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

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### Conflict of Interest

Paolo Boffetta and Carlo La Vecchia authored a manuscript on mouthwash and oral cancer which was prepared based on a contract by Johnson & Johnson and the International Prevention Research Institute (Lyon, France) (Gandini et al., *Ann Agric Environ Med.* 2012;19(2):173–80). Paolo Boffetta acted as expert witness on mouthwash and oral cancer.

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## Abstract

**Background**—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.

**Methods**—We conducted a pooled analysis of 8,981 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.

**Results**—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 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 > 1 per day, based on five studies ( $p$  for linear trend <0.001).

**Conclusions**—Although limited by the retrospective nature of the study and the limited ability to assess risks of mouthwash use in non-users of tobacco and alcohol, this large investigation reveals potential risks for head and neck cancer sub-sites and in long-term and frequent users of mouthwash.

**Impact**—This pooled analysis provides the most precise estimate of the association between mouthwash use and head and neck cancer.

## Introduction

An association between mouthwash use and head and neck cancer risk has been investigated in case-control studies conducted in the United States, Europe and Latin America [1–6]. Several systematic reviews and meta-analyses have detected an association [7], 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, adding

credibility to the observed association [8]. 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, while 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 about mouthwash use in the International Head and Neck Cancer Epidemiology Consortium (INHANCE) [9], while meta-analyses are usually based on studies that have been published in journals and are potentially distorted by publication bias.

## Material and methods

We used pooled data (version 1.5) from INHANCE [9] to assess the association between head and neck cancer and use of mouthwash among 8,981 cases (83.0% confirmed squamous cell carcinomas) and 10,090 controls from nine studies conducted in United States, two studies from Latin America and one international study. Selected characteristics of the studies are reported in Supplement Table 1. Controls were obtained from random digit dialling (3 studies), lists of residents or similar records (3 studies), hospital patients (4 studies), blood donors (one study) and mixed sources (one study). In most studies controls were frequency-matched to cases based on 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 previously reported, at least for some of the subjects [1–6], and were included in reviews and meta-analyses. The studies not previously reported on contribute 3,870 cases to the current analysis (43% of the total). Cases were categorized by tumor site (oral cavity, N=2,790; oropharynx, N=2,632; hypopharynx, N=577; larynx, N=1,793). Subjects with missing information on age, sex or mouthwash use were excluded, while subjects 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 (OR) and 95% confidence intervals (CI) 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 Supplement Table 1). In all analyses, never-users of mouthwash comprised 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 performed using STATA Version 12.1 [17]. 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 conducted by study, sex, cumulative tobacco smoking and amount of alcohol drinking. Separate analyses were conducted 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 were not able to separate the effect of mouthwash with and without alcohol.

## Results

Selected characteristics of the study population are reported in Supplement Table 2. Men comprised 74.3% of cases and 69.6% of controls; mean age was 58.4 (sd 10.7) in cases and 57.9 (sd 11.5) in controls. The prevalence of ever mouthwash use among controls was 42.7% (study-specific range 13.2% to 63.4%, Supplement Table 3); the prevalence of ever-use was higher in heavy smokers (48.6% among controls who smoked more than 50 pack-years), and it was lower in non-drinkers and in heavy alcohol drinkers (36.8% of non-drinkers and 27.3% of drinkers of 5 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 oral cavity cancer 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) (Supplement Table 3). The OR of head and neck cancer for ever mouthwash use among never smokers was 0.95 (95% CI 0.83, 1.10), that among non-drinkers was 0.81 (95% CI 0.68, 0.97). Among subjects who did not smoke and did not drink (364 cases and 1,543 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 (Figure 1). No clear pattern was shown in the analysis according to amount of alcohol drinking (Supplemental Figure 1).

The OR of head and neck cancer for regular mouthwash use (2,612 cases [72% of ever-used] and 2,922 controls [68% of ever-used]; see Supplemental Table 1 for definition) was 1.02 (95% CI 0.94, 1.11). Information on duration of mouthwash use was available in seven studies (1,369 cases and 1,514 controls among users); data on daily frequency of mouthwash use in five studies (4,535 cases and 4,584 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 non drinkers. 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 non drinkers, 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 difference in the prevalence of other risk factors of head and neck cancer; however, such analysis was hampered by the fact that most studies included in the pooled analysis had been conducted in United States; 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 twelve 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 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 greater risks for regular use compared to 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 [18], but we found no evidence for this (Figure 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 non-smokers and non-drinkers. Compared to previous meta-analyses, our pooled analysis of individual-patient data allowed more flexibility in the analytic approach, leading potentially to more stable effect estimates [19]. 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 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 [3, 20] and multicenter studies [21] 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, yet reveals potential risks for head and neck cancer sub-sites and in long-term and frequent users of mouthwash. No prospective cohort studies have been conducted on mouthwash use and oral cancer; these studies would avoid some of the potential biases inherent in the case-control design.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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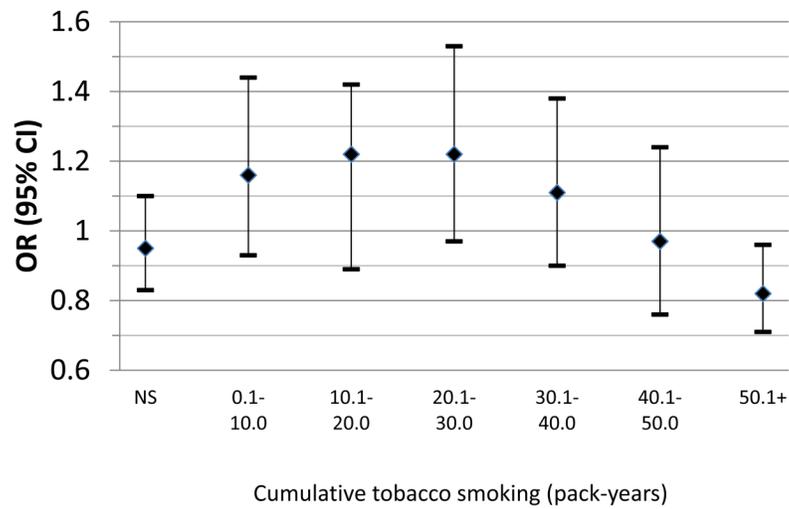
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## References

1. Wynder EL, Kabat G, Rosenberg S, Levenstein M. Oral cancer and mouthwash use. *J Natl Cancer Inst.* 1983; 70:255–60. [PubMed: 6571934]
2. Kabat GC, Hebert JR, Wynder EL. Risk factors for oral cancer in women. *Cancer Res.* 1989; 49:2803–6. [PubMed: 2713863]
3. Winn DM, Diehl SR, Brown LM, Harty LC, Bravo-Otero E, Fraumeni JF Jr, Kleinman DV, Hayes RB. Mouthwash in the etiology of oral cancer in Puerto Rico. *Cancer Causes Control.* 2001; 12:419–29. [PubMed: 11545457]
4. Fernandez Garrote L, Herrero R, Ortiz Reyes RM, Vaccarella S, Anta JL, Ferbeyre L, Munoz N, Franceschi S. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. *Brit J Cancer.* 2001; 85:46–54. [PubMed: 11437401]
5. Guha N, Boffetta P, Wunsch Filho V, Eluf Neto J, Shangina O, Zaridze D, Curado MP, Koifman S, Matos E, Menezes A, Szeszina-Dabrowska N, et al. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case–control studies. *Am J Epidemiol.* 2007; 166:1159–73. [PubMed: 17761691]
6. Divaris K, Olshan AF, Smith J, Bell ME, Weissler MC, Funkhouse WK, Bradshaw PT. Oral health and risk for head and neck squamous cell carcinoma: the Carolina Head and Neck Cancer Study. *Cancer Causes Control.* 2010; 21:567–75. [PubMed: 20049634]
7. La Vecchia C. Mouthwash and oral cancer risk: an update. *Oral Oncol.* 2009; 45:198–200. [PubMed: 18952488]
8. Lachenmeier DW, Gumbel-Mako S, Sohnius EM, Keck-Wilhelm A, Kratz E, Mildau G. Salivary acetaldehyde increase due to alcohol-containing mouthwash use: a risk factor for oral cancer. *Int J Cancer.* 2009; 125:730–5. [PubMed: 19444911]
9. Conway DI, Hashibe M, Boffetta P, Wunsch-Filho V, Muscat J, LaVecchia C, Winn DM. INHANCE Consortium. 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]
10. Rogers MA, Thomas DB, Davis S, Vaughan TL, Nevissi AE. A case-control study of element levels and cancer of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev.* 1993; 2:305–12. [PubMed: 8348053]

11. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. *Cancer Res.* 2004; 64:4049–54. [PubMed: 15173020]
12. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of Human Papilloma virus and oropharyngeal cancer. *N Engl J Med.* 2007; 356:1944–56. [PubMed: 17494927]
13. Muscat JE, Richie JP Jr, Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. *Cancer Res.* 1996; 56:5192–97. [PubMed: 8912856]
14. 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]
15. Cui Y, Morgenstern H, Greenland S, Tashkin DP, Mao J, Cao W, Cozen W, Mack TM, Zhang ZF. 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]
16. Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, Rajkumar T, Sridhar H, Rose B, Pintos J, Fernandez L, Idris A, et al. Human papillomavirus and the risk of Human Papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst.* 2003; 95:1772–83. [PubMed: 14652239]
17. StataCorp. *Stata Statistical Software: Release 12.* College Station, TX: StataCorp LP; 2011.
18. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez F, Wunsch-Filho V, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:541–50. [PubMed: 19190158]
19. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol.* 1999; 28:1–9. [PubMed: 10195657]
20. Gandini S, Negri E, Boffetta P, La Vecchia C, Boyle P. Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies. *Ann Agric Environ Med.* 2012; 19:173–80. [PubMed: 22742785]
21. Ahrens W, Pohlabein H, Foraita R, Nelis M, Lagiou P, Lagiou A, Bouchardy C, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, et al. Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: the ARCAGE study. *Oral Oncol.* 2014; 50:616–25. [PubMed: 24680035]



**Figure 1.** Odds ratio for ever mouthwash use and head and neck cancer risk, stratified by cumulative tobacco smoking, INHANCE Consortium  
OR, odds ratio for ever vs. never use of mouthwash, adjusted for study center, age, sex, education level, average amount of alcohol drinking.  
CI, confidence interval.  
NS, never smokers.

Association of head and neck cancer overall and by site with ever use of mouthwash, INHANCE Consortium

**Table 1**

Tumor site*	Cases (exp/unexp)	Controls (exp/unexp)	aOR	95% CI
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 vs. never mouthwash use, adjusted for study center, age, sex, cumulative tobacco smoking (pack-years), average amount of alcohol drinking, education level. CI, confidence interval.

\* ICD-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

Association of head and neck cancer with duration and frequency of use of mouthwash, INHANCE Consortium

Table 2

	Head and neck cancer				Oral cavity cancer			
	Cases	Controls	aOR	95% CI	Cases	Controls	aOR	95% CI
Duration of use (years) <sup>*</sup>								
0 (Non-users)	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) <sup>**</sup>								
0 (Non users)	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	

<sup>\*</sup> Based on data from six studies (see Supplement Table 1 for details).

<sup>\*\*</sup> Based on data from five studies (see Supplement Table 1 for details).

aOR, odds ratio, adjusted for study center, age, sex, duration of tobacco smoking, average amount of alcohol drinking, education level.

CI, confidence interval.

Ref, reference category.