

Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium

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Most mouthwashes contain alcohol, a known cause of head and neck cancer (oral cavity, pharynx, larynx), likely through the carcinogenic activity of acetaldehyde, formed in the oral cavity from alcohol. We carried out a pooled analysis of 8981 cases of head and neck cancer and 10 090 controls from 12 case-control studies with comparable information on mouthwash use in the International Head and Neck Cancer Epidemiology Consortium. Logistic regression was used to assess the association of mouthwash use with cancers of the oral cavity, oropharynx, hypopharynx, and larynx, adjusting for study, age, sex, pack-years of tobacco smoking, number of alcoholic drinks/day, and education. Compared with never users of mouthwash, the odds ratio (OR) of all head and neck cancers was 1.01 [95% confidence interval (CI): 0.94–1.08] for ever users, based on 12 studies. The corresponding ORs of cancer of the oral cavity and oropharynx were 1.11 (95% CI: 1.00–1.23) and 1.28 (95% CI: 1.06–1.56), respectively. OR for all head and neck cancer was 1.15 (95% CI: 1.01–1.30) for use for more than 35 years, based on seven studies (P for linear trend = 0.01), and OR 1.31 (95% CI: 1.09–1.58) for use more than one per day, based on five studies (P for linear trend < 0.001). Although limited by the retrospective nature of the study and the limited ability to assess risks of mouthwash use in nonusers of tobacco and alcohol, this large investigation shows potential risks for head and neck cancer subsites and in long-term and frequent users of mouthwash. This pooled analysis provides the most precise estimate of the association between mouthwash use and

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Introduction

An association between mouthwash use and the risk of head and neck cancer has been investigated in case-control studies carried out in the USA, Europe, and Latin America

(Wynder *et al.*, 1983; Kabat *et al.*, 1989; Garrote *et al.*, 2001; Winn *et al.*, 2001; Guha *et al.*, 2007; Divaris *et al.*, 2010). Several systematic reviews and meta-analyses have detected an association (La Vecchia, 2009), but confounding and other forms of bias could not be excluded. Many mouthwashes contain alcohol, typically in the order of 20%; alcohol is an established oral carcinogen, lending credibility to the observed association (Lachenmeier *et al.*, 2009).

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We sought to provide more definitive evidence on the presence or absence of an association between mouthwash use and head and neck cancer using individual-level data on a very large number of cases and controls. Our approach presents two advantages over meta-analyses. First, we could use standard methods to control for confounding, whereas meta-analyses are limited to summary effect estimates reported in the original studies, which may not adequately control for confounders. Second, we used data from all studies with questionnaire items on mouthwash use in the International Head and Neck Cancer Epidemiology Consortium (INHANCE) (Conway *et al.*, 2009), whereas meta-analyses are usually based on studies that have been published in journals and are potentially distorted by publication bias.

Materials and methods

We used pooled data (version 1.5) from INHANCE (Conway *et al.*, 2009) to assess the association between head and neck cancer and use of mouthwash among 8981 cases (83.0% confirmed squamous cell carcinomas) and 10 090 controls from nine studies carried out in the USA, two studies from Latin America, and one international study. Selected characteristics of the studies are reported in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A8>. Controls were recruited from random digit dialling (three studies), lists of residents or similar records (three studies), hospital patients (four studies), blood donors (one study), and mixed sources (one study). In most studies, controls were frequency-matched to cases on the basis of age and sex. Although the exact wording of questions on mouthwash use differed across studies, questions were conceptually similar. For five of the 12 studies, results on mouthwash use have been reported previously, at least for some of the participants (Wynder *et al.*, 1983; Kabat *et al.*, 1989; Garrote *et al.*, 2001; Winn *et al.*, 2001; Guha *et al.*, 2007; Divaris *et al.*, 2010), and were included in reviews and meta-analyses. The studies not previously reported on contribute 3870 cases to the current analysis (43% of the total). Cases were categorized by tumor site (oral cavity, $N=2790$; oropharynx, $N=2632$; hypopharynx, $N=577$; larynx, $N=1793$). Participants with missing information on age, sex, or mouthwash use were excluded, whereas participants with missing data on tobacco smoking (0.9%), alcohol drinking (4.7%), and education level (2.8%) were included in separate categories in the regression models.

We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for use of mouthwash using logistic regression. In addition to ever-use, we considered regular mouthwash use, duration of use, and daily frequency of use; these indicators of extent of exposure were available for only some of the studies (details available in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A8>). In all analyses, never-users of mouthwash comprised

Table 1 Association of head and neck cancer overall and by site with ever-use of mouthwash, INHANCE consortium

Tumor site ^a	Cases	Controls	aOR	95% CI
	(exposed/unexposed)	(exposed/unexposed)		
Head and neck	3611/5370	4308/5782	1.01	0.94–1.08
Oral cavity	1167/1623	4288/5732	1.11	1.00–1.23
Oropharynx	1284/1348	4308/5782	1.22	1.10–1.35
Hypopharynx	201/376	3739/4700	0.78	0.64–0.96
Larynx	483/1310	2328/3417	0.70	0.60–0.82

aOR, odds ratio for ever versus never mouthwash use, adjusted for study center, age, sex, cumulative tobacco smoking (pack-years), average amount of alcohol drinking, and education level; CI, confidence interval; INHANCE, International head and neck cancer epidemiology.

^aICD-O-2 codes: oral cavity, C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, C06.9; oropharynx, C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, C10.9; hypopharynx, C12.9, C13.0–13.2, C13.8, C13.9; larynx, C32.0–C32.3, C32.8–C32.9.

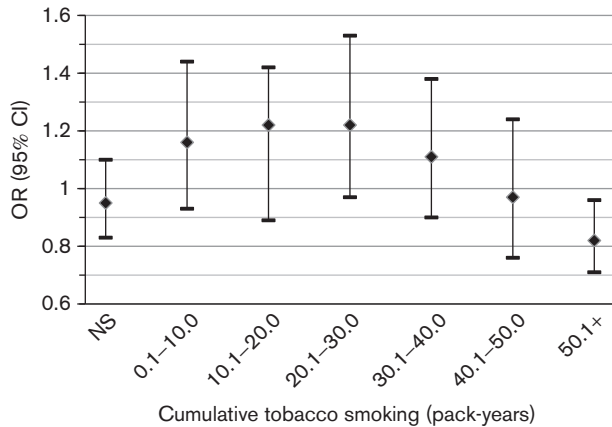
the referent (unexposed) category. Linear trends in duration and frequency of use were assessed by examining P -values obtained from modeling the continuous forms of those variables. All analyses were carried out using STATA, version 12.1 (StataCorp, 2011). All ORs were adjusted for study (and center for multicenter studies), sex, age (nine groups), education (six categories), amount of alcohol drinking (five categories), and cumulative tobacco smoking (pack-years; seven categories). Stratified analyses were carried out by study, sex, cumulative tobacco smoking, and amount of alcohol drinking. Separate analyses were carried out for cancers of specific sites within the head and neck (oral cavity, oropharynx, hypopharynx, larynx), as well as for duration and frequency of mouthwash use. Information on alcohol content in mouthwash was available from five US-based studies, and most of the products used in these studies contained alcohol: therefore, we could not separate the effect of mouthwash with and without alcohol.

Results

Selected characteristics of the study population are reported in Supplementary Table 2 (Supplemental digital content 2, <http://links.lww.com/EJCP/A9>). Overall, 74.3% of cases and 69.6% of controls were men; the mean age was 58.4 years (SD 10.7) among the cases and 57.9 years (SD 11.5) among the controls. The prevalence of ever mouthwash use among the controls was 42.7% (study-specific range 13.2–63.4%, Supplementary Table 3, Supplemental digital content 3, <http://links.lww.com/EJCP/A10>); the prevalence of ever-use was higher among heavy smokers (48.6% among controls who smoked more than 50 pack-years), and it was lower among nondrinkers and heavy alcohol drinkers (36.8% of nondrinkers and 27.3% of drinkers of five or more drinks/day).

The OR of head and neck cancer for ever-use of mouthwash was 1.01 (95% CI: 0.94–1.08); the corresponding OR of cancer of the oral cavity was 1.11 (95% CI: 1.00–1.23) (Table 1). The OR of cancers of other sites ranged from 0.70 to 1.22. Study-specific OR for all sites ranged from 0.42 to 1.86 (P -value of the test of heterogeneity <0.001)

Fig. 1



Odds ratio for ever mouthwash use and head and neck cancer risk, stratified by cumulative tobacco smoking, INHANCE consortium. CI, confidence interval; INHANCE, International head and neck cancer epidemiology; NS, nonsignificant; OR, odds ratio for ever versus never-use of mouthwash, adjusted for study center, age, sex, education level, average amount of alcohol drinking.

(Supplementary Table 3, Supplemental digital content 3, <http://links.lww.com/EJCP/A10>). The OR of head and neck cancer for ever mouthwash use among never-smokers was 0.95 (95% CI: 0.83–1.10) and that among nondrinkers was 0.81 (95% CI: 0.68–0.97). Among participants who did not smoke and did not drink (364 cases and 1543 controls), the OR for mouthwash use was 0.83 (95% CI: 0.66–1.06). The OR of head and neck cancer for ever-use of mouthwash increased up to 30 pack-years and decreased after that level of cumulative smoking (Fig. 1). No clear pattern was found in the analysis according to amount of alcohol drinking (Supplementary Figure 1, Supplemental digital content 4, <http://links.lww.com/EJCP/A11>).

The OR of head and neck cancer for regular mouthwash use [2612 cases (72% of ever-used) and 2922 controls (68% of ever-used); see Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A8> for definition] was 1.02 (95% CI: 0.94–1.11). Information on duration of mouthwash use was available in seven studies (1369 cases and 1514 controls among users) and data on daily frequency of mouthwash use were available in five studies (4535 cases and 4584 controls among users). The OR was higher in the categories with longer duration (36+ years: OR 1.15, CI 1.01–1.30, *P* for trend 0.01) and higher frequency of use (>1 per day vs. never-users: OR 1.31, CI 1.09–1.58, *P* for trend <0.001) than in the other categories (Table 2). Results for oral cavity cancer were similar to those for head and neck cancer; among users of mouthwash for more than 35 years, the OR for oral cavity cancer was 1.28 (95% CI: 1.06–1.56). Compared with never-users of mouthwash, the OR of head and neck cancer for use of mouthwash

twice/day or more for more than 35 years (two studies; 98 cases, 94 controls) was 1.75 (95% CI: 1.25–2.48).

We repeated the analysis for duration and frequency of mouthwash use among never-smokers and nondrinkers. The ORs for 35 or more years of mouthwash use were 1.12 (95% CI: 0.85–1.49) among never-smokers, 0.96 (95% CI: 0.66–1.39) among nondrinkers, and 1.36 (95% CI: 0.79–2.33) among those who did not smoke and did not drink. Corresponding ORs for higher frequency of use (>1 per day) were OR 0.86 (95% CI: 0.60–1.22), 0.57 (95% CI: 0.39–0.83), and 0.48 (95% CI: 0.28–0.82).

Stratification by region might account for differences in the prevalence of other risk factors of head and neck cancer; however, this analysis was hampered by the fact that most studies included in the pooled analysis had been carried out in the USA. The OR for ever mouthwash use in this group of studies was 0.99 (95% CI: 0.72–1.07).

Discussion

Our pooled analysis of 12 case–control studies provided evidence for an association of long-term and high-dose use of mouthwash with the risk of head and neck cancer, potentially related to the alcohol content of many of these products.

Some of our results, however, are not supportive of a causal interpretation. We found no association of mouthwash use with head and neck cancer among never-smokers or never-drinkers, suggesting no effect independent from that of these two habits. We did not observe higher risks for regular use compared with ever use, recognizing that most users were regular users. We assessed mouthwash-related risks with respect to categories of tobacco smoking. If alcohol in mouthwash is a determinant of risk, we might expect interaction with tobacco use, similar to that found for alcoholic beverages (Hashibe *et al.*, 2009), but we found no evidence for this (Fig. 1).

Our study built on a large population of cases and controls, and resulted in statistically more precise risk estimates overall and the ability to analyze specific subgroups such as nonsmokers and nondrinkers. Compared with previous meta-analyses, our pooled analysis of individual-patient data enabled more flexibility in the analytic approach, leading potentially to more stable effect estimates (Blettner *et al.*, 1999). Although the study includes all available reports, the investigation is in the case–control setting, subject to random misclassification errors of self-reported data over a lifetime, limited by the absence of information on mouthwash alcohol content and potentially subject to reporting biases or actual mouthwash differentials related to case status.

In conclusion, the results of this pooled analysis confirm recent systematic reviews and meta-analyses (Winn *et al.*, 2001;

Table 2 Association of head and neck cancer with duration and frequency of use of mouthwash, INHANCE consortium

	Head and neck cancer				Oral cavity cancer			
	Cases	Controls	aOR	95% CI	Cases	Controls	aOR	95% CI
Duration of use (years) ^a								
0 (nonusers)	2438	3060	1.00	Ref.	688	3060	1.00	Ref.
1–15	640	948	0.88	0.77–1.06	193	948	0.95	0.78–1.16
16–35	877	976	1.13	1.00–1.28	251	976	1.15	0.96–1.39
36+	784	864	1.15	1.01–1.30	247	864	1.28	1.06–1.56
P-value of test for linear trend		0.01				0.08		
Frequency of use (times/day) ^b								
0 (nonusers)	3166	3060	1.00	Ref.	1056	3060	1.00	Ref.
Up to 1/day	1022	1154	1.23	1.08–1.40	288	1154	1.20	1.00–1.44
More than 1/day	347	370	1.31	1.09–1.58	122	370	1.26	0.98–1.62
P-value of test for linear trend		<0.001				0.02		

aOR, odds ratio, adjusted for study center, age, sex, duration of tobacco smoking, average amount of alcohol drinking, and education level; CI, confidence interval; INHANCE, International head and neck cancer epidemiology; Ref., reference category.

^aOn the basis of data from six studies (for details, see Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A8>).

^bOn the basis of data from five studies (for details, see Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A8>).

Gandini *et al.*, 2012) and multicenter studies (Ahrens *et al.*, 2014) that reported no overall increased risk of head and neck cancer in individuals who ever used mouthwash, but an association in long-term frequent users. The study is limited by significant methodological issues, and yet shows potential risks for head and neck cancer subsites and in long-term and frequent users of mouthwash. No prospective cohort studies have been carried out on mouthwash use and oral cancer; these studies would avoid some of the potential biases inherent in the case–control design.

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Conflicts of interest

Paolo Boffetta and Carlo La Vecchia contributed to a review on mouthwash and oral cancer that was partially supported by Johnson & Johnson. Paolo Boffetta acted as an expert witness on mouthwash and oral cancer.

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