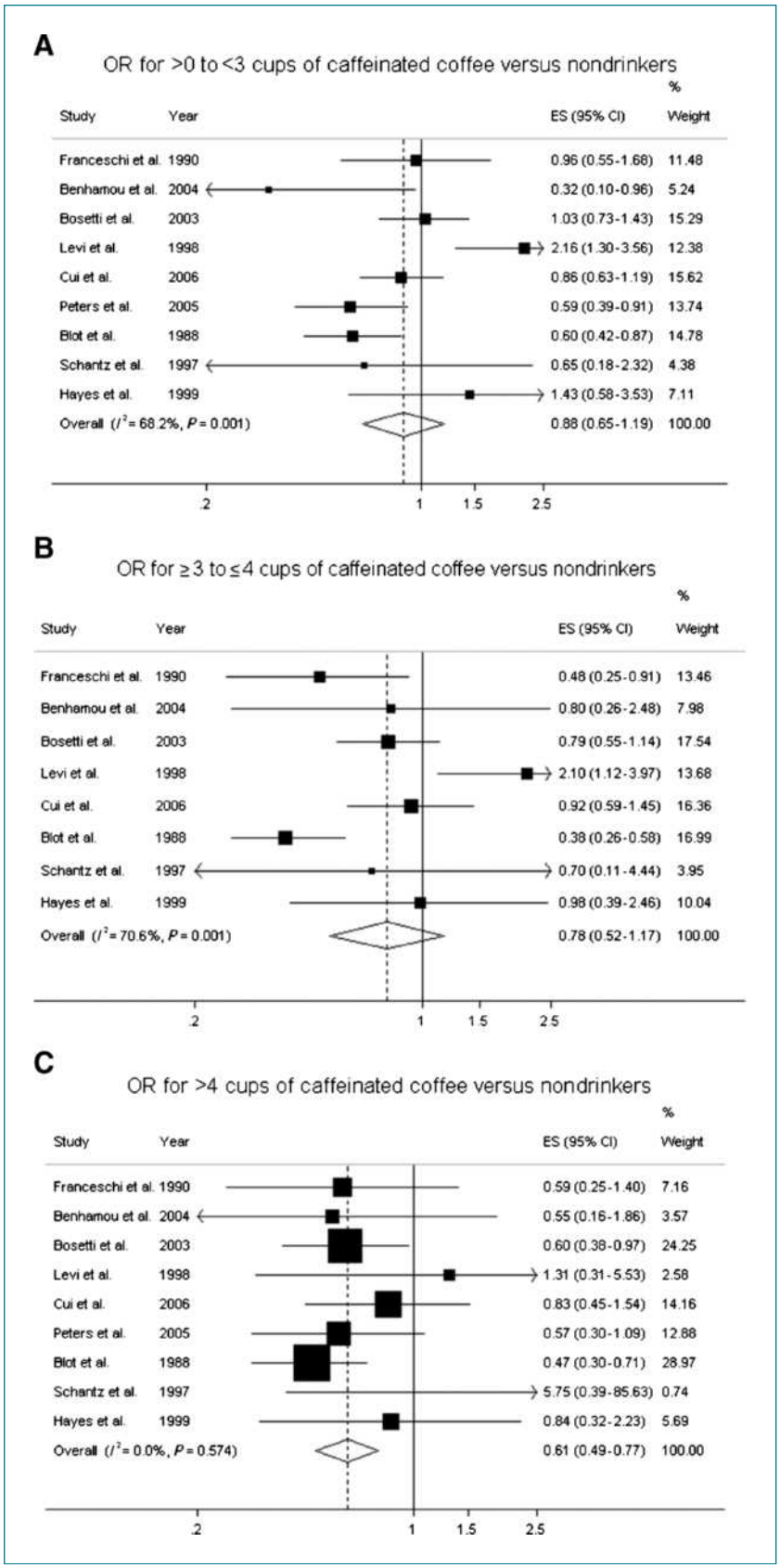

Figure 1. A to C, study-specific and pooled estimates of cancer of the oral cavity and pharynx (OP) for drinkers of caffeinated coffee versus nondrinkers. In B, the study by Peters et al. (37) is missing because no subjects consumed ≥3–≤4 cups of caffeinated coffee per day, due to the ordinal response scale used (i.e., 2–3 cups per day, 4–5 cups per day). Small differences in the estimates between this figure and Table 3 are due to rounding off of data.

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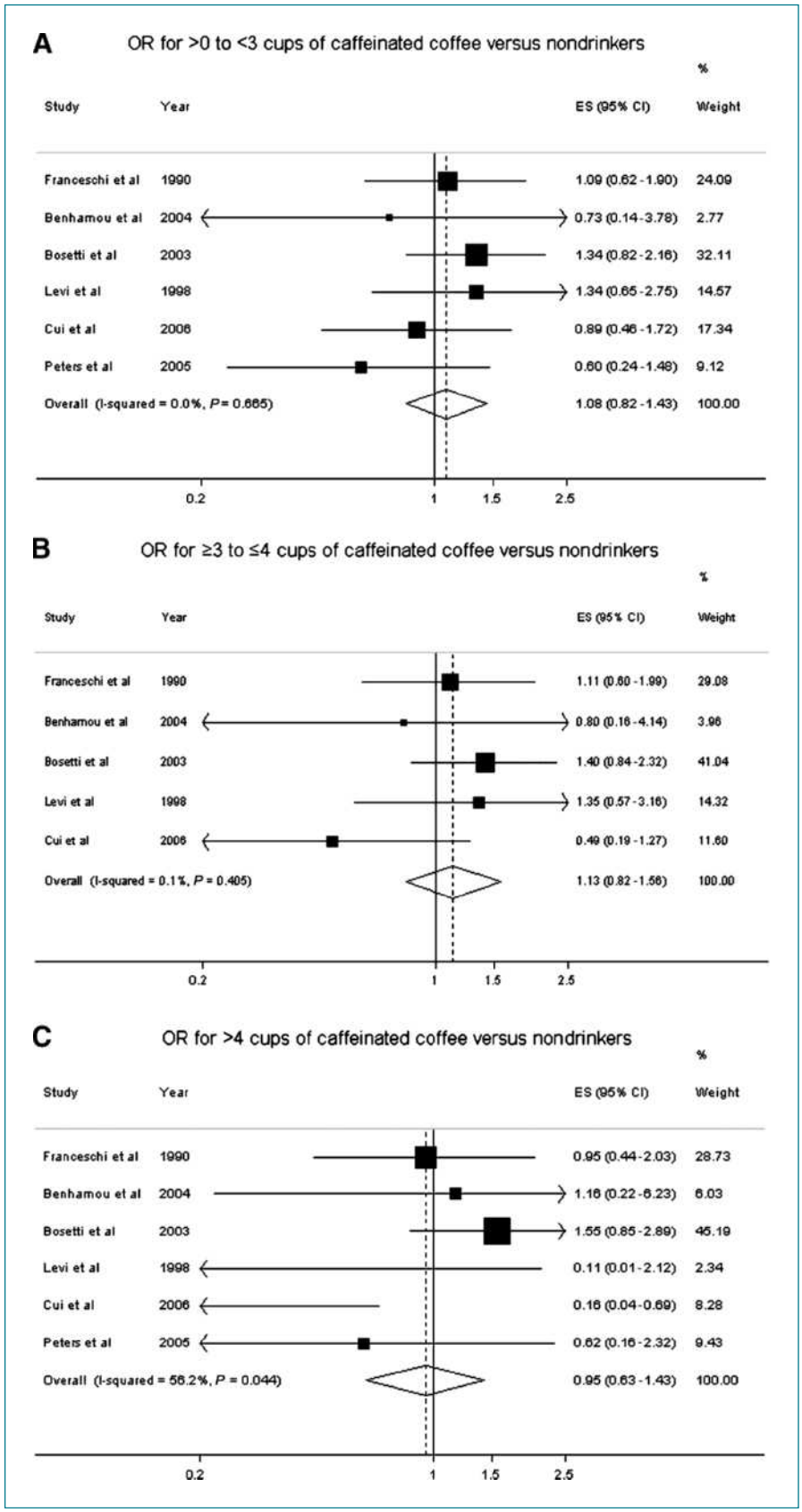

Figure 2. A to C, study-specific and pooled estimates of laryngeal cancer for drinkers of caffeinated coffee versus nondrinkers. In B, two studies are missing. The study by Peters et al. (37) is missing because no subjects consumed ≥3–≤4 cups of caffeinated coffee per day, due to the ordinal response scale used (i.e., 2–3 cups per day, 4–5 cups per day); the study by Schantz et al. (38) is missing because the OR was not estimable. Small differences in the estimates between this figure and Table 3 are due to rounding off of data.

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Table 4. Distribution of cases of cancer of the oral cavity/pharynx and controls, and corresponding ORs and 95% CIs, for drinking >4 cups per day of caffeinated coffee versus nondrinkers in strata of selected covariates

	Cancer of the oral cavity and pharynx			
	Controls (*n* = 830)	Cases (*n* = 525)	OR (95% CI)	*P* for heterogeneity*
Age (y)				
<55	376	184	0.60 (0.41–0.88)	0.06
≥55	454	341	0.55 (0.40–0.75)	0.02
Sex				
Men	645	412	0.59 (0.42–0.81)	<0.01
Women	185	113	0.46 (0.27–0.78)	<0.01
Geographic region†				
Europe	412	132	0.63 (0.43–0.92)	0.07
America	418	393	0.60 (0.45–0.80)	0.11
Education‡				
<High school graduate	317	139	0.55 (0.33–0.93)	<0.01
≥High school graduate	508	383	0.65 (0.45–0.93)	<0.01
Tobacco consumption‡ §				
Never tobacco users	299	69	0.72 (0.31–1.64)	<0.01
Light tobacco users	322	164	0.53 (0.25–1.13)	0.03
Heavy tobacco users	205	290	0.51 (0.35–0.76)	<0.01
Alcohol consumption‡ ‖				
Never or light drinkers	566	227	0.59 (0.42–0.85)	<0.01
Heavy drinkers	243	286	0.61 (0.42–0.85)	<0.01
Vegetable intake				
<Median	388	307	0.59 (0.37–0.92)	<0.01
≥Median	442	218	0.60 (0.39–0.92)	<0.01
Fruit intake‡				
<Median	429	354	0.52 (0.36–0.74)	<0.01
≥Median	401	167	0.65 (0.41–1.02)	<0.01
Type of controls				
Hospital based	418	141	0.65 (0.38–1.11)	<0.01
Population based	412	384	0.58 (0.44–0.78)	0.20

NOTE: Random-effects estimates were used when heterogeneity was detected, and fixed-effects estimates otherwise. Adjusted for age, sex, race/ethnicity, education, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake, weight, and vegetable and fruit intake (as appropriate). Reference category was non–coffee drinkers in each stratum.

*Between studies.

†Europe included two studies from Italy (32, 34), one from France (33), and one from Switzerland (35). America included four studies from the United States (1, 36-38) and one from Puerto Rico (39).

‡The sum does not add up to the total because of some missing values.

§Light tobacco users were smokers of ≤20 pack-years equivalent (combination of pack-years of cigarettes and equivalent amount of cigars or pipe). Heavy tobacco users were smokers of >20 pack-years equivalent.

‖Never/light drinkers were drinkers of <3 drinks per day of alcoholic beverages and heavy drinkers those consuming ≥3 drinks per day.

of heterogeneity is that some subjects with low or irregular consumption of coffee may have been included among nondrinkers because of the way the unexposed group was defined in some studies. In fact, results were heterogeneous among intermediate levels of consumption but not among subjects with high consumption. This possible misclassification, however, if anything, could have attenuated the inverse association.

Other sources of heterogeneity are the different patterns of alcohol drinking and tobacco smoking in various populations, positively correlated with both coffee intake and head and neck cancer risk (42-44). However, the inverse association was similar in the strata of tobacco smoking and alcohol drinking. When we stratified for geographic region, no heterogeneity was detected within European studies and within American studies,

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separately, indicating that it could be at least partly explained by different modalities of consumption among European and U.S. populations (e.g., variety of coffee, type of processing and/or preparation, patterns of consumption, etc.). In a sensitivity analysis, exclusion of each study from the pooled analysis did not materially change the summary estimates, showing that results were not driven by any single study. Recall of coffee drinking has been shown satisfactorily reproducible and valid (45-48) and should not be different on the basis of the disease status or among various types of controls, as coffee is not commonly known to affect cancer risk of the oral cavity and pharynx.

The presence of preneoplastic changes in the oral cavity or symptoms of the disease may cause changes in coffee or tea drinking among the cases, notably a decrease among cases due to high temperature of coffee or tea (reverse causation). However, the difference in results between caffeinated coffee and tea intake would suggest that reverse causality due to disease-related change in drinking patterns is not the main reason for the observed associations for caffeinated coffee intake. Additionally, limited findings from cohort studies—where information on coffee drinking is collected several years before diagnosis—weigh against a relevant role of reverse causation. There are, in fact, two Norwegian cohorts: one cohort (22) included 38 cases of cancer of the oral cavity and pharynx and found a relative risk (RR) of 0.73 for drinkers of $\geq$7 cups per day of coffee compared with $\leq$2; the other cohort included 33 cases of cancers and found a RR of 0.5 for drinkers of 7 or more cups per day, with a significant inverse trend in risk (6). A third cohort study was based on the Miyagi Cohort in Japan, which included 48 cases and found a RR of 0.35 (95% CI, 0.16–0.77) for drinkers of $\geq$1 cups per day (7). Thus, overall, the limited evidence from cohort studies suggests a decreased risk for high coffee intake, although publication bias cannot be excluded.

In this analysis, the risk estimates did not materially change after adjustment for body weight and for vegetable and fruit consumption, which have been inversely associated with oral cancer in several studies (49). More important, caffeinated coffee drinking was moderately correlated with tobacco ($r = 0.24$, $P < 0.001$) and alcohol ($r = 0.14$, $P < 0.001$) consumption. However, careful allowance for alcohol drinking and tobacco smoking did not materially modify any of the risk estimates, indicating that residual confounding is not a plausible explanation of the inverse relation between caffeinated coffee and cancer of the oral cavity and pharynx. Additionally, assuming that coffee drinkers also smoke and drink more, any residual confounding would result in a positive bias away from the null, which we did not observe in our study. Information was not available on human papillomavirus infection, which has been causally associated with oropharyngeal cancer (50); however, there is no reason to think that coffee intake is associated with human papillomavirus infection. Another limitation of this study is the lack of good quality data on duration of coffee drinking or other time-related factors of the exposure in several studies, which did not allow investigation of these issues in the pooled analysis.

With reference to other studies investigating the relation of coffee drinking and head and neck cancer risk, of the at least 11 case-control studies not included in the INHANCE consortium (8, 9, 13-16, 18, 20, 21, 51), one study from the United States (13), one from Brazil (14), and one from Montenegro (20) considering cancer of the oral cavity and pharynx, and six studies considering oral or hypopharyngeal cancer alone (9, 15, 16, 18, 21, 51), found no significant association with coffee drinking; however, the point estimates were below unity in several of them. Each study, however, was not large enough to have adequate statistical power to detect a relatively weak association, and often did not focus on coffee, or had no adjustment for tobacco smoking and alcohol drinking. When we conducted a summary meta-analysis of the six most informative studies not included in the INHANCE consortium, that is, those with a quantification of the amount of coffee (one cohort and five case-control, for a total of 1,628 cases; ref. 7, 13-16, 21), the summary RR for the highest category of coffee consumption compared with the lowest one (as categorized in each study) was 0.72 (95% CI, 0.55–0.95).

As for laryngeal cancer risk, results of studies not included in this pooled analysis were inconsistent and overall compatible with no relation. One Norwegian cohort study (22) found an inverse relation of laryngeal cancer with coffee intake, two case-control studies (8, 26) found an increased risk, and one prospective (6) and two case-control studies (14, 24) found no relation.

For both cancer of the oral cavity/pharynx and larynx, the few other published data on decaffeinated coffee consumption are inadequate for any meaningful inference (52).

With reference to tea intake, one Japanese prospective study (29) on oral cancer, four case-control studies on oral cavity and pharynx and oral cancers (9, 13-15), and two case-control studies on laryngeal cancer (14, 24) found no significant relation, similarly to the results of our pooled analysis. The World Cancer Research Fund Expert Report concluded that the evidence for a relation between tea consumption and head and neck cancers is too limited to draw any conclusion (49).

Support for a real inverse association between caffeinated coffee intake and cancer of the oral cavity and pharynx comes from the significant inverse dose relation in a subset of studies, the consistent relation across strata of potential confounders and effect modifiers, and the consistent association in European and American populations. Furthermore, the absence of a relation observed in the same studies between caffeinated coffee intake and the risk of laryngeal cancer, which shares similar risk factors of cancer of the oral cavity and pharynx (4, 23, 24), supports a real association between caffeinated coffee intake and the risk of cancer of the oral cavity and pharynx.

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The lack of association with tea drinking argues against reverse causality and report bias, too, although tea is generally less consumed than caffeinated coffee in these populations and it is likely to be more misclassified.

The inverse relationship between caffeinated coffee drinking and cancer of the oral cavity and pharynx can be related to various components of coffee. Besides caffeine, coffee contains more than a thousand chemicals (5), some of which have antioxidant and antimutagenic activities in animal models and cell culture systems (53). These include several phenolic compounds (such as chlorogenic, caffeic, ferulic, and cumaric acids), melanoidins, and diterpenes (such as cafestol and kahweol; refs. 54, 55) whose concentration in the beverage varies depending on type of raw coffee (Arabica or Robusta), roasting, and preparation, as unfiltered coffee contains less amounts of lipid component, such as diterpenes (56). In particular, cafestol and kahweol may reduce the genotoxicity of some carcinogens (53) and may activate enzymes involved in cancerogenic detoxification (57, 58), such as glutathione *S*-transferase and *N*-acetyltransferase (59). Still, no definite biological mechanism of the potential healthy role of coffee on head and neck cancers is available (52). Coffee drinking has also been inversely related to colorectal cancer (60), liver cirrhosis and cancer (52), and endometrial cancer (61), again in the absence of a clear interpretation.

In conclusion, the results of this pooled analysis of case-control studies support the hypothesis of an inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx, and provide a more precise estimate of the magnitude of the effect. Bias, confounding, and reverse causality, however, cannot be excluded. Given the widespread use of coffee and the high incidence and low survival of head and neck cancers (62), it is important to conclusively establish whether the observed association between caffeinated coffee drinking and head and neck cancer risk is causal, as this would have appreciable public health relevance, although alcohol and tobacco remain the key risk factors for cancer of the oral cavity and pharynx in most populations (1).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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