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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 (HN) cancers, with inconsistent results.

Methods—We pooled individual-level data from nine case-control studies of HN cancers, including 5139 cases and 9028 controls. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) adjusting for potential confounders.

Results—Caffeinated coffee intake was inversely related with the risk of cancer of the oral cavity and pharynx (OP): the ORs were 0.96 (95% CI 0.94–0.98) for an increment of one cup per day and 0.61 (95% CI 0.47–0.80) in drinkers of >4 cups per day vs. non-drinkers. This latter estimate was consistent for different anatomical sites (ORs were 0.46, 95%CI 0.30–0.71 for oral cavity, 0.58, 95% CI 0.41–0.82 for oropharyngeal/hypopharyngeal and 0.61, 95% CI 0.37–1.01 for OP not otherwise specified), and across strata of selected covariates. No association of

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AUTHOR CONTRIBUTIONS

CG, AT, CP, FT conducted the statistical analysis and drafted the manuscript. MH, PB, CLV designed the study and obtained funding to carry out the study. DMW, FL, GPY, HM, KK, LDM, MPP, MM, RT, RBH, SF, SS, ZFZ contributed data from their individual studies. GF and SC managed the data and contributed to the statistical analysis. All co-authors contributed to the final manuscript draft.

caffeinated coffee drinking was found with laryngeal cancer (OR=0.96, 95% CI 0.64–1.45 in drinkers of >4 cups per day vs. non-drinkers). Data on decaffeinated coffee were too sparse for detailed analysis, but indicated no increased risk. Tea intake was not associated with HN cancer risk (OR=0.99, 95% CI 0.89–1.11 for drinkers vs. non-drinkers).

Conclusions—This pooled-analysis of case-control studies support the hypothesis of an inverse association between caffeinated coffee drinking and OP cancer risk.

Impact—Given widespread use of coffee and the relatively high incidence and low survival of HN cancers, the observed inverse association may have appreciable public health relevance.

Keywords

coffee; head-neck cancer; laryngeal cancer; oral cancer; pharyngeal cancer; pooled analysis; tea

INTRODUCTION

Tobacco smoking and alcohol drinking are the major risk factors for cancers of the oral cavity and pharynx (OP) and of the larynx (head and neck, HN, cancers) and together are responsible of about 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 (IARC) evaluated the evidence of an association between coffee intake and HN 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 OP cancer risk was examined in at least two other prospective studies (6,7) and several case-control studies (8–21). Two cohort (6,7) and three case-control studies (10,12,19) 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 HN 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 oesophagus besides HN: a multicenter case-control study, conducted in several European countries (Alcohol-Related Cancers And Genetic susceptibility in Europe, ARCAGE) (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 HN 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 HN cancer risk, while 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 HN cancers using data from a pooled-analysis of studies collected by the International Head and Neck Cancer Epidemiology (INHANCE) consortium (30).

METHODS

The INHANCE consortium includes 33 epidemiologic studies providing data on 24,571 cases of HN cancers, and 33,013 controls, from many countries and regions, including carcinomas of the oral cavity and 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 the nine case-control studies included OP cancer and 7 studies included also laryngeal cancer. The characteristics of the studies are reported in Table 1.

Cases were subdivided in the following sites: 1) oral cavity (including lip, tongue, gum, floor of mouth and hard palate); 2) oropharynx (including base of tongue, lingual tonsil, soft palate, uvula, tonsil and oropharynx); 3) hypopharynx (including pyriform sinus); 4) oral cavity, pharynx unspecified or overlapping (not otherwise specified, NOS); 5) larynx (including glottis, supraglottis and subglottis); 6) HN cancers unspecified (including overlapping lesions not listed above).

This pooled-analysis is based on a total of 3915 cases of cancer of the OP (1191 of the oral cavity, 2112 of oropharynx/hypopharynx and 612 of OP NOS) and 9028 controls from 9 studies (1,32–39), and 1224 cases of cancer of the larynx and 7239 controls from 7 studies (32–38).

Controls were patients in hospital for acute, non neoplastic diseases, not related to tobacco smoking and alcohol drinking, in five studies (32–35,38); and they were population controls in the other studies (1,36,37,39). Two studies were multicenter themselves (1,34) (Table 1). In the present report, the Italian multicentric study includes also 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, pooled in a standardized way into a common database including a range of sociodemographic, behavioural, lifestyle and health information (30).

The questions about caffeinated, decaffeinated coffee and tea drinking were similar across studies, although the exact wording differed. The information was collected as cups of caffeinated, 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). The information across the 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 HN cancers and caffeinated coffee, decaffeinated coffee or tea intake was assessed by estimating odds ratios (OR) and the corresponding 95% confidence intervals (CI) using unconditional logistic regression models. All the models included study centre, 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 packs/year, categorically), duration of cigar smoking (continuously), duration of pipe smoking (continuously), alcohol drinking (non drinkers, >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 imputation (5 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 HN cancers combined and of each anatomical 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, geographical 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 multicentre study (1) and the Central American study (39) did not include laryngeal cancer.

The distribution of cases at various organs within HN and controls according to age, sex and other selected covariates is shown in Table 2. Males were 76% of OP and 90% of laryngeal cancer cases, and non-Hispanic Whites were 86% and 95%, respectively. Cases were less educated than controls, more often smokers and heavy alcohol drinkers.

The ORs of HN cancer for consumption of caffeinated coffee, decaffeinated coffee and tea are reported in Table 3. Compared with non drinkers, the ORs of OP cancer 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 OP NOS cancer (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 OP cancer (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 OP NOS cancer), 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 OP or laryngeal cancers. Decaffeinated coffee was consumed by 11–15% of cases of OP cancer and by 12%

of controls, with corresponding ORs of 1.05 (95% CI 0.85–1.29) for OP cancer, 1.17 (95% CI 0.81–1.69) for oral, 0.94 (95% CI 0.72–1.23) for oropharyngeal/hypopharyngeal, and 1.40 (95% CI 0.93–2.12) for OP NOS cancer. 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 OP cancer 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 to non drinkers of any type of coffee, the ORs for drinkers of both types of coffee were 0.79 (95% CI: 0.51–1.21) for OP cancer, 0.72 (95% CI: 0.39–1.33) for oral, 0.80 (95% CI: 0.46–1.38) for oropharyngeal/hypopharyngeal and 1.11 (95% CI: 0.54–2.29) for OP NOS cancer. The corresponding OR for laryngeal cancer was 0.92 (95% CI: 0.34–2.53).

Compared to tea non drinkers, the ORs for tea drinkers were 0.99 (95% CI: 0.89–1.11) for OP cancer, 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 OP 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 OP cancer. Panel A gives the ORs for >0–<3 cups per day, panel B gives the ORs for ≥3–≤4 cups per day, and panel C gives the ORs for >4 cups per day, versus non drinkers of caffeinated coffee. For an intake of >4 cups per day of caffeinated coffee, the ORs of OP cancer were below unity in seven studies (significant in two studies) and above unity in two studies (non significant), resulting in a summary OR of 0.61 (95% CI: 0.49–0.77) with 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–<3 cups per day, panel B gives the ORs for ≥3–≤4 cups per day, and panel C gives the ORs for >4 cups per day, versus non drinkers 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 (non significant), 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 OP cancer varying between 0.58 and 0.68.

Table 4 reports the ORs of OP cancer 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, 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 OP cancer. 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 OP cancer 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, but most studies had inadequate information on these issues. Another source of heterogeneity is that some subjects with low or irregular consumption of coffee may have been included among non drinkers 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 HN cancer risk (42–44). However, the inverse association was similar in strata of tobacco smoking and alcohol drinking. When we stratified for geographic region, no heterogeneity was detected within European studies and within American studies, separately, indicating that it could be at least partly explained by different modalities of consumption among European and US 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 OP cancer risk.

The presence of pre-neoplastic 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 OP cancer and found a relative risk (RR) of 0.73 for drinkers of 7 or more cups per day of coffee compared to 2 or less; 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, included 48 cases and found a RR of 0.35 (95% CI: 0.16–0.77) for drinkers of one or more 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 OP cancer. 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 (HPV) infection, which has been causally associated with oropharyngeal cancer (50), but there is no reason to think that coffee intake is associated with HPV 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 HN cancer risk, of the at least eleven case-control studies not included in the INHANCE consortium (8,9,13–16,18,20,21,51), one study from the USA (13), one from Brazil (14) and one from Montenegro (20) considering OP cancer, and six studies considering oral or hypopharyngeal cancer (9,15,16,18,21,51) found no significant association with coffee drinking, but 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, i.e., those with a quantification of the amount of coffee (one cohort and five case-control, for a total of 1628 cases) (7,13–16,21), the summary RR for the highest category of coffee consumption as compared to 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 OP and laryngeal cancers, 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 OP/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 HN cancers is too limited to draw any conclusion (49).

Support for a real inverse association between caffeinated coffee intake and OP cancer 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 OP cancer (4,23,24), support a real association between caffeinated coffee intake and the risk of OP cancer. The lack of association with tea drinking argues against reverse causality and report bias too, though 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 OP cancer 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) (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 inhibiting N-acetyltransferase (59). Still, no definite biological mechanism of the potential healthy role of coffee on HN 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 OP cancer risk, and provide a more precise estimate of the magnitude of the effect. Bias, confounding and reverse causality, however, cannot be excluded. Given widespread use of coffee and the high incidence and low survival of HN cancers (62), it is important to conclusively establish whether the observed association between caffeinated coffee drinking and HN cancer risk is causal as this would have appreciable public health relevance, though alcohol and tobacco remain the key risk factors for OP cancer in most population (1).

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Abbreviations

ARCAGE	Alcohol-Related Cancers And Genetic susceptibility in Europe
CI	confidence interval
HN	head and neck
IARC	International Agency for Research on Cancer
INHANCE	International Head and Neck Cancer Epidemiology
OP	oral cavity and pharynx
OR	odds ratio
RR	relative risk

References

1. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Research 1988;48:3282. [PubMed: 3365707]

2. Negri E, La Vecchia C, Franceschi S, Tavani A. Attributable risk for oral cancer in northern Italy. Cancer Epidemiol Biomarkers Prev 1993;2:189–93. [PubMed: 8318870]
3. Goldenberg D. Maté: a risk factor for oral and oropharyngeal cancer. Oral Oncology 2002;38:646–9. [PubMed: 12167417]
4. Mayne, ST.; Morse, DE.; Winn, DM., editors. Cancer epidemiology and prevention. New York: Oxford Press; 2006. Cancers of the oral cavity and pharynx.
5. IARC. IARC Monogr Eval Carcinog Risks Hum. Lyon, France: IARC Press; 1991. Coffee, tea, mate, methylxanthines and methylglyoxal.
6. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994;5:401–8. [PubMed: 7999961]
7. Naganuma T, Kuriyama S, Kakizaki M, et al. Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. Am J Epidemiol 2008;168:1425–32. [PubMed: 18974083]
8. Restrepo HE, Correa P, Haenszel W, Brinton LA, Franco A. A case-control study of tobacco-related cancers in Colombia. Bull Pan Am Health Organ 1989;23:405–13. [PubMed: 2611462]
9. Franco EL, Kowalski LP, Oliveira BV, et al. Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer 1989;43:992–1000. [PubMed: 2732011]
10. Franceschi S, Bidoli E, Baron AE, et al. Nutrition and cancer of the oral cavity and pharynx in north-east Italy. Int J Cancer 1991;47:20–5. [PubMed: 1985874]
11. La Vecchia C, Negri E, D'Avanzo B, Boyle P, Franceschi S. Dietary indicators of oral and pharyngeal cancer. Int J Epidemiol 1991;20:39–44. [PubMed: 2066242]
12. Franceschi S, Barra S, La Vecchia C, et al. Risk factors for cancer of the tongue and the mouth. A case-control study from northern Italy. Cancer 1992;70:2227–33. [PubMed: 1394055]
13. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993;72:1369–75. [PubMed: 8339227]
14. Pintos J, Franco EL, Oliveira BV, et al. Mate, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in southern Brazil. Epidemiology 1994;5:583–90. [PubMed: 7841239]
15. Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control 1995;6:57–67. [PubMed: 7718736]
16. Takezaki T, Hirose K, Inoue M, et al. Tobacco, alcohol and dietary factors associated with the risk of oral cancer among Japanese. Jpn J Cancer Res 1996;87:555–62. [PubMed: 8766517]
17. Uzcudun AE, Retolaza IR, Fernandez PB, et al. Nutrition and pharyngeal cancer: results from a case-control study in Spain. Head Neck 2002;24:830–40. [PubMed: 12211047]
18. Petridou E, Zavras AI, Lefatzis D, et al. The role of diet and specific micronutrients in the etiology of oral carcinoma. Cancer 2002;94:2981–8. [PubMed: 12115387]
19. Tavani A, Bertuzzi M, Talamini R, et al. Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. Oral Oncol 2003;39:695–700. [PubMed: 12907209]
20. Vlajinac HD, Marinkovic JM, Sipetic SB, et al. Case-control study of oropharyngeal cancer. Cancer Detect Prev 2006;30:152–7. [PubMed: 16647226]
21. Heck JE, Sapkota A, Vendhan G, et al. Dietary risk factors for hypopharyngeal cancer in India. Cancer Causes Control 2008;19:1329–37. [PubMed: 18704720]
22. Jacobsen BK, Bjelke E, Kvale G, Heuch I. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. J Natl Cancer Inst 1986;76:823–31. [PubMed: 3457969]
23. La Vecchia C, Negri E, D'Avanzo B, et al. Dietary indicators of laryngeal cancer risk. Cancer Res 1990;50:4497–500. [PubMed: 2369728]
24. Zatonski W, Becher H, Lissowska J, Wahrendorf J. Tobacco, alcohol, and diet in the etiology of laryngeal cancer: a population-based case-control study. Cancer Causes Control 1991;2:3–10. [PubMed: 1873431]
25. Bosetti C, La Vecchia C, Talamini R, et al. Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. Int J Cancer 2002;100:355–60. [PubMed: 12115553]

26. Zvrko E, Gledovic Z, Ljaljevic A. Risk factors for laryngeal cancer in Montenegro. Arh Hig Rada Toksikol 2008;59:11–8. [PubMed: 18407867]
27. Lagiou P, Talamini R, Samoli E, et al. Diet and upper-aerodigestive tract cancer in Europe: the ARCAGE study. Int J Cancer 2009;124:2671–6. [PubMed: 19230023]
28. Chyou PH, Nomura AM, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. Int J Cancer 1995;60:616–21. [PubMed: 7860134]
29. Ide R, Fujino Y, Hoshiyama Y, et al. A prospective study of green tea consumption and oral cancer incidence in Japan. Ann Epidemiol 2007;17:821–6. [PubMed: 17606381]
30. Conway DI, Hashibe M, Boffetta P, et al. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. Oral Oncol 2009;45:743–6. [PubMed: 19442571]
31. Elahi A, Zheng Z, Park J, et al. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis 2002;23:1229–34. [PubMed: 12117782]
32. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res 1990;50:6502–7. [PubMed: 2208109]
33. Benhamou S, Tuimala J, Bouchardy C, et al. DNA repair gene XRCC2 and XRCC3 polymorphisms and susceptibility to cancers of the upper aerodigestive tract. Int J Cancer 2004;112:901–4. [PubMed: 15386379]
34. Bosetti C, Gallus S, Trichopoulou A, et al. Influence of the Mediterranean diet on the risk of cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 2003;12:1091–4. [PubMed: 14578148]
35. Levi F, Pasche C, La Vecchia C, et al. Food groups and risk of oral and pharyngeal cancer. Int J Cancer 1998;77:705–9. [PubMed: 9688303]
36. Cui Y, Morgenstern H, Greenland S, et al. Polymorphism of Xeroderma Pigmentosum group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. Int J Cancer 2006;118:714–20. [PubMed: 16094634]
37. Peters ES, McClean MD, Liu M, et al. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. Cancer Epidemiol Biomarkers Prev 2005;14:476–82. [PubMed: 15734975]
38. Schantz SP, Zhang ZF, Spitz MS, Sun M, Hsu TC. Genetic susceptibility to head and neck cancer: interaction between nutrition and mutagen sensitivity. Laryngoscope 1997;107:765–81. [PubMed: 9185733]
39. Hayes RB, Bravo-Otero E, Kleinman DV, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. Cancer Causes Control 1999;10:27–33. [PubMed: 10334639]
40. Rossi M, Garavello W, Talamini R, et al. Flavonoids and the risk of oral and pharyngeal cancer: a case-control study from Italy. Cancer Epidemiol Biomarkers Prev 2007;16:1621–5. [PubMed: 17684136]
41. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88. [PubMed: 3802833]
42. Morabia A, Wynder EL. Dietary habits of smokers, people who never smoked, and exsmokers. Am J Clin Nutr 1990;52:933–7. [PubMed: 2239771]
43. La Vecchia C, Negri E, Franceschi S, Parazzini F, Decarli A. Differences in dietary intake with smoking, alcohol, and education. Nutr Cancer 1992;17:297–304. [PubMed: 1437648]
44. Wynder EL, Hall NE, Polansky M. Epidemiology of coffee and pancreatic cancer. Cancer Res 1983;43:3900–6. [PubMed: 6861152]
45. Ferraroni M, Tavani A, Decarli A, et al. Reproducibility and validity of coffee and tea consumption in Italy. Eur J Clin Nutr 2004;58:674–80. [PubMed: 15042137]
46. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200. [PubMed: 1415141]
47. Jacobsen BK, Bonaa KH. The reproducibility of dietary data from a self-administered questionnaire. The Tromso Study. Int J Epidemiol 1990;19:349–53. [PubMed: 2376446]

48. Johansson L, Solvoll K, Opdahl S, Bjorneboe GE, Drevon CA. Response rates with different distribution methods and reward, and reproducibility of a quantitative food frequency questionnaire. Eur J Clin Nutr 1997;51:346–53. [PubMed: 9192190]
49. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and Prevention of Cancer: A Global Perspective. Washington DC: American Institute for Cancer Research; 2007.
50. IARC. IARC Monogr Eval Carcinog Risks Hum. Lyon France: IARC Press; 2007. Human Papillomaviruses.
51. Guneri P, Cankaya H, Yavuzer A, et al. Primary oral cancer in a Turkish population sample: association with sociodemographic features, smoking, alcohol, diet and dentition. Oral Oncol 2005;41:1005–12. [PubMed: 16139559]
52. La Vecchia C, Tavani A. Coffee and cancer risk: an update. Eur J Cancer Prev 2007;16:385–9. [PubMed: 17923807]
53. Cavin C, Holzhaeuser D, Scharf G, et al. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. Food Chem Toxicol 2002;40:1155–63. [PubMed: 12067578]
54. Daglia M, Papetti A, Gregotti C, Berte F, Gazzani G. In vitro antioxidant and ex vivo protective activities of green and roasted coffee. J Agric Food Chem 2000;48:1449–54. [PubMed: 10820041]
55. Anese M, Nicoli MC. Antioxidant properties of ready-to-drink coffee brews. J Agric Food Chem 2003;51:942–6. [PubMed: 12568553]
56. Viani, R. The composition of coffee. In: Garattini, editor. Caffeine, Coffee, and Health. New York, NY: Raven Press; 1993. p. 17-41.
57. Cavin C, Holzhauser D, Constable A, Huggett AC, Schilter B. The coffee-specific diterpenes cafestol and kahweol protect against aflatoxin B1-induced genotoxicity through a dual mechanism. Carcinogenesis 1998;19:1369–75. [PubMed: 9744531]
58. Majer BJ, Hofer E, Cavin C, et al. Coffee diterpenes prevent the genotoxic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and N-nitrosodimethylamine in a human derived liver cell line (HepG2). Food Chem Toxicol 2005;43:433–41. [PubMed: 15680679]
59. Huber WW, Parzefall W. Modification of N-acetyltransferases and glutathione S-transferases by coffee components: possible relevance for cancer risk. Methods Enzymol 2005;401:307–41. [PubMed: 16399395]
60. Je Y, Liu W, Giovannucci E. Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. Int J Cancer 2009;124:1662–8. [PubMed: 19115212]
61. Bravi F, Scotti L, Bosetti C, et al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol 2009;200:130–5. [PubMed: 19110217]
62. Boyle, P.; Levin, B. World cancer report 2008. IARC Press; 2008.

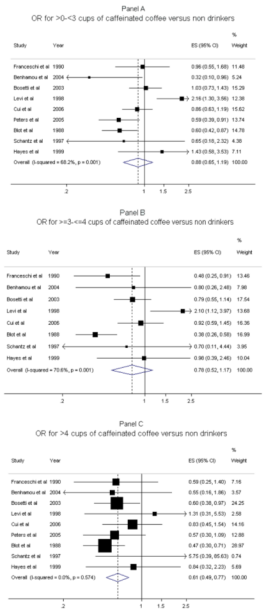

Figure 1.

Study specific and pooled estimates of OP cancer for drinkers of caffeinated coffee versus non drinkers

NOTE In Panel B the study by Peters et al 2005 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, 3–4 cups per day). Small differences in the estimates between the figure and Table 3 are due to rounding off of data.

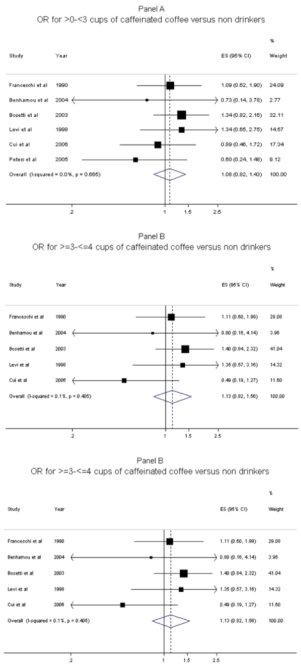

Figure 2.

Study specific and pooled estimates of laringeal cancer for drinkers of caffeinated coffee versus non drinkers

NOTE In Panel B two studies are missing. Study by Peters et al. 2005 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, 3–4 cups per day); study by Schantz et al 1997 is missing because the OR was not estimable, respectively. Small differences in the estimates between the figure and Table 3 are due to rounding off of data.

TABLE 1

Characteristics of individual studies of the International Head and Neck Cancer Epidemiology (INHANCE) consortium pooled analysis and including information on caffeinated coffee, decaffeinated coffee or tea drinking

Study reference[a]	Study location	Reicruitment period	Source (cases/controls)	Information on			Participation rate of cases and controls (%)	Age eligibility (years)	Total oral cavity/pharynx			Larynx	Controls[b]
				Caffeinated Coffee	Decaffeinated coffee	Tea			Oral cavity	Oropharynx/ hypopharynx	Oral cavity/ pharynx NOS		
	Europe												
(32)	Italy (Milan)	1984–1989	hospital/hospital	Yes	Yes	Yes	95[c]-95[c]	<80	48	61	65	242	1531
(33)	France	1987–1992	hospital/hospital	Yes	No	Yes	95[c] -95[c]	Not reported	49	102	18	154	234
(34,40)	Italy Multicenter (Aviano, Milan, Latina)	1990–2005	hospital/hospital	Yes	Yes	Yes	>95[c]-95	18–80	209	502	90	460	2716
(35)	Switzerland (Lausanne)	1991–1997	hospital/ hospital	Yes	Yes	Yes	95[c] -95[c]	<80	138	247	7	124	883
	North America												
(36)	USA (Los Angeles)	1999–2004	cancer registry/ neighborhood	Yes	Yes	Yes	49–67.5	18–65	53	173	112	90	1040
(37)	USA (Boston)	1999–2003	hospital/residential records	Yes	Yes	Yes	88.7–87.3	≥18	139	291	43	111	659
(1)	USA Multicenter (Atlanta, Los Angeles, San Francisco, New Jersey)	1983–1984	cancer registry/random digit dialing-healthcare financing	Yes	No	Yes	75–76	18–79	386	510	218	-	1268
(38)	MSKCC New York	1992–1994	hospital/hospital	Yes	Yes	Yes	95[c] -95[c]	>20	75	26	2	43	176
	Central America												
(39)	Puerto Rico	1992–1995	cancer registry/residential records	Yes	No	Yes	71–83	21–79	94	200	521	-	521
	Total subjects								1191	2112	612	1224	9028

[a] Representative publications in which study methods are available.

[b] The total number of controls for the analyses on laryngeal cancer was 7239, as two studies were not included (1,39).

[c] Participation rate was not formally assessed.

TABLE 2

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

	Cancer of the oral cavity/pharynx (n=3915)		Controls (n=9028)		Cancer of the larynx (n=1224)		Controls (n=7239)	
	n	%	n	%	n	%	N	%
Age (years)								
<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	1457	16.1	180	14.7	1245	17.2
55–59	754	19.3	1604	17.8	262	21.4	1351	18.7
60–64	624	15.9	1320	14.6	247	20.2	1010	14.0
65–69	583	14.9	1253	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	2970	76.0	6343	70.3	1105	90.3	5089	70.4
Women	940	24.0	2680	29.7	118	9.7	2145	29.6
Missing	5		5		1		5	
p (χ^2 test, two-sided)		<0.001				<0.001		
Race/ethnicity								
Non-Hispanic white	3354	86.0	8116	90.3	1157	95.0	6753	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[a]	133	3.4	190	2.1	10	0.8	94	1.2
Missing	13		36		6		36	
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	1173	30.1	3635	40.5	675	55.5	3409	47.4

	Cancer of the oral cavity/pharynx (n=3915)		Controls (n=9028)		Cancer of the larynx (n=1224)		Controls (n=7239)	
	n	%	n	%	n	%	N	%
Some high school	835	21.4	1221	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	1021	26.2	1987	22.1	147	12.1	1060	14.7
College graduate/postgraduate	430	11.1	1289	14.3	110	9.0	1233	17.2
Missing	220		250		168		249	
p (χ^2 test, two-sided)	<0.001				<0.001			
Cigarette smoking (pack/year)								
Never smokers	570	14.8	3571	40.1	58	4.8	2907	40.8
1–10	261	6.8	1477	16.6	71	5.9	1234	17.3
11–20	340	8.8	1039	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	1240	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 (years)								
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			
Duration of pipe smoking (years)								
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 per day)								
Non drinkers	356	9.4	1894	21.5	113	9.6	1618	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	1230	14.0	73	6.2	942	13.3

	Cancer of the oral cavity/pharynx (n=3915)		Controls (n=9028)		Cancer of the larynx (n=1224)		Controls (n=7239)	
	n	**%**	**n**	**%**	**n**	**%**	**N**	**%**
>18 – 40	565	14.9	1603	18.2	146	12.4	1365	19.3
>40 – 75	640	16.9	1358	15.4	248	21.0	1245	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			

[a]Other includes Brazilian, Asian and Pacific islanders and other races

TABLE 3

Distribution of cases of head and neck cancers by anatomical site and of controls, and corresponding odds ratios[a] (OR) and 95% confidence intervals (CI), according to caffeinated coffee, decaffeinated coffee and tea drinking

	Oral cavity/pharynx (OP)									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 [b]												
Non drinkers	1435	542	1[c]	177	1[c]	284	1[c]	81	1[c]	1293	144	1[c]
Drinkers	7496	3203	0.84 (0.60–1.18)	953	0.62 (0.40–0.99)	1739	0.82 (0.55–1.23)	511	0.76 (0.52–1.11)	5855	1034	1.04 (0.80–1.36)
Cups per day												
>0 to <3	4637	1827	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)	3796	568	1.08 (0.82–1.42)
3 to 4	2029	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)	1527	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	9028	3915		1191		2112		612		7239	1224	
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 one cup per day			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[d]												
Non drinkers	6102	1845	1[c]	512	1[c]	1076	1[c]	257	1[c]	6102	945	1[c]
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 per day												
>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	7005	2281		662		1300		319		7005	1070	
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

	Oral cavity/pharynx (OP)									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)
For an increment of one cup per day			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[d]												
Non drinkers	1004	314	1[c]	96	1[c]	180	1[c]	38	1[c]	1004	105	1[c]
Only caffeinated coffee drinkers	5093	1530	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)	5093	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)
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	7005	2281		662		1300		319		7005	1070	
P for heterogeneity between studies			<0.01		0.14		<0.01		0.25			0.02
Tea[b]												
Non drinkers	4850	2096	1[c]	604	1[c]	1182	1[c]	310	1[c]	3991	779	1[c]
Drinkers	4076	1648	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)	3155	399	0.97 (0.80–1.18)
Cups per day												
≤1	3398	1362	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)	2670	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	9028	3915		1191		2112		612		7239	1224	
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 one cup per day			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)

[a] We used the random effects estimates when heterogeneity was detected, and the 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, vegetable and fruit intake.

[b] Includes nine studies for OP cancers (1,32–39) and seven studies for laryngeal cancer (32–38).

[c] Reference category.

[d] Includes six studies for both OP and laryngeal cancers (32,34–38)

TABLE 4

Distribution of cases of oral cavity and pharyngeal cancer and controls, and corresponding odds ratios (OR)[a] and 95% confidence intervals (CI), for drinking >4 cups per day of caffeinated coffee vs. non drinkers, in strata of selected covariates

	Oral cavity and pharynx cancer			
	Controls (n=830)	Cases (n=525)	OR (95% CI)	p for heterogeneity[b]
Age (years)				
<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[c]				
Europe	412	132	0.63 (0.43–0.92)	0.07
America	418	393	0.60 (0.45–0.80)	0.11
Education[d]				
<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[d,e]				
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[d,f]				
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[d]				
<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

[a] We used the random effects estimates when heterogeneity was detected, and the 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, vegetable and fruit intake (as appropriate). Reference category was coffee non drinkers in each stratum.

[b] Between studies

[c] Europe included two studies from Italy (32,34), one from France (33) and one from Switzerland (35). America included four studies from USA (1,36–38) and one from Puerto Rico (39).

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

[e] 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.

[f] Never/Light drinkers were drinkers of <3 drinks per day of alcoholic beverages and heavy drinkers those consuming ≥3 drinks per day.