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Original Article

Association between coffee consumption and the risk of oral cancer: a meta-analysis of observational studies

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Abstract: Objective: Quantification of the association between the coffee consumption and risk of oral cancer is still conflicting. Thus, we conducted a meta-analysis to summarize the evidence from epidemiological studies of coffee consumption with the risk of oral cancer. Methods: Pertinent studies were identified by a search of PubMed and Web of Knowledge to March 2015. The random effect model was used. Sensitivity analysis and publication bias were conducted. Results: Data from 12 studies including 4,037 oral cancer cases and 1,872,231 participants were used in this meta-analysis. Pooled results suggested that highest coffee consumption amount versus lowest amount was significantly associated with the risk of oral cancer [summary relative risk (RR) = 0.694, 95% CI = 0.543-0.886, I^2 = 65.0%]. The association was also significant in Europe [summary RR = 0.571, 95% CI = 0.378-0.863], but not in America. No publication bias was found. Conclusions: Our analysis suggested that the higher coffee consumption might reduce the risk of oral cancer, especially in Europe.

Keywords: Coffee consumption, oral cancer, meta-analysis

Introduction

Oral cavity cancer, comprising cancer of tongue, buccal mucosa, upper or lower gingival, floor of mouth and hard palate, represents the eighth most frequent cancer worldwide [1]. It is a serious problem in many parts of the world [2], mainly due to its low survival rate [3] and poor life quality [4, 5], especially for advanced oral cancer cases. Thus, primary prevention is important. Many studies have shown that oral cancer is associated with genetic factors [6, 7]. Furthermore, many environmental factors such as tobacco smoking and alcohol drinking [8] can also affect the incidence of oral cancer.

The recent meta-analysis had suggested that higher tea consumption may have a protective effect on oral cancer, especially in green tea consumption [9]. Coffee and tea are the most favorite beverages in people's lives. Coffee contains a variety of anitoxidants, polyphenols, and other biologically active compounds that may help to protect against development or progression of cancer [10, 11]. Besides, coffee is considered to help protect against cancers through the activity of its anticarcinogenic constituents [12, 13]. Up to date, a number of epidemiologic studies have been published to explore the relationship between coffee consumption and oral cancer risk. However, the results are not consistent. Therefore, we conducted a meta-analysis to (1) first assess the oral cancer risk for the highest vs. lowest categories of coffee consumption; (2) assess the heterogeneity among studies and publication bias.

Methods

Search strategy

Studies were identified using a literature search of PubMed and Web of Knowledge through March 2015 and by hand-searching the reference lists of the retrieved articles. The key search terms were 'coffee', or 'caffeine', or 'diet', or 'lifestyle' for exposure factors, and 'oral cancer', or 'oral oncology' for outcome factors. Two investigators searched articles and reviewed all the retrieved studies independently. Disagreements between the two investigators were resolved by consensus with a third reviewer.

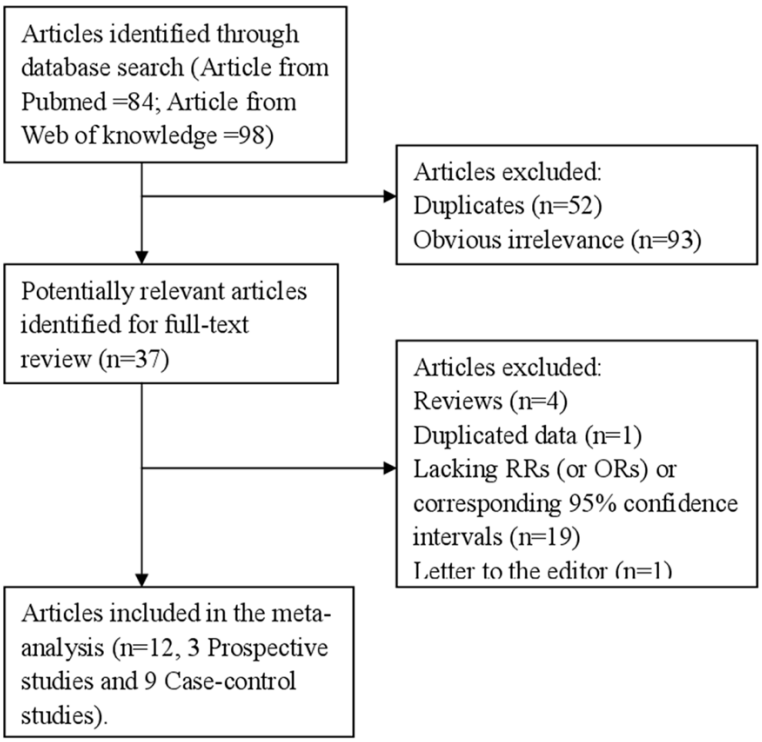

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

Study selection

For inclusion, studies had to fulfill the following criteria: (1) have a prospective or case-control study design; (2) coffee consumption was the independent variable of interest; (3) the dependent variable of interest was oral cancer; (4) relative risk (RR) or odds ratio (OR) with a 95% confidence interval (CI) was provided (or data available to calculate them). If data were replicated in more than one study, we included the study with the largest number of cases. Accordingly, the following exclusion criteria were also used: (1) reviews; (2) repeated or overlapped publications.

Data extraction

Two researchers independently extracted the following data from each study that met the criteria for inclusion: the first author's last name, year of publication, geographic locations, study design, sample source, the age range of study participants, the number of cases and participants, and RR (95% CI) for coffee consumption and oral cancer risk. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Quality assessment

The quality of studies was examined and controlled in accordance with checklists of Preferred Reporting Items for Systematic reviews and Meta-Analyses for randomized trials (PRISMA). To determine the quality score of included studies, two reviewers independently performed the quality assessment by using the Newcastle-Ottawa Scale, which is a validated scale for non-randomized studies in meta-analyses. The Newcastle-Ottawa Scale is a nine-point scale that allocates points based on the selection process of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the identification of the exposure and the outcomes of study participants (0-3 points). We assigned scores of 0-3, 4-6, and 7-9 for low, moderate, and high quality of studies, respectively.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the association between coffee consumption and oral cancer risk. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [14]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [15], respectively. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [16]. Publication bias was evaluated using Egger regression asymmetry test [17]. A study of influence analysis [18] was conducted to describe how robust the pooled estimator was to removal of individual studies. An individual study was sus-

Table 1. Characteristics of studies between coffee consumption and oral cancer

Author (year)	Country	Study design	Quality score	Participants (case); age range	Coffee amount (cups/day)	RR (95% CI)	Adjustment for covariates or match for
Bundgaard et al. 1995	Denmark	Case-control	7	561 (161)	No-drinker	1	Adjust for lifetime consumption of tobacco and alcohol.
				45-75	drinker	1.4 (0.4-4.5)	
Franceschi et al. 1992	Italy	Case-control	6	830 (104)	Low	1	Adjust for age, area of residence, occupation, smoking, and alcohol habits.
				≤ 75	intermediate	0.7 (0.4-1.2)	
					high	0.3 (0.2-0.6)	
Franco et al. 1989	Brazil	Case-control	7	696 (232)	≤ 1	1	Adjust for age, sex, study site, and admission period.
				NA	2-5	1.1 (0.7-1.8)	
					≥ 6	1.5 (0.9-2.6)	
Hildebrand et al. 2012	United States	Prospective	8	968432 (868)	Never	1	Adjusted for age, sex, race, education, body mass index, alcohol use, smoking, vegetable intake, and intake of the other beverages as shown.
				≥ 30	< 1	0.85 (0.44-1.61)	
					1-2	0.80 (0.51-1.24)	
					3-4	0.68 (0.44-1.07)	
					> 4	0.58 (0.37-0.92)	
Mashberg et al. 1993	United States	Case-control	6	991 (62)	0	1	Adjust for age, race, tobacco smoking, and alcohol drinking.
				NA	1-2	0.7 (0.3-1.4)	
					3-4	0.7 (0.3-1.6)	
					≥ 5	0.6 (0.3-1.3)	
Pintos et al. 1994	Brazil	Case-control	6	507 (169)	≤ 1	1	Matched for age, sex and admission period. Adjust for tobacco, alcohol, rural residency, dietary, consumption of other nonalcoholic beverages.
				NA	2	0.72 (0.4-1.4)	
					3	1.21 (0.6-2.7)	
					≥ 4	0.68 (0.3-1.4)	
Radoi et al. 2013	France	Case–control	7	4170(689)	Never	1	Adjust for age, gender, area of residence, tobacco smoking, alcohol consumption, and education level, BMI and lifetime cumulative consumption of tea.
				≤ 75	< 2	0.69 (0.39-1.23)	
					2-3.9	0.52 (0.33-0.99)	
					≥ 4	0.62 (0.36-1.07)	
Ren et al. 2010	United States	Prospective	8	481563 (392)	< 1	1	Adjust for age, sex, tobacco, alcohol, BMI, education, ethnicity, physical activity, and the daily intake of fruit, vegetables, red meat, white meat, and calories.
				50-71	1	1.07 (0.78-1.48)	
					2-3	0.85 (0.65-1.11)	
					> 3	0.85 (0.62-1.16)	
Rodriguez et al. 2004	Italy	Case-control	7	435 (137)	0	1	Adjust for sex, age and study centre, and adjusted for education, marital status, body mass index, tobacco and alcohol consumption.
				≤ 46	1	0.74 (0.29-1.90)	
					2	0.35 (0.14-0.86)	
					≥ 3	0.25 (0.10-0.59)	

Takezaki et al. 1996	Japan	Case-control	6	21902 (150)	Low	1	Adjust for age, sex, smoking, drinking and year of visit.
				20-79	intermediate	0.8 (0.5-1.4)	
					high	0.9 (0.6-1.4)	
Tavani et al. 2003	Italy Switzerland	Case-control	7	2520 (748)	≤ 1	1	Adjust for terms for centre, age, sex, education, tobacco smoking, alcohol drinking, and intake of fruit and vegetables.
				≤ 80	1-2	0.9 (0.7-1.2)	
					2-3	0.9 (0.7-1.2)	
					≥ 3	0.6 (0.5-0.9)	
Tverdal et al. 2011	Norway	Prospective	8	389624 (325)	1-4	1	Adjusted for sex, daily smoking, body mass index and education.
				40-45	5-8	1.12 (0.88-1.44)	
					≥ 9	0.96 (0.68-1.36)	

NA: not available.

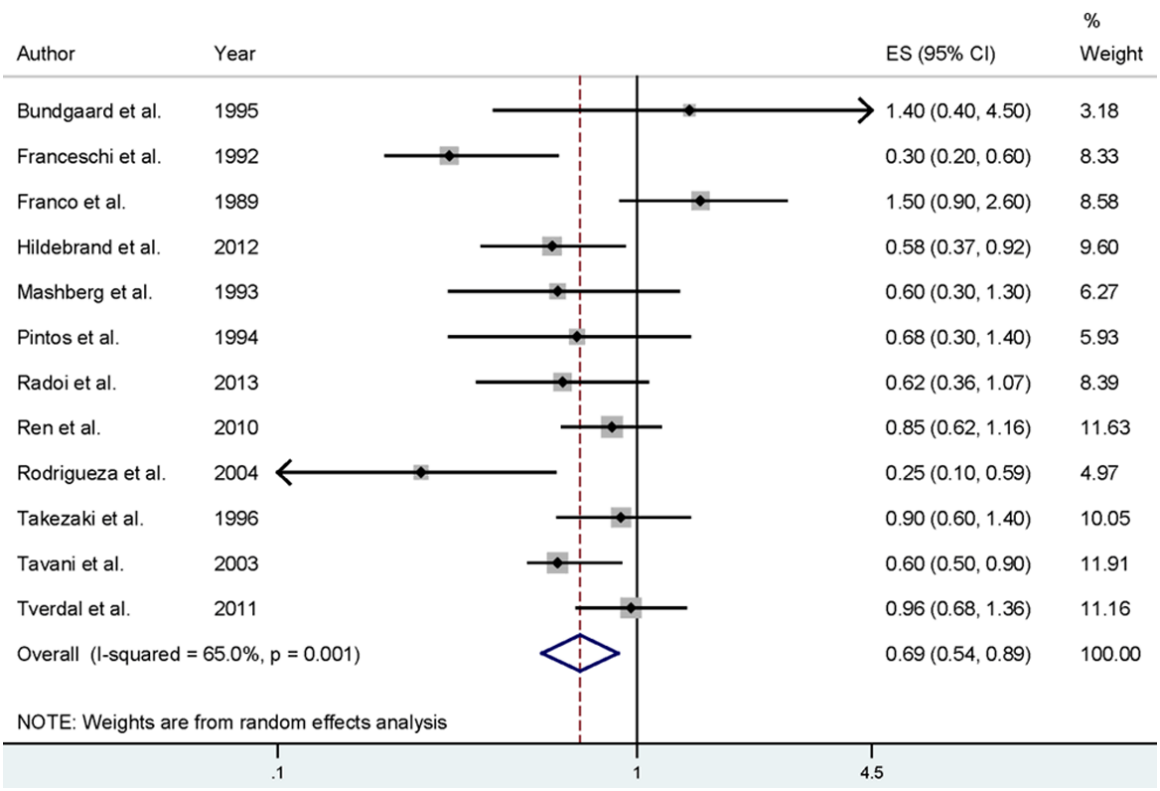

Figure 2. The forest plot between highest versus lowest categories of coffee consumption and oral cancer risk.

Table 2. Summary risk estimates of the association between coffee consumption and oral cancer risk

Subgroups	No. (cases)	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
All studies	4037	12	0.694 (0.543-0.886)	65.0	0.001
Study design					
Prospective	1585	3	0.809 (0.623-1.049)	34.8	0.216
Case-control	2452	9	0.649 (0.459-0.916)	69.0	0.001
Geographic locations					
America	1723	5	0.808 (0.579-1.127)	51.1	0.085
Europe	2164	6	0.571 (0.378-0.863)	73.2	0.002

pected of excessive influence if the point estimate of its omitted analysis lay outside the 95% CI of the combined analysis. All statistical analyses were conducted with STATA version 12.0 (StataCorp LP, College Station, Texas, USA). Two-tailed *p*-value ≤ 0.05 was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 84 articles from PubMed and 98 from the Web of Knowledge, and 37 articles were reviewed in full after reviewing the title/abstract. Twelve articles [19-30] (3 prospective studies and 9 case-control studies) involving 4,037 oral cancer cases and 1,872,231 participants were used in this meta-analysis after reviewed in full articles. The detailed steps of our literature search are shown in **Figure 1**. Three studies come from Italy, 3 from United States, 2 from Brazil, 1 from Denmark, 1 from Norway, 1 from Japan and 1 from French. The characteristics of these studies are presented in **Table 1**. The quality of studies was generally good, with results of study quality assessment yielded a score of 6 or above for all included studies, with an average score of 6.92.

High versus low analyses

Data from 12 studies including 4,037 pancreatic cancer cases were used in this meta-analysis. Four studies reported that coffee consumption could reduce the risk of oral cancer,

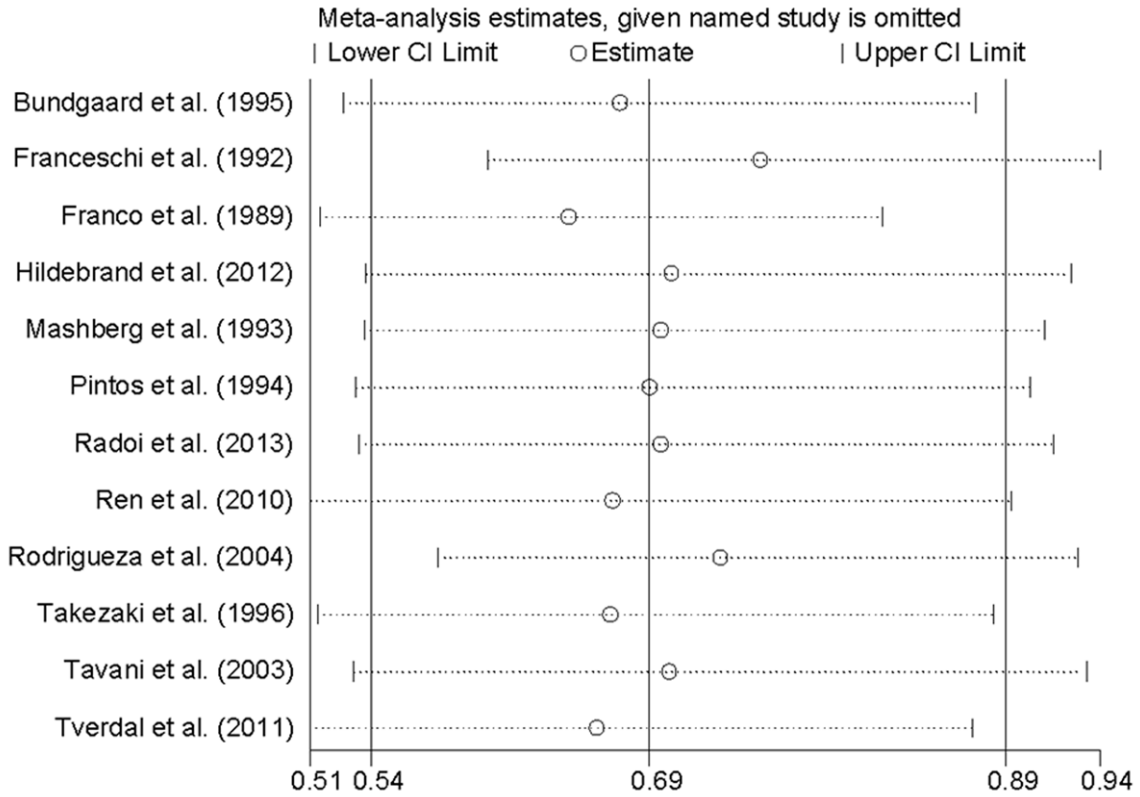

Figure 3. Analysis of influence of individual study on the pooled estimate in coffee consumption and oral cancer risk. Open circle, the pooled RR, given named study is omitted. Horizontal lines represent the 95% CIs.

while no significant association was reported in 8 studies. Pooled results suggested that highest coffee consumption versus lowest amount was significantly associated with the risk of oral cancer [summary RR = 0.694, 95% CI = 0.543-0.886, I^2 = 65.0%] (**Figure 2**).

In stratified analysis by study design, the association was found in the case-control studies [summary RR = 0.649, 95% CI = 0.459-0.916], but not in the prospective studies. In subgroup analyses for geographic locations, highest coffee consumption level versus lowest level was significantly associated with the risk of oral cancer in Europe [summary RR = 0.571, 95% CI = 0.378-0.863], but not in the America. The detailed results are summarized in **Table 2**.

Sources of heterogeneity and meta-regression

As seen in the pooled results, moderate to high heterogeneity (I^2 = 65.0%, $P_{heterogeneity}$ = 0.001) was found in the analysis. In order to explore the moderate to high between-study heterogeneity founded in the pooled results, univariate meta-regression with the covariates of publication year, location where the study was conducted, study design (case-control or prospective), and number of cases were performed. No significant findings were found in the above-mentioned analysis.

Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the association of coffee consumption and oral cancer risk (**Figure 3**). Egger's test (P = 0.556) showed no evidence of significant publication bias between coffee consumption and oral cancer risk.

Discussion

Finding from this meta-analysis suggested that the higher coffee consumption could reduce the risk of oral cancer. The associations were also found in subgroups of Europe and case-control studies for coffee consumption and oral cancer risk.

Coffee contains multiple biologically active compounds that may help to lower the risk of developing and/or dying from cancer [31]. In

addition to caffeine, the polyphenol caffeic acid and 2 coffee-specific diterpenes, cafestol and kahweol, have been studied and found in vitro and in animals to protect against oxidative DNA damage, promote apoptosis, or have antiproliferative activity [32, 33]. As one of the most widely consumed beverages in the world, coffee and its effects on human health are of considerable interest. Although some health conditions will preclude the consumption of any caffeinated beverages on a regular basis, our results contribute to the body of research suggesting that there may be beneficial effects to coffee, and its daily enjoyment.

Between-study heterogeneity is common in meta-analysis because of diversity in design quality, population stratification, characteristics of the sample, publication year, variation of the covariates, etc [34]. For coffee consumption with the risk of oral cancer, high between-study heterogeneity was found in the pooled results. Thus, meta-regression we used to explore the causes of heterogeneity for covariates. However, no covariate had significant impact on between-study heterogeneity for the above mentioned covariates. Considering the pooled meta-analysis was fraught with the problem of heterogeneity, subgroup analyses by the type of study design and location where the study conducted were performed to explore the source of heterogeneity. However, the between-study heterogeneity persisted in some subgroups, suggesting the presence of other unknown confounding factors. Oral cancer is a complex etiology and pathophysiology disease generated by the combined effects of genes and environment factors. Thus, other genetic and environment variables, as well as their possible interaction, may well be potential contributors to the heterogeneity observed.

As a meta-analysis of published studies, our findings showed some advantages. First, large number of cases and participants were included, allowing a much greater possibility of reaching reasonable conclusions between coffee consumption and oral cancer risk. Second, no significant publication bias was found, indicating that our results are stable. However, there were some limitations in this meta-analysis. First, significant association was only found in the case-control studies, but not in the prospective studies. A meta-analysis of observational studies is susceptible to potential bias inherent in the original studies, especially for case-control studies. Overstated association may be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. Therefore, more studies with prospective design are wanted in the future studies while only 3 studies included in this meta-analysis were prospective design. Second, for the subgroups of geographic locations, the association was significant only in the Europe, but not in the America. And only one study come from Japan. Due to this limitation, the results are applicable to Europe, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between coffee consumption and oral cancer risk. Third, between-study heterogeneity was found in the pooled analysis, but the between-study heterogeneity was not successfully explained by the subgroup analysis and meta-regression. However, other genetic and environment variables, as well as their possible interaction may be potential contributors to this disease-effect unconformity. Fourth, Tavani et al. [29] found that different coffee beverages (caffeinated, decaffeinated and coffee) have different effects on oral cancer risk. However, few studies reported separate effect estimates for caffeinated, decaffeinated and coffee intake. Therefore, we did not perform the subgroup analyses according the species of coffee beverages. Further studies should be conducted to examine the effect of different coffee beverages on oral cancer risk.

In summary, results from this meta-analysis suggested that the higher coffee consumption might reduce the risk of oral cancer, especially in Europe.

Disclosure of conflict of interest

None.

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References

[1] Siegel R, Ward E, Brawley O and Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on pre-

mature cancer deaths. CA Cancer J Clin 2011; 61: 212-236.
[2] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; 45: 309-316.
[3] Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, Sutton D, Errington D and Vaughan D. Survival following primary surgery for oral cancer. Oral Oncol 2009; 45: 201-211.
[4] Infante-Cossio P, Torres-Carranza E, Cayuela A, Hens-Aumente E, Pastor-Gaitan P and Gutierrez-Perez JL. Impact of treatment on quality of life for oral and oropharyngeal carcinoma. Int J Oral Maxillofac Surg 2009; 38: 1052-1058.
[5] Nordgren M, Hammerlid E, Bjordal K, Ahlner-Elmqvist M, Boysen M and Jannert M. Quality of life in oral carcinoma: a 5-year prospective study. Head Neck 2008; 30: 461-470.
[6] Wang Z, Wang C, Zhao Z, Liu F, Guan X, Lin X and Zhang L. Association between -251A > T polymorphism in the interleukin-8 gene and oral cancer risk: a meta-analysis. Gene 2013; 522: 168-176.
[7] Li W, Chen J and Liu C. Glutathione S-transferase P1 Ile105Val polymorphism and oral cancer risk: a meta-analysis. Int J Med Sci 2013; 10: 392-398.
[8] Ferreira Antunes JL, Toporcov TN, Biazevic MG, Boing AF, Scully C and Petti S. Joint and independent effects of alcohol drinking and tobacco smoking on oral cancer: a large case-control study. PLoS One 2013; 8: e68132.
[9] Wang W, Yang Y, Zhang W and Wu W. Association of tea consumption and the risk of oral cancer: a meta-analysis. Oral Oncol 2014; 50: 276-281.
[10] Nkondjock A. Coffee consumption and the risk of cancer: an overview. Cancer Lett 2009; 277: 121-125.
[11] Scalbert A, Andres-Lacueva C, Arita M, Kroon P, Manach C, Urpi-Sarda M and Wishart D. Databases on food phytochemicals and their health-promoting effects. J Agric Food Chem 2011; 59: 4331-4348.
[12] Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW and Schilter B. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. Food Chem Toxicol 2002; 40: 1155-1163.
[13] Daglia M, Papetti A, Gregotti C, Berte F and Gazzani G. In vitro antioxidant and ex vivo protective activities of green and roasted coffee. J Agric Food Chem 2000; 48: 1449-1454.
[14] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[15] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[16] Higgins JP and Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004; 23: 1663-1682.
[17] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[18] Tobias A. Assessing the in fluence of a single study in the meta-analysis estimate. Stata Tech Bull 1999; 47: 15-17.
[19] Bundgaard T, Wildt J, Frydenberg M, Elbrond O and Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control 1995; 6: 57-67.
[20] Franceschi S, Barra S, La Vecchia C, Bidoli E, Negri E and Talamini R. Risk factors for cancer of the tongue and the mouth. A case-control study from northern Italy. Cancer 1992; 70: 2227-2233.
[21] Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva ME, Fava AS and Torloni H. Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer 1989; 43: 992-1000.
[22] Hildebrand JS, Patel AV, McCullough ML, Gaudet MM, Chen AY, Hayes RB and Gapstur SM. Coffee, tea, and fatal oral/pharyngeal cancer in a large prospective US cohort. Am J Epidemiol 2013; 177: 50-58.
[23] Mashberg A, Boffetta P, Winkelman R and Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993; 72: 1369-1375.
[24] Pintos J, Franco EL, Oliveira BV, Kowalski LP, Curado MP and Dewar R. Mate, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in southern Brazil. Epidemiology 1994; 5: 583-590.
[25] Radoi L, Paget-Bailly S, Menvielle G, Cyr D, Schmaus A, Carton M, Guida F, Cenee S, Sanchez M, Guizard AV, Velten M, Stucker I and Luce D. Tea and coffee consumption and risk of oral cavity cancer: results of a large population-based case-control study, the ICARE study. Cancer Epidemiol 2013; 37: 284-289.
[26] Ren JS, Freedman ND, Kamangar F, Dawsey SM, Hollenbeck AR, Schatzkin A and Abnet CC. Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. Eur J Cancer 2010; 46: 1873-1881.
[27] Rodriguez T, Altieri A, Chatenoud L, Gallus S, Bosetti C, Negri E, Franceschi S, Levi F, Talamini R and La Vecchia C. Risk factors for oral and pharyngeal cancer in young adults. Oral Oncol 2004; 40: 207-213.
[28] Takezaki T, Hirose K, Inoue M, Hamajima N, Kuroishi T, Nakamura S, Koshikawa T, Matsuura H and Tajima K. Tobacco, alcohol and di-

etary factors associated with the risk of oral cancer among Japanese. Jpn J Cancer Res 1996; 87: 555-562.
[29] Tavani A, Bertuzzi M, Talamini R, Gallus S, Parpinel M, Franceschi S, Levi F and La Vecchia C. Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. Oral Oncol 2003; 39: 695-700.
[30] Tverdal A, Hjellvik V and Selmer R. Coffee intake and oral-oesophageal cancer: follow-up of 389,624 Norwegian men and women 40-45 years. Br J Cancer 2011; 105: 157-161.
[31] Bakuradze T, Lang R, Hofmann T, Stiebitz H, Bytof G, Lantz I, Baum M, Eisenbrand G and Janzowski C. Antioxidant effectiveness of coffee extracts and selected constituents in cell-free systems and human colon cell lines. Mol Nutr Food Res 2010; 54: 1734-1743.
[32] Higgins LG, Cavin C, Itoh K, Yamamoto M and Hayes JD. Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein. Toxicol Appl Pharmacol 2008; 226: 328-337.
[33] Rajendra Prasad N, Karthikeyan A, Karthikeyan S and Reddy BV. Inhibitory effect of caffeic acid on cancer cell proliferation by oxidative mechanism in human HT-1080 fibrosarcoma cell line. Mol Cell Biochem 2011; 349: 11-19.
[34] Munafo MR and Flint J. Meta-analysis of genetic association studies. Trends Genet 2004; 20: 439-444.