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Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies

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Background: Data of epidemiological studies on the relation between coffee drinking and upper aerodigestive tract cancer risk are scattered and inconclusive. We therefore conducted systematic meta-analyses of observational studies published before October 2009.

Materials and methods: We combined relative risks (RR) with 95% confidence intervals (CI) for cancers of the oral cavity/pharynx (OP) and larynx, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), comparing the highest versus the lowest categories of coffee consumption, using random-effects models.

Results: For OP cancer, the pooled RR was 0.64 (95% CI 0.51–0.80) for highest versus lowest coffee drinking, based on a total of 2633 cases from one cohort and eight case–control studies, with no significant heterogeneity across studies. The RRs were 0.61 (95% CI 0.41–0.89) for European, 0.58 (95% CI 0.36–0.94) for American and 0.74 (95% CI 0.48–1.15) for Asian studies, where coffee consumption is lower. The corresponding RRs were 1.56 (95% CI 0.60–4.02) for laryngeal cancer (732 cases from three case–control studies), 0.87 (95% CI 0.65–1.17) for ESCC (2115 cases from one cohort and six case–control studies) and 1.18 (95% CI 0.81–1.71) for EAC (415 cases from three case–control studies).

Conclusion: Coffee drinking is inversely related to OP cancer risk, while there is no relation with laryngeal cancer, ESCC and EAC.

Key words: coffee, esophageal cancer, laryngeal cancer, meta-analysis, oral cancer, pharyngeal cancer

introduction

Tobacco smoking and alcohol drinking are the major risk factors for cancers of the oral cavity and pharynx (OP) and larynx, and esophageal squamous cell carcinoma (ESCC) [1, 2]. Tobacco, obesity and gastroesophageal reflux are the major risk factors for esophageal adenocarcinoma (EAC) in the absence of a role of alcohol [2]. Still a role of dietary factors for these cancers is probable, but not yet defined [3].

Several epidemiological studies analyzed the relation between coffee intake and the risk of OP, laryngeal and esophageal cancers. Their results are however scattered and largely inconclusive [4].

Because of the widespread consumption of coffee in several populations [5], any relation with the risk of these neoplasms would have appreciable public health relevance. To provide overall quantitative estimates of such associations, we combined all published data on coffee, and head and neck and esophageal cancers using a meta-analytic approach.

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materials and methods

study identification and data extraction

We carried out a Medline search in PubMed of all case–control and cohort studies published up to October 2009 using the string '(coffee OR caffeine OR beverages OR diet OR drinking) AND (oral OR pharyngeal OR oropharyngeal OR oropharynx OR pharynx OR mouth OR hypopharyngeal OR hypopharynx OR laryngeal OR larynx OR head OR neck OR esophagus OR oesophagus OR esophageal OR oesophageal OR aerodigestive) AND (cancer OR carcinoma OR tumor OR neoplasm) AND risk', following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [6] and limiting the search to the English language. We selected the papers reporting data on the association between coffee consumption and risk of OP, laryngeal and esophageal cancer incidence, with no previous diagnosis of cancer at any site. Figure 1 gives the flowchart for selection of articles. We checked the reference list of all articles of interest to obtain other pertinent publications. We did not consider abstracts and unpublished results.

Papers were included if they provided a quantitative estimate of the association between coffee drinking and OP (or specific anatomical sites of OP cancer), laryngeal or esophageal cancer risk, expressed as relative risks (RR) or odds ratios (OR) and their 95% confidence intervals (CI) or information sufficient to calculate them. A total of 37 studies met those

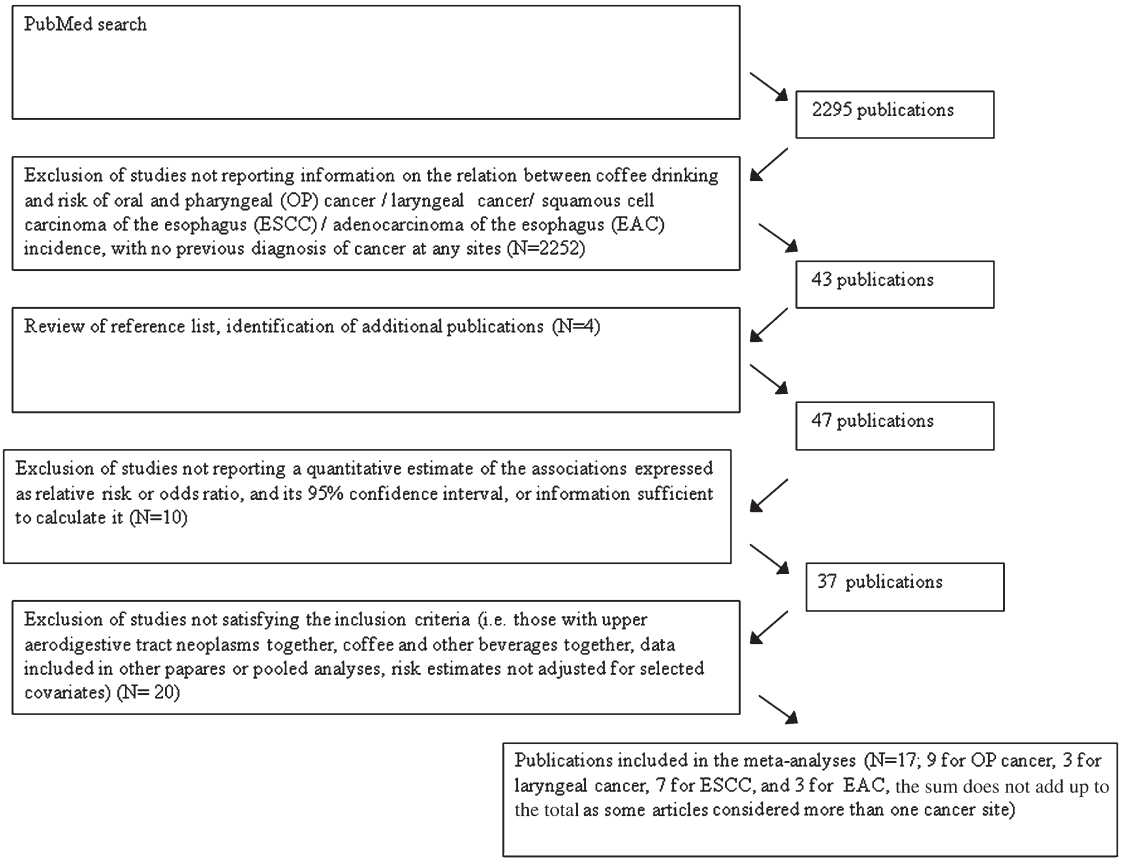

Figure 1. Flow chart of the selection of publications included in the meta-analyses.

criteria. We excluded two studies that considered all upper aerodigestive tract neoplasms together [7, 8] and one study that considered coffee together with hot calvados [9]. A case–control study from Italy and Switzerland on laryngeal cancer that evaluated tea and coffee consumption together [10] was included, due to the limited tea consumption in those countries [11]. When two or more articles provided results from the same study, we included only the more updated one. With regard to esophageal cancer, we analyzed separately ESCC and EAC. For the meta-analyses on the association between coffee intake and OP cancer, laryngeal cancer and ESCC risk, we selected only studies reporting risk estimates adjusted at least for age, sex, smoking habit and alcohol consumption. For EAC, we included in the meta-analysis only studies providing RRs/ORs adjusted at least for age, sex, body mass index, and/or energy intake. When more than one risk estimate was reported, we used the one that adjusted for the largest number of potential confounding factors.

Some of the 17 papers selected reported data for more than one cancer anatomical site. Nine reports gave information for OP cancer, including a total of 2633 cases; three for laryngeal cancer, including 732 cases; seven for ESCC, including 2117 cases and three for EAC, including 415 cases.

statistical analysis

Given the heterogeneity between the categories of coffee consumption across studies, we pooled the risk estimates for the highest versus the lowest drinking categories from each study. For one study reporting the adjusted OR but not the corresponding 95% CI, we used the distribution of cases and controls to compute the standard error of the corresponding crude OR and then the approximate CI for the adjusted one [12]. For the study by Franceschi et al. [13], presenting ORs for cancers of the tongue and mouth separately, with a common control group, we calculated the pooled risk estimate for OP cancer using the method proposed by Hamling et al. [14], taking into account the lack of independence between the ORs. For a Greek study on ESCC and EAC reporting the adjusted OR for the increment of one cup of coffee per day, we calculated the OR and 95% CI for comparison of three versus zero cups per day [15], according to the upper cut-off of two studies from southern Europe [12, 16].

Summary measures were calculated using random-effects models that consider both within- and between-study variations [17]. We presented combined estimates using forest plots. In these graphs, a square was plotted for each study, whose center projection on the underlying scale corresponds to the study-specific RR and whose area is proportional to the inverse of the variance of the natural logarithm of the RR. A diamond was used to plot the summary RR, whose center represents the RR and the extremes the 95% CIs. Statistical heterogeneity among studies was assessed using the χ^2 tests (results were defined as heterogeneous for $P < 0.10$) [18] and the inconsistence was quantified using the I^2 statistic [19]. We evaluated the presence of publication bias using funnel plots [20] and the Begg's and Egger's tests [21].

results

The main characteristics of the studies included in the meta-analyses are summarized in Table 1. For each study, we reported data on study design, country, length of follow-up (for cohort studies) or period of enrollment (for case–control studies), number of subjects (cases and controls or cohort size), the lowest and highest categories of drinking, and covariates included in the multivariate analysis. The *P* values for the

Table 1. Main characteristics of the studies on oral/pharyngeal (OP), laryngeal and esophageal cancers and coffee consumption included in the meta-analyses

First author [reference]	Country	Years of study/ duration of follow-up	No. of cases	No. and type of controls/size of cohort	Coffee, highest versus lowest category	Adjustment factors
OP cancers						
Case–control studies						
La Vecchia [12]	Italy	1983–1988	50[a,b]	1944 hospital based	≥3 versus ≤1 cups per day	Age, sex, social class, education, marital status, smoking, alcohol
Franceschi [13]	Italy	1986–1990	102[c] (Men); 104[d] (Men)	726 (Men) hospital based	Highest versus lowest tertile	Age, residence, occupation, smoking, alcohol
Mashberg [27]	United States	1972–1983	359[e] (Men)	2280 (Men) hospital based	≥5 versus 0 cups per day	Age, race, smoking, alcohol
Pintos [26]	Brazil	1987–1989	169[f]; 112[g]	338; 224 hospital based	≥4 versus ≤1 cups per day	Age, sex, admission period, smoking, alcohol, income, rural residence
Bundgaard [22]	Denmark	1986–1990	161[h]	483 population based	Drinkers versus nondrinkers	Age, sex, smoking, alcohol
Takezaki [23]	Japan	1988–1993	266[i]	36 527 hospital based	Highest versus lowest tertile	Age, sex, year of visit, smoking, alcohol
Tavani [16]	Italy and Switzerland	1991–1997	749[j]	1772 hospital based	>3 versus ≤1 cups per day	Age, sex, center, education, smoking, alcohol, fruits, vegetables
Heck [24]	India	2001–2004	513[k]	718 hospital based	Highest versus lowest quartile	Age, sex, center, socioeconomic status, religion, alcohol, fresh fruits, spices, cereal and smoking in ever tobacco users stratum
Cohort studies						
Naganuma [25] (The Miyagi Cohort Study)	Japan	1990–2003 (13.6 years)	48[l]	38 679 persons at risk, 495 138 persons per year	≥1 cup per day versus never drinkers	Age, sex, body mass index, smoking, alcohol, vegetables, fruits, green tea
Laryngeal cancer						
Case–control studies						
Pintos [26]	Brazil	1987–1990	97	194 hospital based	≥4 versus ≤1 cups per day	Age, sex, admission period, income, rural residency, smoking, alcohol, some dietary variables, nonalcoholic beverages
Bosetti [10]	Italy and Switzerland	1992–2000	527	1297 hospital based	Highest versus lowest quintile (>77 versus ≤14.4 servings per week)	Age, sex, center, education, smoking, alcohol, nonalcoholic energy
Zvrko [28]	Montenegro	2001–2003	108	108 hospital based	>5 versus not specified	Age, sex, residence, alcohol, smoking and other risk factors not reported
ESCC						
Case–control studies						
La Vecchia [12]	Italy	1983–1988	209	1944 hospital based	≥3 versus ≤1 cups per day	Age, sex, social class, education, marital status, smoking, alcohol
Garidou [15]	Greece	1989–1991	43	200 hospital based	Continuous variable (cups per day)	Age, sex, birthplace, education, height, analgesics, alcohol, smoking, energy

Table 1. (*Continued*)

First author [reference]	Country	Years of study/ duration of follow-up	No. of cases	No. and type of controls/size of cohort	Coffee, highest versus lowest category	Adjustment factors
Inoue [29]	Japan	1990–1995	185	21 128 hospital based	≥3 cups per day versus rarely drinkers	Age, sex, years and season at first visit, physical activity, smoking, alcohol, tea, coffee, fruit, rice, beef
Castellsague [31]	Argentina	1986–1992	830	1779 hospital based	>500 ml/day versus never drinkers	Age, sex, center, residence, education, smoking, alcohol
Tavani [16]	Italy and Switzerland	1991–1997	395	1066 hospital based	>3 versus ≤1 cups per day	Age, sex, center, education, smoking, alcohol, fruit, vegetables
Chen [30]	Taiwan	1996–2005	343 (Men)	755 (Men) hospital based	≥1 versus <1 time/week	Age, education, ethnicity, center, smoking, alcohol, areca nut chewing
Cohort studies						
Naganuma [25] (Miyagi Cohort Study)	Japan	1990–2003 (13.6 years)	112	38 679 persons at risk, 495 138 persons per year	≥1 cup per day versus never drinkers	Age, sex, body mass index, alcohol, smoking, vegetables, fruit, green tea
EAC						
Case–control studies						
Brown [33]	United States	1986–1989	174 (Men)	750 (Men) population based	Drinkers of hot coffee versus nondrinkers	Age, area, body mass index, smoking, liquor, income, energy
Garidou [15]	Greece	1989–1991	56	200 hospital based	Continuous variable (cups per day)	Age, sex, birthplace, education, height, analgesics, alcohol, smoking, energy
Terry [32]	Sweden	1994–1997	185	815 population based	>7 versus ≤2 cups per day	Age, sex, body mass index, energy, energy adjusted alcohol, fruit, vegetables, smoking, antacids

ESCC, esopgageal squamous cell carcinoma; EAC, esopgageal adenocarcinoma; ICD, International Classification of Diseases.
[a]A few of these cancer cases are included also in Franceschi et al. [13].
[b]Oral cavity and pharynx.
[c]Tongue (ICD-9: 141).
[d]Other oral cavity (ICD-9: 143–145, 149).
[e]Oral cavity and oropharynx.
[f]Oral cavity (ICD-9: 140, 141, 143–145).
[g]Pharynx (ICD-9: 146, 148, 149).
[h]Oral cavity.
[i]Oral cavity and pharynx (ICD-9; 141, 143–146, 148).
[j]Oral cavity and pharynx.
[k]Hypopharynx.
[l]Oral cavity and pharynx (ICD-10: C00.0–09.9, C10.0–10.9, C12.9–14.8).

Begg's and Egger's tests were not significant. For OP cancer, we selected eight case–control studies and one cohort study. Three studies were conducted in southern Europe [12, 13, 16] and accounted together for ~38% of all cases (1005 cases) of OP cancer; one case–control study was from northern Europe [22] (161 cases), two case–control and one prospective studies were from Asia [23–25] (827 cases), one case–control study from South America [26] (281 cases), and one from North America [27] (359 cases). For laryngeal cancer, we considered two case–control studies from southern Europe [10, 28] (635 cases) and one from South America [26] (97 cases). Three of the seven studies on ESCC were from southern Europe [12, 15, 16] (647 cases), one cohort and two case–control studies from Asia [25, 29, 30] (640 cases), and one was a pooled analysis combining five case–control studies from South America [31] (830 cases). As concern EAC, one case–control study was conducted in southern Europe [15] (56 cases), one in northern Europe [32] (185 cases), and one in North America [33] (174 cases).

Figure 2 shows the RRs for the highest versus the lowest coffee drinking level, as categorized in each study, for OP

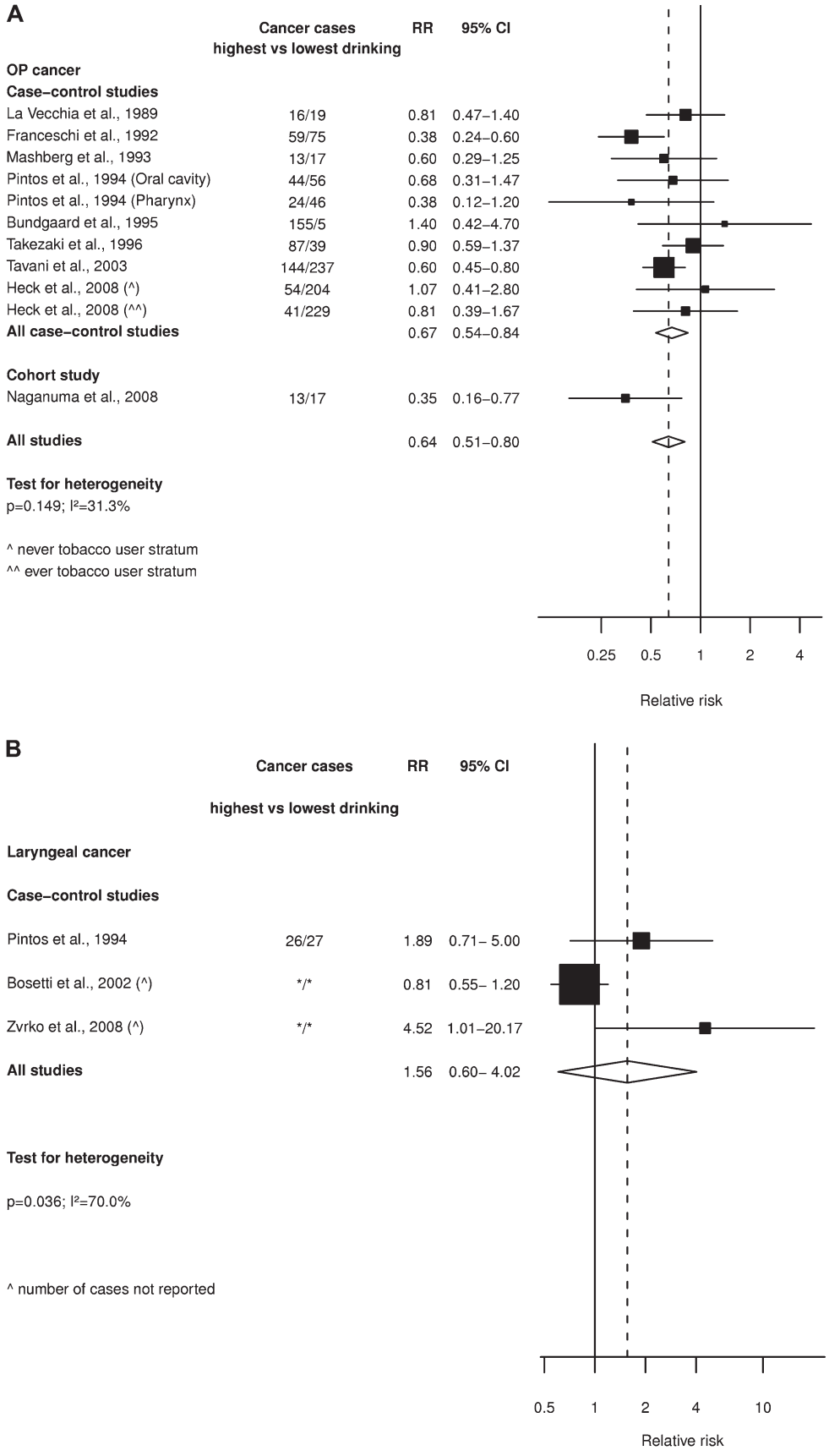

Figure 2. Forest plots of studies on the risk of (A) oral and pharyngeal (OP) cancer, (B) laryngeal cancer, (C) esopgageal squamous cell carcinoma (ESCC) and (D) esopgageal adenocarcinoma (EAC) for highest versus lowest coffee drinking. The combined relative risks (RR) are calculated using the random-effects method.

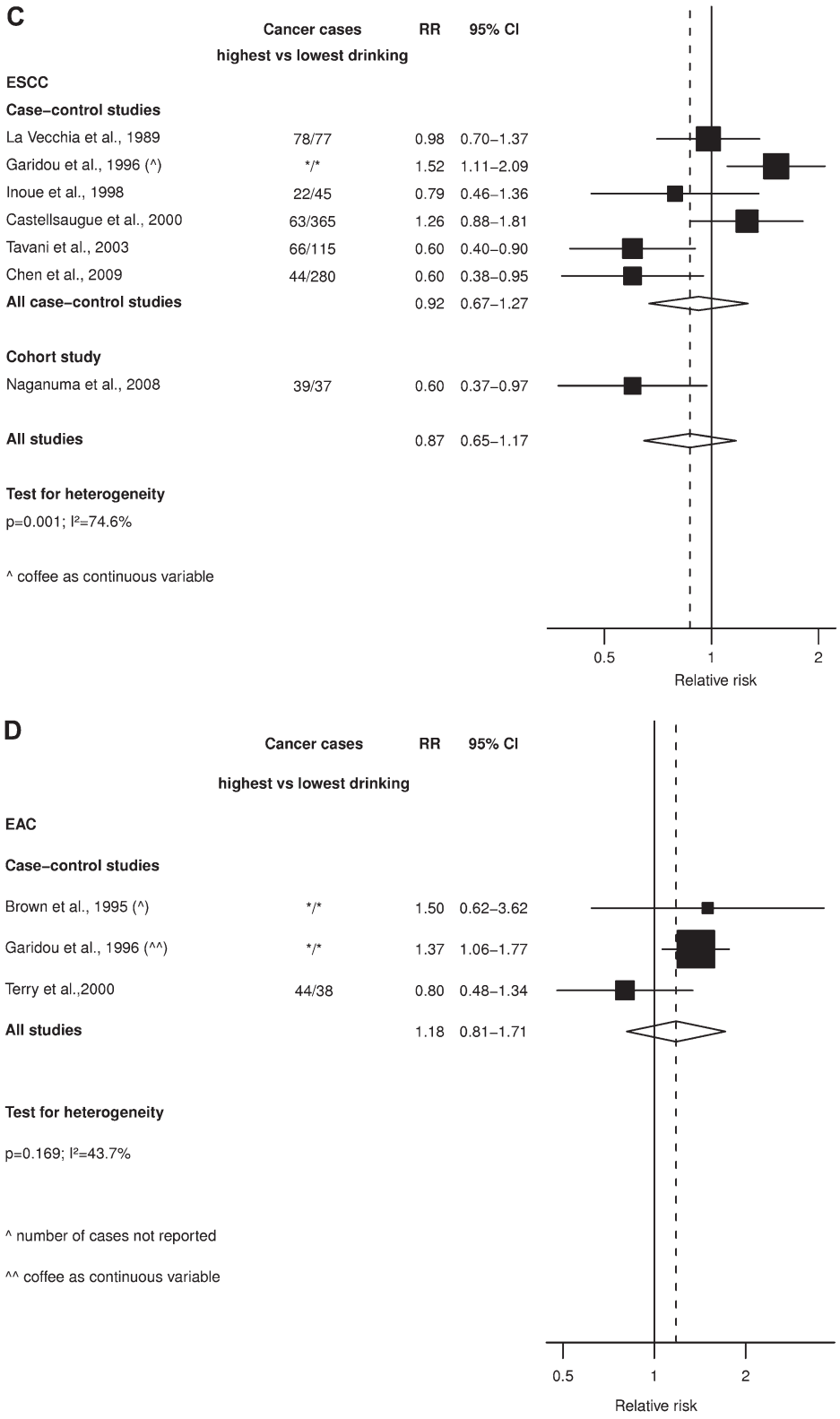

Figure 2. (*Continued*)

cancer (Figure 2A), laryngeal cancer (Figure 2B), ESCC (Figure 2C), and EAC (Figure 2D). For OP cancer, nine RR estimates were below unity (significant in three studies) and two were above unity (nonsignificant), resulting in a summary RR of 0.64 (95% CI 0.51–0.80), with no significant heterogeneity across studies (P for heterogeneity = 0.149, I^2 = 31.3%). Considering only the studies with the upper cut-off of at least three cups per day [12, 16, 26, 27], we found a pooled OR of

0.65 (95% CI 0.54–0.77) compared with consumption of one or less cup per day. We also considered the RR of OP cancer in strata of geographic region. The cumulative RRs for highest versus lowest coffee drinking were 0.61 (95% CI 0.41–0.89) for studies conducted in Europe [12, 13, 16, 22], 0.58 (95% CI 0.36–0.94) for those conducted in the Americas [26, 27], and 0.74 (95% CI 0.48–1.15) for those conducted in Asia [23–25], without heterogeneity across strata (P for heterogeneity = 0.724). The summary RR for laryngeal cancer (Figure 2B) was 1.56 (95% CI 0.60–4.02), with heterogeneity across studies (P for heterogeneity = 0.036, I^2 = 70.0%). For ESCC (Figure 2C), five RRs were below unity (significant in three studies) and two were above unity (significant in one study), resulting in a summary RR of 0.87 (95% CI 0.65–1.17), with significant heterogeneity across studies (P for heterogeneity = 0.001, I^2 = 74.6%). The summary RR for EAC (Figure 2D) was 1.18 (95% CI 0.81–1.71), without heterogeneity across studies (P for heterogeneity = 0.169, I^2 = 43.7%).

discussion

The present meta-analysis of all published data found a significant reduction in the risk of OP cancer of ∼35% in highest coffee drinkers as compared with lowest ones, while no relation of coffee drinking with laryngeal and esophageal cancer.

An inverse association with OP cancer was found in a prospective study, based on a Japanese cohort [25], and in six case–control studies [12, 13, 16, 23, 26, 27]. However, the small number of studies did not allow stratified analyses by study design (cohort versus case–control, hospital versus population based) or anatomical subsites of OP cancers. We also were unable to analyze coffee drinkers versus nondrinkers and the dose–risk relation for coffee consumption and OP cancer, given the lack of a noncoffee drinkers category in many original reports and the heterogeneity across studies in the categorization of coffee drinking. Moreover, the different categorization of coffee drinking across studies did not allow to quantitatively assess the relation of OP cancer risk with number of cups of coffee. However, a favorable effect of coffee at moderate/high doses is suggested by the protection of 35% observed for a consumption of three or more cups per day and by the apparently stronger inverse relation in studies conducted in Europe and America than in those conducted in Asia, where the prevalence of coffee drinking and the amount of coffee drunk is generally lower.

Although we excluded studies reporting risk estimates not adjusted for tobacco smoking and alcohol intake, which are correlated to coffee consumption [34, 35] and represent the major risk factors for OP and laryngeal cancers and ESCC, we cannot exclude residual confounding. Given the very strong association of these two risk factors with head and neck cancers [36], most studies included in this meta-analysis had too few nonsmokers and nonalcohol drinkers for stratified analyses. Consequently, only a few studies considered the relation with coffee intake in strata of tobacco smoking and alcohol drinking. For at least one cup of coffee per day, a Japanese prospective study [25] found a RR for OP and esophageal cancers combined of 0.50 (95% CI 0.14–1.81) (based on 4 cases) for never smokers and 0.49 (95% CI 0.30–0.79) (based on 40 cases) for current smokers. It also found an RR of 0.43 (95% CI 0.13–1.41) (based on 5 cases) for never alcohol drinkers and 0.49 (95% CI 0.31–0.77) (based on 41 subjects) for current alcohol drinkers. A pooled analysis of nine case–control studies [37] found a slight stronger inverse association of OP cancer with coffee intake in heavy tobacco users (OR = 0.51, 95% CI 0.35–0.76 for more than four cups per day, based on 290 cases) than in never tobacco users (OR = 0.72, 95% CI 0.31–1.64, 69 cases), but similar ORs in never or light alcohol drinkers (OR = 0.59, 95% CI 0.42–0.85) and in heavy drinkers (OR = 0.61, 95% CI 0.42–0.85). Similarly, an Italian case–control study [16] found a stronger inverse association in smokers of ≥25 cigarettes per day, with ORs of 0.2 (95% CI 0.1–0.6) and 0.4 (95% CI 0.1–1.4) for at least three cups of coffee per day for OP and esophageal cancers, respectively; the ORs were similar in heavy and light alcohol drinkers. A slight inverse association in smokers was found also in an Indian case–control study of hypopharyngeal cancer [24], which found an OR of 1.07 (95% CI 0.41–2.81) in never tobacco users and 0.81 (95% CI 0.39–1.66) in ever tobacco users, for the highest quartile of coffee consumption, based on 11 and 21 cases, respectively. Thus, a slightly stronger inverse association may exist in smokers, but it is difficult to quantify, given the low number of nonsmoking cases of OP and laryngeal cancers, and ESCC.

A support for a real inverse association of coffee intake with OP cancer comes from the lack of association of coffee with risk of laryngeal cancer and ESCC, which shares similar general risk factors with OP cancer, as well as from the absence of association with EAC. Studies included in these meta-analyses did not consider genetic variants associated with coffee drinking, such as CYP1A2, which is responsible for more than 95% of caffeine metabolism [38]. Thus, these genetic variants may be a further source of confounding.

Our meta-analyses have some limitations. First, recall and selection bias may be present in the original studies. Moreover, original studies did not provide information on the characteristics of coffee, such as cup size, type of coffee power (Robusta or Arabica) and brewing methods, which are responsible for the different concentrations of caffeine and other chemicals in the beverage [39]. The assessment of coffee intake was based on patients' self-reporting. However, recall of coffee drinking has been shown to be satisfactorily reproducible and valid [40–43]. No information was available on human papillomavirus (HPV), which is related to OP cancer [44]. However, there is no reason to suppose that coffee consumption is associated to or modified by HPV infection.

The inverse association between coffee intake and OP cancer both in the cohort (RR = 0.35) and in case–control studies (pooled OR = 0.67) is against a major role of reverse causation, i.e. the reduction of coffee consumption by cases after the onset of symptoms of cancer.

There are no definite biological mechanisms of the potential favorable role of coffee on OP cancer [4], thus there are still no explanations for the different effects of coffee on OP and laryngeal cancers. Coffee drinking has also been inversely related to liver cirrhosis [4] and liver cancer [45], endometrial cancer [46] and colorectal cancer, the last at least in case–control studies [47]. The inverse association between coffee

consumption and OP cancer can be related to the presence in the beverage of many chemicals with antioxidant and antimutagenic activities, whose concentration varies depending on type of coffee power (Arabica or Robusta), roasting and preparation [48]. In particular, coffee contains several phenolic compounds (such as chlorogenic, caffeic, ferulic and cumaric acids), melanoidins and diterpenes (such as cafestol and kahweol), which are shown to reduce genotoxicity of several carcinogens [48].

In conclusion, the results of these meta-analyses provide additional evidence of a real inverse association with OP cancer but not with laryngeal and esophageal cancers.

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disclosure

The authors declare no conflict of interest.

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