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ORIGINAL ARTICLE

Coffee and tea consumption and the risk of head and neck cancer: An updated pooled analysis in the International Head and Neck Cancer Epidemiology Consortium

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Abstract

Introduction: The relations between coffee and tea consumption and head and neck cancer (HNC) incidence are unclear. With increasing global HNC burden, this study aims to examine the association between coffee, tea, and HNC.

Methods: A pooled analysis of 9548 HNC cases and 15,783 controls from 14 individual-level case-control studies was conducted from the International Head and Neck Cancer Epidemiology consortium. Random-effects logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for HNC and its subsites, adjusting for sociodemographic and lifestyle factors.

Results: Compared to non–coffee drinkers, drinking >4 cups of caffeinated coffee daily was inversely associated with HNC (OR, 0.83; 95% CI, 0.69–1.00), oral cavity (OR, 0.70; 95% CI, 0.55–0.89), and oropharyngeal cancers (OR, 0.78; 95% CI, 0.61-0.99). Drinking 3–4 cups of caffeinated coffee was inversely associated with hypopharyngeal cancer (OR, 0.59; 95% CI, 0.39–0.91). Drinking decaffeinated coffee and drinking between >0 to <1 cup daily were inversely associated with oral cavity cancer (OR, 0.75; 95% CI, 0.64–0.87 and OR, 0.66; 95% CI, 0.54–0.81). Drinking tea was inversely associated with hypopharyngeal cancer (OR, 0.71; 95% CI, 0.59–0.87). Daily tea consumption of >0 to ≤1 cup was inversely associated with HNC (OR,

0.91; 95% CI, 0.84–0.98) and hypopharyngeal cancer (OR, 0.73; 95% CI, 0.59–0.91), but drinking >1 cup was associated with laryngeal cancer (OR, 1.38; 95% CI, 1.09–1.74).

Conclusion: These findings support reduced HNC risk among coffee and tea drinkers. Future studies are needed to address geographical differences in types of coffee and tea to improve our understanding of the association of coffee and tea and global HNC risk.

KEYWORDS
coffee and tea, head and neck cancer, pooled analysis

INTRODUCTION

Head and neck cancer (HNC), including cancers of the oral cavity, oropharynx, hypopharynx, and larynx, is the seventh most common cancer worldwide, with approximately 745,000 new cases and 364,000 deaths in 2020.[1] Although overall HNC burden is declining in high-income countries, oropharyngeal cancer incidence has steadily increased with the rising prevalence of human papillomavirus infections.[2,3] Low- and middle-income countries shoulder two-thirds of global HNC cases, largely due to limited public health resources for HNC prevention and treatment efforts. With increasing trends for mortality and incidence in low- and middle-income countries, the global HNC burden is projected to increase.[4] Although the 5-year survival rates are increasing, increasing oropharyngeal cancer incidence in high-income countries and overall HNC burden in low- and middle-income countries warrant a focus on understanding HNC risk factors for primary prevention to reduce global HNC incidence.[5]

Although tobacco and alcohol are established HNC risk factors, the role of dietary factors including coffee and tea consumption have not yet been fully understood.[6] Coffee and tea are two popular beverages consumed worldwide, containing bioactive compounds with potential antioxidant, anticancer, and anti-inflammatory effects. Coffee contains compounds such as caffeine, polyphenols, trigonelline, chlorogenic acids, cafestol, and kahweol,[7] whereas tea consists of caffeine, polyphenols, catechins, flavanols, lignans, and phenolic acid.[8]

Coffee has been studied as a potential factor associated with HNC risk. Several epidemiological studies observed inverse associations between coffee consumption and the risk of oral cavity and pharyngeal cancers.[7,9–11] However, other studies have shown inconsistent findings related to HNC subsites. In the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial cohort study, no association was observed between coffee and HNC risk.[6] A meta-analysis of 10 studies showed an increased risk between coffee consumption and laryngeal cancer,[12] whereas another meta-analysis of eight laryngeal cancer studies found no association.[13]

Studies examining the association between tea consumption and HNC risk found similar inconsistent findings. A review of meta-analyses and a case-control study on tea and the risk of HNC reported a protective effect of tea on oral cancer.[5,14,15] Another case-control study and meta-analysis observed inverse associations between green tea consumption and HNC and oral cavity cancer,[8,16] whereas three meta-analyses[12,13,17] and a previous International Head and Neck Cancer Epidemiology consortium (INHANCE) pooled analysis found no association between tea drinking and HNC risk.[9]

The relationship between coffee and tea consumption and HNC risk has been previously examined within the INHANCE consortium. In the prior pooled analysis of nine case-control studies, an inverse association was reported between caffeinated coffee and oral cavity and pharyngeal cancers. Decaffeinated coffee data were too sparse to conduct detailed analyses and no associations were observed between decaffeinated coffee or tea consumption and HNC risk. To better understand the relationship between coffee and tea consumption and the risk of HNC, we assessed the associations using an updated larger set of cases and controls identified in the INHANCE consortium.

MATERIALS AND METHODS

The INHANCE pooled data were used in this analysis. Each INHANCE study collected data using study-specific questionnaires, including questions on sociodemographic and lifestyle factors such as dietary intake, tobacco consumption, and alcohol intake. Data on demographic, behavioral, and clinical characteristics were included to account for potential confounders. Individuals with missing data for age, sex, and race/ethnicity were excluded from this analysis. Informed consent was obtained for each participant, and institutional review board approval was obtained for each study site.

Fourteen case-control studies included information on coffee and tea consumption, with nine also collecting information about decaffeinated coffee. All questionnaires were similar in asking participants to recall their prior consumption of caffeinated coffee, decaffeinated coffee, and tea in cups per day/week/month/year. From the 14 studies, the Boston and Seattle studies used food frequency questionnaires to ascertain coffee and tea consumption, whereas the other studies included recall questions in the diet or beverage-specific section. The Boston, Seattle, and Germany-Saarland studies collected cups of coffee and tea consumption

using ranges, whereas the other studies asked participants to specify the exact number of cups consumed per day/week/month/year. For the Boston and Seattle studies, the midpoint of the ranges was used as the value of daily consumption. The Germany-Saarland study was excluded in analyses for daily consumption categories due to broad ranges. Caffeinated coffee consumption data was standardized to cups per day and categorized into INHANCE categories of nondrinker, >0 to <3 cups, 3–4 cups, and >4 cups per day. In prior literature, the highest level of daily caffeinated coffee consumption was measured at either >4 or >5 cups. In our study, caffeinated coffee consumption was measured at >4 cups to prevent sparse data when stratifying by subsite. Decaffeinated coffee was standardized to nondrinker, >0 to <1 cup, and ≥1 cups per day whereas tea consumption was categorized as nondrinker, >0 to ≤1 cup, and >1 cups per day. The caffeinated coffee and tea analyses included seven studies from Europe, six studies from North America, and one study from Latin America. For the decaffeinated coffee analysis, four studies from Europe and five studies from North America were included. The characteristics of the studies are summarized in Table S1.

In our updated analysis, five additional case-control studies were added, and the pharynx subsite was further divided into the oropharynx and hypopharynx subsites. HNC cases were included in this analysis if they were classified by their original study investigators as invasive cancers of the oral cavity, oropharynx, hypopharynx, or larynx. Patients with cancers of the salivary glands, nasal cavity/ear/paranasal sinuses, and overlapping head and neck subsites were excluded. The HNC subsites were classified according to the International Classification of Diseases for Oncology, version 2 (ICDO-2) for: 1) oral cavity cancer (lip, tongue, gum, floor of mouth, and hard palate): C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, and C06.9; 2) oropharyngeal cancer (base of the tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx): C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2–C10.4, C10.8, and C10.9; 3) hypopharyngeal cancer (pyriform sinus and hypopharynx): C12.9, C13.0–C13.2, C13.8, and C13.9; and 4) laryngeal cancer (glottis, supraglottis, and subglottis): C10.1, C32.0–C32.3, and C32.8–C32.9 (Lee et al., 2019). For studies using the International Classification of Diseases, 9th (ICD-9) or 10th Revision (ICD-10) coding, cases were converted to ICDO-2 codes. Controls were selected from the same source population as their respective cases. Several studies frequency matched cases and controls on factors such as age, sex, study center, and neighborhood (Table S1).

Statistical analysis

Demographic characteristics and known HNC risk factors for cases and controls were compared with χ^2 or *t*-tests. The associations between HNC risk and caffeinated coffee, decaffeinated coffee, and tea consumption were assessed with logistic regression models by estimating adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). All models were adjusted for study center, age, sex, race/ethnicity, education level, body mass index (BMI), daily number of cigarettes smoked, duration of cigarette smoking, duration of cigar smoking, duration of pipe smoking, daily number of alcoholic drinks, fruit consumption, and vegetable consumption (see Supporting Information for further details on covariate definitions).

Missing education data were imputed with methods used in previous INHANCE studies.[9] Missing data on fruit and vegetable consumption were imputed based on the average quartile for cases and controls. To calculate study-specific and pooled estimates of association, a two-stage random-effects logistic regression model with the maximum likelihood method was used. A likelihood ratio test was used to determine heterogeneity between studies by comparing models with a product term between the study center and coffee and tea consumption and a model without the product term, for the risk of HNC and its subsites. Random-effect estimates were reported when heterogeneity across study centers were detected ($p < .05$); otherwise, fixed-effect estimates were used.[18]

A stratified analysis for the consumption of >4 cups of caffeinated coffee daily compared with non–coffee drinkers for the oral cavity and oropharyngeal cancers combined was used to assess for potential effect modification for dichotomized covariates of age, sex, tobacco consumption, alcohol consumption, fruit intake, vegetable intake, study geographical region, study period, and types of controls (see Supporting Information for dichotomized definitions). A sensitivity analysis was also conducted by excluding each study individually, to ensure that the statistical significance and magnitude of the overall risk estimate were not dependent on any single study. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) or STATA 18.0 (StataCorp LLC., College Station, Texas).

RESULTS

A total of 9548 HNC cases and 15,783 controls were included in this analysis. Of the cases, 92.9% were non-Hispanic White individuals and 79.3% were males (Table 1). Cases had lower education levels, lower BMI, smoked a greater number of cigarettes daily, and consumed higher daily alcoholic drinks compared to controls. Controls had higher fruit and vegetable intake and shorter duration of cigarette smoking.

Caffeinated coffee drinking status was not associated with the risk of HNC, and its subsites compared to non–coffee drinkers (Table 2). However, drinking >4 cups of caffeinated coffee daily was associated with a decreased risk of HNC (OR, 0.83; 95% CI, 0.69–1.00), oral cavity (OR, 0.70; 95% CI, 0.55–0.89), and oropharyngeal cancers (OR, 0.78; 95% CI, 0.61–0.99). Drinking 3–4 cups daily was inversely associated with hypopharyngeal cancer (OR, 0.59; 95% CI, 0.39–0.91). A dose–response relationship was observed across increasing levels of daily caffeinated coffee drinking for HNC, oral cavity, oropharyngeal, hypopharyngeal, and laryngeal cancers (p_{trend}

TABLE 1 Characteristics of head and neck cancer cases and controls of select INHANCE consortium studies.

Characteristics	Cases (n = 9548) No.	%	Controls (n = 15,783) No.	%
Age (years)				
<40	292	3.1	800	5.1
40–44	356	3.7	1019	6.5
45–49	932	9.8	1524	9.7
50–54	1479	15.5	2176	13.8
55–59	1891	19.8	2735	17.3
60–64	1675	17.5	2476	15.7
65–69	1470	15.4	2482	15.7
70–74	1041	10.9	1912	12.1
≥75	412	4.3	659	4.2
Sex				
Female	1981	20.7	4456	28.2
Male	7567	79.3	11,327	71.8
Race/ethnicity				
Non-Hispanic White	8867	92.9	14,795	93.7
Black	356	3.7	451	2.9
Hispanic	151	1.6	317	2.0
Asian and Pacific Islander	47	0.5	80	0.5
American Indian/Alaskan Native	127	1.3	140	0.9
Education level[a]				
No education	69	0.7	91	0.6
Less than junior high school	3115	32.7	5085	32.3
Some high school	2284	24.0	2921	18.5
High school graduate	1295	13.6	1905	12.1
Technical school/some college	1827	19.2	3253	20.7
College graduate/postgraduate	943	9.9	2498	15.9
Missing	15		30	
BMI, kg/m^2				
<18.5	582	6.4	210	1.4
18.5 to <25	5011	54.9	6335	40.8
25 to <30	2696	29.5	6533	42.1
≥30	837	9.2	2443	15.7
Missing	422		262	
No. of cigarettes smoked, daily				
Never smoker	1118	11.9	6069	39.1
1–10	1047	11.1	2881	18.5
11–20	3365	35.7	3983	25.6
21–30	1636	17.4	1226	7.9
31–40	1509	16.0	900	5.8
>40	746	7.9	473	3.0
Missing	127		251	
Duration of cigarette smoking (years)				
Mean ± SD	31.6 ± 16.1		16.6 ± 17.1	
No. of alcohol drinks, daily				
Never drinker	808	8.9	2762	18.2
>0 to <1	1753	19.4	5372	35.4
1 to <3	2223	24.6	4148	27.3
3 to <5	1525	16.9	1635	10.8
≥5	2738	30.3	1257	8.3
Missing	501		609	
Fruit intake[a]				
First quartile	2748	28.8	2822	17.9
Second quartile	4250	44.5	3094	19.6
Third quartile	1462	15.3	7063	44.8
Fourth quartile	1088	11.4	2804	17.8
Vegetable intake[a]				
First quartile	2565	26.9	2934	18.6
Second quartile	4246	44.5	3101	19.7
Third quartile	1481	15.5	6685	42.4
Fourth quartile	1256	13.2	3063	19.4

Note: p value for two-sided χ^2 test for all characteristics were at <.05 statistical significance.

Abbreviations: BMI, body mass index; INHANCE, International Head and Neck Cancer Epidemiology.

[a]Included imputed values.

< .01). For decaffeinated coffee, an inverse association was detected with the risk of oral cavity cancer (OR, 0.75; 95% CI, 0.64–0.87). Drinking between >0 to <1 cup of decaffeinated coffee daily was associated with a reduced risk of oral cavity cancer (OR, 0.66; 95% CI, 0.54–0.81). Caffeinated and decaffeinated coffee consumption were not associated with the risk of laryngeal cancer.

Tea drinkers had a reduced risk of hypopharyngeal cancer (OR, 0.71; 95% CI, 0.59–0.87) compared with non–tea drinkers (Table 3). Daily tea consumption of >0 to ≤1 cup was inversely associated with the risk of overall HNC (OR, 0.91; 95% CI, 0.84–0.98) and hypopharyngeal cancer (OR, 0.73; 95% CI, 0.59–0.91), but drinking >1 cup was associated with an increased risk of laryngeal cancer (OR, 1.38; 95% CI, 1.09–1.74). A dose–response relationship was detected for daily tea consumption for HNC, hypopharyngeal, and laryngeal cancers (p_{trend} < .01). No associations were observed between tea consumption and oral cavity or oropharyngeal cancers.

TABLE 2 The association with HNC by anatomical subsite for coffee drinking status and daily coffee consumption among HNC cases and controls from select INHANCE consortium studies.

				Subsites			
		HNC		Oral cavity		Oropharynx	
	Control	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Caffeinated coffee drinking status							
Non–coffee drinker	2155	1052	Reference	287	Reference	311	Reference
Drinker	13,304	7809	0.90 (0.78, 1.04)	1783	0.82 (0.66, 1.02)[k]	2226	0.87 (0.70, 1.08)[k]
Missing	324	687		159		254	
p for heterogeneity			<.01		<.01		<.01
Daily caffeinated coffee consumption							
Non–coffee drinker	2151	1050	Reference	287	Reference	261	Reference
>0 to <3 cups	7580	4014	0.94 (0.83, 1.06)[k]	938	0.87 (0.71, 1.06)[k]	1163	0.95 (0.74, 1.22)[e]
3–4 cups	3587	2181	0.85 (0.70, 1.03)[k]	498	0.78 (0.58, 1.04)[k]	524	0.80 (0.61, 1.05)[e]
>4 cups	2048	1526	0.83 (0.69, 1.00)[k]	347	0.70 (0.55, 0.89)[k]	441	0.78 (0.61, 0.99)[e]
Missing	323	683		159		254	
p for trend			<.01		<.01		<.01
p for heterogeneity			<.01		<.01		<.01
Decaffeinated coffee drinking status[a]							
Non–coffee drinker	7712	3882	Reference	825	Reference	950	Reference
Drinker	1862	875	0.83 (0.65, 1.08)	237	0.75 (0.64, 0.87)[a]	251	0.81 (0.62, 1.06)[j]
Missing	537	673		171		284	
p for heterogeneity			<.01		<.01		<.01
Daily decaffeinated coffee consumption[a]							
Non–coffee drinker	7712	3882	Reference	643	Reference	915	Reference
>0 to <1 cup	859	387	0.81 (0.64, 1.02)	96	0.66 (0.54, 0.81)[f]	140	0.78 (0.53, 1.15)[g]
≥1 cup	1003	488	0.85 (0.63, 1.15)	134	0.83 (0.66, 1.05)[f]	109	0.84 (0.62, 1.15)[g]
Missing	537	673		170		284	
p for trend			.27		<.01		.04
p for heterogeneity			<.01		<.01		<.01

	Hypopharynx		Larynx[h]	
Caffeinated coffee drinking status				
Non–coffee drinker	2155	122	Reference	227	Reference
Drinker	13,304	913	0.73 (0.51, 1.04)	2086	1.16 (0.93, 1.45)[k]
Missing	324	85		150	
p for heterogeneity			<.01		<.01
Daily caffeinated coffee consumption					
Non–coffee drinker	2151	117	Reference	227	Reference
>0 to <3 cups	7580	459	0.82 (0.59, 1.15)[i]	987	1.12 (0.92, 1.37)[k]
3–4 cups	3587	223	0.59 (0.39, 0.91)[i]	701	1.23 (0.98, 1.54)[k]
>4 cups	2048	208	0.68 (0.43, 1.06)[i]	398	1.18 (0.91, 1.53)[k]
Missing	323	85		150	
p for trend			<.01		<.01
p for heterogeneity			<.01		<.01

(Continues)

TABLE 2 (Continued)

		Hypopharynx		Larynx[h]	
Decaffeinated coffee drinking status[a]					
Non–coffee drinker	7712	338	Reference	1392	Reference
Drinker	1862	67	0.99 (0.49, 1.98)[j]	252	0.84 (0.59, 1.19)
Missing	537	44		846	
p for heterogeneity			<0.01		<0.01
Daily decaffeinated coffee consumption[a]					
Non–coffee drinker	7712	232	Reference	1392	Reference
>0 to <1 cup	859	23	0.72 (0.21, 2.39)[d]	95	0.87 (0.69, 1.11)
≥1 cup	1003	39	1.08 (0.57, 2.04)[d]	157	0.82 (0.54, 1.25)
Missing	537	44		846	
p for trend			.33		<.01
p for heterogeneity			<.01		<.01

Note: Random-effects estimates were used when heterogeneity was detected between studies ($p < .05$). Otherwise, fixed-effects models are used. Study-specific odds ratios were adjusted for study center, age, sex, race/ethnicity, education, body mass index, daily cigarette consumption, duration of cigarette consumption (continuous), duration of cigar usage(continuous), duration of pipe usage(continuous), daily alcohol consumption, fruit consumption, and vegetable consumption.

Abbreviations: CI, confidence interval; HNC, head and neck cancer; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a]Included Milan (1984–1989), Italy Multicenter, Switzerland, Milan (2006–2009), Los Angeles, Boston, Memorial Sloan-Kettering Cancer Center, Seattle, and Buffalo studies.

[b]Included France, Italy Multicenter, Saarland, France Multicenter, Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[c]Included France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Buffalo, and Puerto Rico studies.

[d]Included France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[e]Included Milan (1984–1989), France, Italy Multicenter, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[f]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[g]Included France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[h]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, Memorial Sloan-Kettering Cancer Center, Seattle, and Buffalo studies.

[i]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, France Multicenter, Milan (2006–2009), Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[j]Included France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[k]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[l]Included Milan (1984–1989), France, Italy Multicenter, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[m]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

To assess potential effect modifiers for drinking >4 cups of caffeinated coffee daily and oral cavity and oropharyngeal cancers, we conducted a stratified analysis (Table 4). Inverse associations were observed when comparing drinkers of >4 cups of caffeinated coffee daily to non–coffee drinkers for oral cavity and oropharyngeal cancers across all strata of age, sex, tobacco smoking, alcohol intake, fruit intake, vegetable intake, study region, study period, and type of controls. Figure 1 shows study-specific OR for drinking >4 cups of caffeinated coffee daily compared to non–coffee drinkers for oral cavity and oropharyngeal cancers combined. The summary OR was 0.55 (95% CI, 0.43–0.67; $p_{\text{heterogeneity}} = .54$). A sensitivity analysis was performed by removing one study at a time, and no significant changes in the overall risk estimates were observed.

TABLE 3 The association with HNC by anatomical subsite for tea drinking status and daily tea consumption among HNC cases and controls from select INHANCE consortium studies.

				Subsites							
		HNC		Oral cavity		Oropharynx		Hypopharynx		Larynx[c]	
	Control	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Tea drinking status											
Non–tea drinker	7960	4940	Reference	1079	Reference	1354	Reference	657	Reference	1413	Reference
Drinkers	7309	3555	0.94 (0.88, 1.00)	930	0.95 (0.87, 1.04)	1100	0.96 (0.88, 1.05)	326	0.71 (0.59, 0.87)	834	0.98 (0.87, 1.11)
Missing	514	1053		235		367		137		243	
p for heterogeneity			<.01		<.01		<.01		<.01		<.01
Daily tea consumption											
Non–tea drinker	7932	4898	Reference	1030	Reference	1347	Reference	587	Reference	1398	Reference
>0 to ≤1 cup	5771	2781	0.91 (0.84, 0.98)[d]	716	0.95 (0.86, 1.05)[b]	846	0.93 (0.84, 1.03)[d]	261	0.73 (0.59, 0.91)[a]	638	0.89 (0.78, 1.02)[d]
>1 cup	1481	730	1.08 (0.93, 1.25)[d]	183	0.92 (0.75, 1.14)[b]	235	1.09 (0.88, 1.34)[d]	56	0.73 (0.53, 1.00)[a]	185	1.38 (1.09, 1.74)[d]
Missing	505	1045		234		363		136		242	
p for trend			<.01		.25		.02		<.01		<.01
p for heterogeneity			<.01		<.01		<.01		<.01		<.01

Note: Random-effects estimates were used when heterogeneity was detected between studies ($p < .05$). Otherwise, fixed-effects models are used. Study-specific odds ratios were adjusted for study center, age, sex, race/ethnicity, education, body mass index, daily cigarette consumption, duration of cigarette consumption (continuous), duration of cigar usage(continuous), duration of pipe usage(continuous), daily alcohol consumption, fruit consumption, and vegetable consumption.

Abbreviations: CI, confidence interval; HNC, head and neck cancer; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a]Included Italy Multicenter, Switzerland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[b]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, France Multicenter, Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[c]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, Memorial Sloan-Kettering Cancer Center, Seattle, and Buffalo studies.

[d]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

[e]Included Milan (1984–1989), France, Italy Multicenter, Switzerland, Saarland, France Multicenter, Milan (2006–2009), Los Angeles, Boston, US Multicenter, Memorial Sloan-Kettering Cancer Center, Seattle, Buffalo, and Puerto Rico studies.

DISCUSSION

In this updated pooled case-control analysis from the INHANCE consortium, new associations were observed. Inverse associations were observed between drinking >4 cups of caffeinated coffee daily and the risk of HNC, oral cavity cancer, and oropharyngeal cancer, as well as between drinking 3–4 cups and the risk of hypopharyngeal cancer. For decaffeinated coffee, we identified an inverse association between drinking decaffeinated coffee and oral cavity cancer risk. Furthermore, tea consumption was inversely related to the risk of HNC overall and hypopharyngeal cancer. On the other hand, tea consumption was associated with an increased risk of laryngeal cancer.

In line with these findings, two meta-analyses observed a similar decreased risk of oral cavity and pharyngeal cancers among caffeinated coffee drinkers.[11,19] Another meta-analysis on caffeinated coffee consumption and oral cavity cancer studies reported an inverse association when comparing the highest level of coffee intake to lowest level, for both case-control and cohort study designs.[10] These results were consistent with the prior INHANCE study, where drinking >4 cups of caffeinated coffee daily was inversely associated with the risk of oral cavity and pharyngeal cancers.[9] With the additional studies and larger sample size, this current study was able to estimate the risk for oropharyngeal and hypopharyngeal cancers separately with respect to coffee and tea consumption. We observed

TABLE 4 ORs for oral cavity and oropharyngeal cancer risk for drinking >4 cups of caffeinated coffee daily versus non–coffee drinkers across strata of selected factors from select INHANCE consortium studies.

	Oral cavity and oropharyngeal cancer cases		Controls		
	>4 cups (n = 788)	Non–coffee drinker (n = 598)	>4 cups (n = 2048)	Non–coffee drinker (n = 2151)	OR (95% CI)
Age (years)					
<55	335	240	841	837	0.74 (0.59, 0.93)
≥55	453	358	1207	1314	0.74 (0.55, 1.00)
Sex					
Male	636	402	1601	1362	0.70 (0.53, 0.92)
Female	152	196	447	789	0.68 (0.52, 0.89)
Tobacco smoking[a]					
Never user	42	120	434	1060	0.98 (0.59, 1.63)
Tobacco user	742	461	1603	1020	0.86 (0.70, 1.05)
Alcohol intake[a]					
Never drinker	46	86	252	623	0.69 (0.43, 1.12)
Drinker	734	492	1764	1474	0.76 (0.61, 0.93)
Fruit intake					
Below median	626	373	561	964	0.83 (0.62, 1.10)
Above median	162	225	1487	1187	0.65 (0.46, 0.93)
Vegetable intake					
Below median	580	366	521	995	0.76 (0.56, 1.04)
Above median	208	232	1527	1156	0.71 (0.52, 0.96)
Study region					
Europe	407	248	1410	1100	0.56 (0.34, 0.94)
America	381	350	638	1051	0.86 (0.69, 1.06)
Study period					
Before 2000	410	406	951	1387	0.70 (0.52, 0.94)
After 2000	378	192	1097	764	0.90 (0.65, 1.24)
Type of controls					
Hospital-based	156	286	647	1253	0.74 (0.49, 1.11)
Population-based	632	311	1401	898	0.74 (0.59, 0.91)

Note: Random-effects estimates were used when heterogeneity was detected between studies ($p < .1$). Otherwise, fixed-effects models are used. Study-specific ORs were adjusted for study center, age, sex, race/ethnicity, education, body mass index, daily cigarette consumption, duration of cigarette consumption (continuous), duration of cigar usage (continuous), duration of pipe usage (continuous), daily alcohol consumption, fruit consumption, and vegetable consumption; This analysis does not include the Saarland study due to sparse stratum data.

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a]The sum does not add up to the total because of some missing values.

inverse associations between drinking caffeinated coffee and the risk of oropharyngeal and hypopharyngeal cancers at different levels of daily consumption, which was not previously reported in the literature. Hypopharyngeal cancer is the rarest cancer of the four subsites and is often diagnosed at a more advanced stage. Therefore, the potential protective mechanism of caffeinated coffee may differ between the hypopharynx and oropharynx.[20]

With the larger sample size, we observed an inverse association between decaffeinated coffee and oral cavity cancer risk. Previous studies only reported on caffeinated coffee due to sparse decaffeinated coffee data. Perhaps bioactive compounds other than caffeine contribute to the potential anticancer effect of coffee and tea. Polyphenols, bioactive compounds found in caffeinated coffee, decaffeinated coffee, and tea, have exhibited antioxidative and

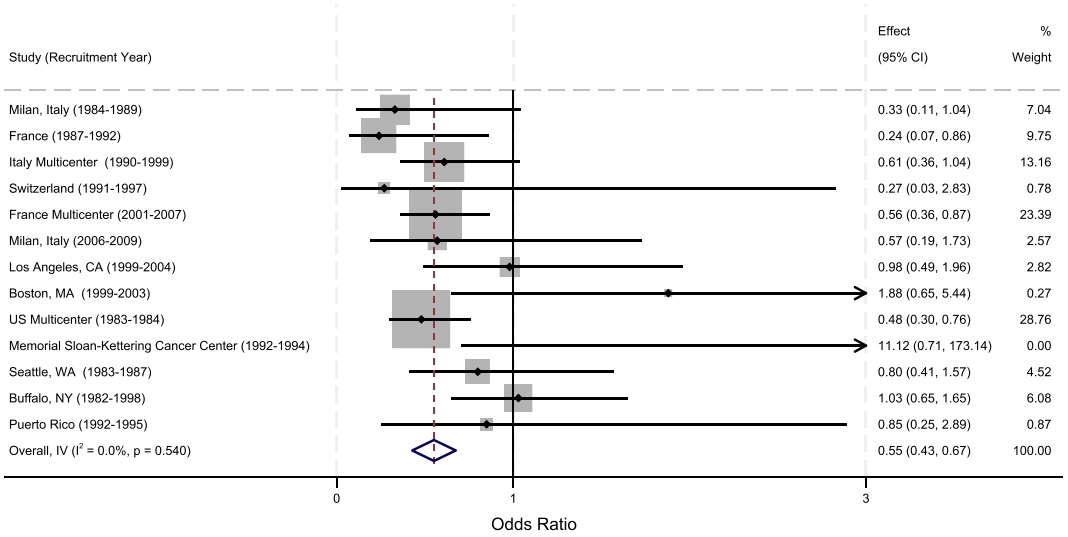

FIGURE 1 Study-specific odds ratios for >4 cups of caffeinated coffee daily versus non–coffee drinkers for oral cavity and oropharyngeal cancers.

anticancer properties that contribute to the inhibition of angiogenesis, proliferation, invasion, and metastasis of cancer cells.[8]

A prior meta-analysis and a case-control study reported an inverse association between green tea and oral cavity cancer risk, which was not consistent with our results.[5,8] Unlike the previous literature, our investigation included the separate assessment of oropharyngeal and hypopharyngeal cancers. These inconsistencies with the protective effect of tea may be due to the type of tea consumed and study region. The protective effect of tea on oral cavity cancer is primarily observed in Asia, where the primary tea consumed is green tea.[21] Our analysis consisted of studies in Europe and North America, where black tea may be consumed more frequently. Even though both green and black tea are derived from *Camelia sinensis* leaves, black tea is oxidized, resulting in lower concentrations of catechins and decreased antioxidant activity.[22] We also observed an association between drinking >1 cup of tea daily and an increased risk of laryngeal cancer. A potential mechanism for tea consumption and increased laryngeal cancer risk is mediation by gastroesophageal reflux disease (GERD). Theophylline, a bioactive compound in tea, can reduce lower esophageal sphincter pressure and can induce acid flux and GERD.[23,24] In prior studies, GERD has been associated with a higher risk of laryngeal squamous cell carcinoma.[25–27] Therefore, the higher levels of tea consumption could increase the likelihood of GERD, resulting in the observed positive association with laryngeal cancer risk.

Dose–response relationships were observed between drinking >4 cups of caffeinated coffee daily and decreased risks of HNC and all its subsites. In vitro coffee studies on human cancer cell lines for osteosarcoma, glioblastoma, breast, prostate, esophageal, urinary, bladder, lung, oral, kidney, and colon cancers have identified bioactive capabilities of coffee, which included antiproliferative and antioxidant effects, cell cycle arrest, apoptosis epithelial–mesenchymal transition downregulation, and gene downregulation.[7] The ability of coffee to downregulate biological cancer pathways may be similar for HNC. Greater consumption of coffee may increase the biological effects that prevent HNC development.

With stratification by potential effect modifiers, the inverse association between drinking >4 cups of caffeinated coffee daily and the risk of oral cavity and oropharyngeal cancers remained. We did not observe effect modification across strata of age, sex, tobacco smoking, alcohol intake, fruit intake, vegetable intake, study region, study period, and type of controls. The nonsignificant associations for the never tobacco smokers and never alcohol drinkers may be due to the low statistical power to detect the associations because the majority of HNC cases are tobacco users and alcohol drinkers. Additionally, caffeine consumption has been associated with smoking reinforcement.[28] Even though the associations were not significant across all strata for certain factors, the point estimates for the ORs suggested a decreased risk of oral cavity and oropharyngeal cancers with drinking >4 cups of caffeinated coffee daily.

The strengths of our study are inherent to the nature of the INHANCE consortium and pooled analysis.[29] Within the INHANCE consortium, new study data have been added to the pooled data set, contributing to the largest sample of HNC cases and controls in the investigation of coffee and tea consumption, to our knowledge. With the new studies, we had sufficient data to make inferences about associations between decaffeinated coffee and tea with the risk of oropharyngeal and hypopharyngeal cancers. Because three of the new studies recruited participants in the 2000s, this analysis included data from nearly three decades. Detailed information on coffee and tea, as well as patient and demographic information, was available from the INHANCE studies. This allowed for adjustment of known HNC risk factors, such as alcohol consumption and tobacco smoking, that may otherwise bias the risk estimates. Additionally, the larger sample size allowed us to examine different subsites of HNC, and stratify the risk estimates on potential confounders or effect

modifiers such as race/ethnicity, education, and diet. The pooled analysis allowed this study to address research gaps that individual studies are not able to address.[30]

Potential limitations should also be considered. With case–control studies, there was potential for recall bias and misclassification of coffee and tea exposures. Retrospective self-reporting of coffee and tea consumption may result in nondifferential misclassification among cases and controls, which might bias the risk estimates toward the null and underestimate the true effect of coffee and tea consumption on HNC risk. The possibility of differential misclassification is unlikely because the general population might not associate coffee and tea consumption with HNC risk. For pooled case–control studies, another potential limitation is data harmonization. Although the questions were similar across studies, three studies ascertained coffee and tea consumption using ranges of cups consumed rather than specifying the exact cup counts. In additional stratified analysis comparing ORs for studies with exact counts versus ranges, similar ORs were found for the HNC analysis, with differences for hypopharyngeal cancer and decaffeinated coffee possibly due to the small sample size for the studies with ranges.

Additionally, the studies in this analysis were primarily from North America and Europe, which limits the generalizability of these results to other populations because coffee and tea consumption habits in South America, Africa, and Asia are different. Further studies encompassing other regions are needed to account for the possible variation in types and processing of coffee and tea with respect to their favorable effect on HNC incidence. Missing data were also imputed for an INHANCE study that did not collect information on fruit and vegetable intake. However, similar risk estimates were observed after exclusion of the study from the main analysis. Finally, questions for both coffee and tea did not include duration of coffee/tea consumption, concentrations, types of coffee/tea, beverage temperature, and processing techniques. Although our study was able to examine differences between caffeinated and decaffeinated coffee, we were unable to examine differences between caffeinated and herbal/decaffeinated tea due to insufficient data for decaffeinated tea. Caffeinated teas, such as green, black, and oolong teas, are derived from leaves of the *Camellia sinensis*, whereas herbal teas are derived from roots, leaves, and flowers of other plant species.[31] Although both contain polyphenols with antioxidative effects, caffeinated tea has been more commonly consumed and studied in the past. The increasing trend of decaffeinated/herbal tea consumption warrants examination in future studies.

In conclusion, our findings support associations on the protective effects of coffee and tea consumption on HNC risk. Further studies should assess the effects of coffee and tea consumption in regions beyond North America and Europe, especially in low- and middle-income countries burdened by HNC, as well as including different coffee and tea types and processing styles, which may further help contribute to an understanding of the mechanisms for the association between coffee and tea consumption and HNC risk.

AUTHOR CONTRIBUTIONS

Timothy Nguyen: Software, formal analysis, visualization, writing–original draft, writing–review and editing, and validation. **Alzina Koric**: Data curation and writing–review and editing. **Chun-Pin Esther Chang**: Writing–review and editing. **Christine Barul**: Investigation and writing–review and editing. **Loredana Radoi**: Investigation and writing–review and editing. **Diego Serraino**: Investigation and writing–review and editing. **Mark P. Purdue**: Investigation and writing–review and editing. **Karl T. Kelsey**: Investigation and writing–review and editing. **Michael D. McClean**: Investigation and writing–review and editing. **Eva Negri**: Investigation and writing–review and editing. **Valeria Edefonti**: Investigation and writing–review and editing. **Kirsten Moysich**: Investigation and writing–review and editing. **Zuo-Feng Zhang**: Investigation and writing–review and editing. **Hal Morgenstern**: Investigation and writing–review and editing. **Fabio Levi**: Investigation and writing–review and editing. **Thomas L. Vaughan**: Investigation and writing–review and editing. **Carlo La Vecchia**: Investigation and writing–review and editing. **Werner Garavello**: Investigation and writing–review and editing. **Richard B. Hayes**: Investigation and writing–review and editing. **Simone Benhamou**: Investigation and writing–review and editing. **Stimson P. Schantz**: Investigation and writing–review and editing. **Guo-Pei Yu**: Investigation and writing–review and editing. **Hermann Brenner**: Investigation and writing–review and editing. **Shu-Chun Chuang**: Data curation. **Paolo Boffetta**: Investigation and writing–review and editing. **Mia Hashibe**: Conceptualization, project administration, investigation, writing–review and editing, and supervision. **Yuan-Chin Amy Lee**: Conceptualization, data curation, methodology, project administration, writing–review and editing, writing–original draft, supervision, and validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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