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Mouthwash Use and Oral Conditions in the Risk of Oral and Pharyngeal Cancer

Deborah M. Winn, William J. Blot,[1] Joseph K. McLaughlin, Donald F. Austin, Raymond S. Greenberg, Susan Preston-Martin, Janet B. Schoenberg, and Joseph F. Fraumeni, Jr.

National Cancer Institute, Bethesda, Maryland 20892 [D. M. W., W. J. B., J. K. M., J. F. F.]; National Center for Health Statistics, Hyattsville, Maryland 20782 [D. M. W.]; California State Department of Health Services, Emeryville, California 94608 [D. F. A.]; Emory University, Atlanta, Georgia 20322 [R. S. G.]; University of Southern California, Los Angeles, California 90033 [S. P-M.]; and New Jersey Department of Health, Trenton, New Jersey 08625 [J. B. S.]

ABSTRACT

Interviews with 866 patients with cancer of the oral cavity and pharynx and 1249 controls of similar age and sex from the general population in four areas of the United States revealed increased risks associated with the regular use of mouthwash. Risks of oral cancer were elevated by 40% among male and 60% among female mouthwash users, after adjusting for tobacco and alcohol consumption. Risks among both sexes generally increased in proportion to duration and frequency of mouthwash use. The increased risks were confined to users of mouthwash high in alcohol content, consistent with the elevated risks associated with drinking alcoholic beverages. Except for a higher prevalence of leukoplakia among cases, little relationship was found with oral or dental conditions, although denture wearing was reported more often by patients with cancer of the gums. These findings, together with other studies, provide further incentive for clarifying the association between mouthwash use and oral cancer.

INTRODUCTION

Tobacco smoking and alcohol consumption are the primary causes of oral and pharyngeal cancer, accounting for approximately three fourths of these tumors in the United States (1). Among other suspected risk factors are poor dentition, inadequate oral hygiene, and use of mouthwash, particularly among nonusers of tobacco and alcohol (2). In this study oral health practices and conditions were evaluated as risk factors, utilizing data from the largest case-control study of this cancer yet conducted.

METHODS

Details of the design and methods of this study have been presented elsewhere (1). Briefly, the cancer patients were identified from 4 population-based cancer registries from the following geographic areas: Los Angeles county, CA, Santa Clara and San Mateo counties in the San Francisco Bay area, CA, the greater Atlanta, GA, metropolitan area, and the state of New Jersey. The cases were all residents 18 to 79 years of age with incident primary cancer of the oral cavity or pharynx (International Classification of Diseases, Rev. 9, codes 141, 143–146, 148, and 149) diagnosed between January 1, 1984, and March 31, 1985. Excluded were cancers of the lip, salivary glands, and nasopharynx. For brevity, the remaining cancers are referred to as oral cancer in this analysis, with histological confirmation required for inclusion in the study.

Controls from the same geographic areas were identified using two methods. Random digit dialing was used to select subjects between the ages of 18 and 64 years, and files of the Health Care Financing Administration were used for controls aged 65 to 79 years. The number of controls was chosen to approximately equal the number of cases anticipated based on the number of diagnoses reported to the individual cancer registries during the 3 years preceding case accrual. Group frequency matching was used to ensure that the distribution of controls matched the expected distribution of cases on age (5-year groups), race (white, black), sex, and study center.

Interviews were sought with all cases and controls, or their next of kin in the event of death or disability of the subject. A structured questionnaire was administered by trained interviewers to elicit information concerning tobacco use, alcohol use, diet, occupation, oral health status, and other characteristics of the participants. Oral health indicators included number of teeth, use of dentures, number of dental X-rays, tooth-brushing frequency, occurrence of several oral diseases, bleeding of gums, and frequency, intensity, duration, and reason for use of mouthwashes. Mouthwash users were defined as those who ever used mouthwash on a regular basis, *i.e.*, at least once/week for 6 months or more. Mouthwashes were categorized by alcohol content in 1984 (3), if available, or by alcohol concentrations listed on bottle labels in 1987.

The measure of association between cancer risk and oral hygiene was the OR.[2] ORs and corresponding 95% CIs were estimated from multiple logistic regression analyses for stratified data (4). ORs were calculated separately for males and females from models including terms for age group (<50, 50–59, 60–69, 70+ years), race (black, white), education (0–11, 12, 12+ years), smoking (6 categories defined in Table 1), alcoholic beverage drinking (5 categories defined in Table 1), and dietary intake of fruit (in quartiles), which was associated with a reduced risk of oral cancer in this population (5). Additional adjustments for study center (4 categories) made little difference.

RESULTS

Interviews were completed for 1114 oral cancer cases and 1268 controls, respectively 75% of all incident cases and 76% of interview-eligible controls. By design, the case and control groups were balanced with respect to age (median, 63 years) and sex (male, 67%). The largest numbers of cases were from New Jersey (44%) and Los Angeles (38%), and the smallest were from Atlanta (12%) and Santa Clara/San Mateo (6%). Because another study (6) had reported less clear results when information concerning oral hygiene factors was reported by next of kin, we excluded from the analyses the 2% of controls and 22% of cases for whom information was provided by next of kin rather than the subjects themselves (although their inclusion resulted in little change in our analyses). Thus, results are based on interviews with 573 male and 293 female cases and 821 male and 428 female controls. Excluded from the tables that follow are subjects (typically <2% of the total) with missing information concerning the oral hygiene variable being discussed.

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[1] To whom requests for reprints should be addressed, at National Cancer Institute, EPN 431, Bethesda, MD 20892.

[2] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Mouthwash. Table 1 shows the patterns of mouthwash use in the general population, as indicated by responses from the controls. Forty-four % of the males and 45% of the females reported mouthwash use (*i.e.*, had used mouthwash at least once/week for 6 months or more). There was little difference in use according to sex, but the percentages tended to increase with age and were markedly higher among blacks and among those with lower education levels. Smokers more often reported use of mouthwash, but there were no trends with amount smoked. Among nonsmokers, proportionately more women than men used mouthwash, and overall more women than men (12 *versus* 9%) used mouthwash twice or more/day, but these differences were not statistically significant. Differences in mouthwash use according to alcoholic beverage intake were small. Mouthwash use was more common in those who wore *versus* did not wear dentures (51 *versus* 37%) and in those who reported periodontal or gum disease (53 *versus* 41%).

Among all subjects, cases were more likely to report mouthwash use than controls. Forty-nine % of the male and 58% of the female cases reported that they had used mouthwash on a regular basis at some period >1 year prior to the interview. The crude ORs associated with mouthwash use were 1.2 and 1.7, respectively. After adjustment for tobacco, alcohol, education, and other factors, the corresponding sex-specific ORs (and 95% CIs) were 1.4 (1.0–1.8) and 1.6 (1.1–2.3).

The excess risk was not attributable to recently initiated use of mouthwash (perhaps associated with early or precursor stages of oral cancer), since most users started early in life (Table 2). Indeed, the ORs tended to increase with early age at start of use, reaching 1.5 among men and 2.4 among women who began using mouthwash before age 20 years. More than 90% of regular users reported that they still used mouthwash at the time of the interview. The ORs tended to increase with increasing duration of mouthwash use, but the trends were not uniform. Table 2 also shows that risk increased with monthly frequency of use. Most persons reported using mouthwash full strength, but risk was not lower among those using diluted forms. Only a minority of users (18% of both cases and controls) stated that mouthwash was used entirely or partly for medical (as opposed to personal) reasons. Risk was not higher among the <5% of persons who kept mouthwash in their mouths ≥30 s as opposed to "swishing." The alcohol content of common brands of mouthwash ranged from 1 to 30%. Table 2 shows that ORs were elevated only for mouthwashes having an alcohol content of 25% or higher.

Table 1 *Characteristics of mouthwash users among controls*

Characteristic	% ever used mouthwash regularly	
	Males (n = 821)	Females (n = 428)
Age (yr)		
<50	39	45
50–59	42	39
60–69	44	45
70+	48	51
Race		
Black	66	65
White	39	42
Education (yr)		
0–11	54	56
12	43	43
12+	36	38
Tobacco use		
Nonsmoker	38	42
Former	45	55
1–19 cigarettes/day	48	54
20–39	46	32
40+	43	61
Cigar/pipe only	45	
Alcohol		
None, <1	46	48
1–4 drinks/wk	43	40
5–14 drinks/wk	43	45
15–29 drinks/wk	44	45
30+ drinks/wk	45	56
Total	44	45

Table 2 *Adjusted odds ratios for oral cancer associated with mouthwash use*

Mouthwash use indicator	Males				Females			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Age started (yr)								
<20	104	116	1.5	1.0–2.1	78	71	2.4	1.5–3.9
20–29	90	116	1.4	0.9–2.0	42	46	1.3	0.8–2.4
30–49	57	81	1.5	1.0–2.2	33	51	1.1	0.6–2.0
50+	20	43	0.7	0.3–1.3	11	17	1.6	0.6–3.9
Never	293	461	1.0		124	236	1.0	
Duration (yr)								
0	293	461	1.0		124	236	1.0	
1–19	55	98	1.0	0.7–1.5	32	49	1.6	0.9–3.0
20–39	127	134	1.6	1.1–2.2	55	69	1.3	0.8–2.2
40+	95	125	1.4	1.0–2.0	81	72	1.9	1.2–3.0
Frequency (times/mo)								
0	293	461	1.0		124	236	1.0	
1–29	42	59	1.0	0.6–1.7	21	34	1.2	0.6–2.4
30–59	163	227	1.3	0.9–1.7	102	106	1.7	1.1–2.6
60+	75	73	2.0	1.3–3.0	46	52	1.7	1.0–2.9
Alcohol content								
None	293	461	1.0		124	236	1.0	
Low[b]	36	68	0.7	0.4–1.1	26	51	0.8	0.4–1.5
High[c]	100	114	1.6	1.1–2.3	40	47	1.9	1.1–3.3
Mixed	144	177	1.5	1.1–2.1	103	94	2.0	1.3–3.1

[a] ORs adjusted for age, race, education, smoking, drinking, and fruit intake.
[b] Used only mouthwashes containing <25% alcohol.
[c] Used only mouthwashes containing ≥25% alcohol.

ORs for the variables in Table 2 were calculated among the subgroup of persons who were nonusers of tobacco and alcohol. Within this small group (11 cases, 63 controls among males; 30 cases, 108 controls among women), the associations with mouthwash use were less pronounced (OR 1.3, 95% CI 0.3–4.6 for men; OR 1.1, 95% CI 0.5–2.6 for women). The small number of abstainers limited evaluation of trends by duration and frequency of use, although risks were highest (OR 3.2 and 1.4 among men and women) among those using mouthwash ≥60 times/month. Among smokers, the ORs associated with mouthwash use tended to be elevated in each level of smoking category, although among females the smaller numbers of subjects resulted in greater variation in the ORs between categories.

Mouthwash use was associated individually with tongue, other mouth, and pharynx cancers. The adjusted ORs for the 3 subsites were 1.2, 1.2, and 1.4 among males and 1.4, 2.0, and 1.5 among females. Trends in risk with duration and frequency of use also tended to be similar by subsite.

Dentition. Most subjects reported the loss of wisdom or other teeth due to decay, gum disease, accidents, or other reasons, but case-control differences were unremarkable. For example, the smoking- and alcohol-adjusted ORs associated with tooth loss from decay were 0.8 for both males and females, while ORs for tooth loss due to gum disease were 1.0 and 1.1 for men and women, respectively. More cases (1.7%) than controls (0.6%), however, had lost all of their teeth.

About one half of the subjects wore dentures, with a higher percentage among cases (58%) than controls (50%). Although the crude ORs associated with denture wearing were 1.4 in both males and females, the adjusted ORs were lower, 1.1 for men and 1.0 for women (Table 3). Most individuals began wearing dentures more than 5 years prior to interview, but there were

Table 3 *Adjusted odds ratios for oral cancer associated with dentition and oral hygiene*

Indicator	Males				Females			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Dentures								
No	244	418	1.0		109	195	1.0	
Yes	317	396	1.1	0.8–1.4	181	233	1.0	0.7–1.5
Periodontal disease								
No	433	631	1.0		210	338	1.0	
Yes	139	190	0.8	0.6–1.1	83	90	1.1	0.7–1.6
Bleeding gums								
No	504	712	1.0		255	375	1.0	
Yes	68	108	0.8	0.6–1.2	37	53	1.0	0.6–1.7
Sores in mouth								
No	439	623	1.0		210	283	1.0	
Yes	133	198	1.2	0.9–1.6	83	144	0.8	0.5–1.2
Cold sores								
No	394	525	1.0		197	283	1.0	
Yes	178	296	0.9	0.7–1.2	96	144	1.1	0.7–1.6
Leukoplakia								
No	529	815	1.0		276	422	1.0	
Yes	42	6	12.7	4.8–33.3	17	6	4.3	1.4–13.3

[a] ORs adjusted for age, race, education, smoking, drinking, and fruit intake.

no consistent trends in risk with age started or with duration of wearing dentures in either sex. Risks were not consistently higher among those reporting problems with their dentures. Among those with cancer of the gums, however, there was a positive correlation between location of the cancer and site of denture placement. Among the 13 patients with cancer in the upper gums, 10 (77%) wore upper dentures *versus* 47% of the controls. Among the 29 patients with cancer in the lower gums, 16 (55%) wore lower dentures *versus* 35% of the controls. For each group, denture wearing usually started many years before the onset of gum cancer. As shown in Table 3, there were no significant case-control differences for prior periodontal disease, cold sores, sores in the mouth, and bleeding gums. Leukoplakia, although uncommonly reported, was much more often noted by the patients, particularly males, with the most lesions said to occur within 10 years of diagnosis.

X-rays. Fewer cases (84% in males, 86% in females) than controls (89% in males, 92% in females) reported having dental X-rays. Adjustment for education and other factors had little impact; therefore, the adjusted ORs remained low (OR 0.6, 95% CI 0.4–0.9 for males; OR 0.6, 95% CI 0.3–1.0 for females). Among those X-rayed, there were no trends in risk according to the numbers of X-rays received.

DISCUSSION

Several years ago an increased risk of oral cancer among users of mouthwash was observed in two case-control studies (2, 6). The studies were prompted by clinical observation of 11 oral cancer patients who used neither tobacco nor alcohol, with 10 being long-term mouthwash users (7). In the case-control studies also, the increased risk was most prominent among nonusers of tobacco. In one, a hospital-based investigation (153 cases, 149 controls among females; 402 cases, 404 controls among males) conducted by the American Health Foundation, a significant 2.8-fold excess risk was found among women who used mouthwash daily, with the OR increasing to 3.6 among nonsmokers and nondrinkers, while the OR among men was 1.1 (2). In the other, an investigation into the high risk of oral cancer among Southern women involving 206 cancer patients and 352 controls, the OR associated with mouthwash use was 1.1 overall but 1.9 among those abstaining from tobacco use (6). In the interim, no evidence of an increased risk associated with mouthwash use was observed in a study of 95 male patients admitted to a New Jersey Veterans Administration Hospital (8) or in an update of the American Health Foundation study adding 125 female patients and 107 controls, although a nonsignificant excess risk (OR 1.4) was found for daily mouthwash use among nonsmokers and nondrinkers (9). None of the studies showed clear trends with intensity or duration of use.

The investigation reported here, the largest to date, revealed statistically significant increases in risk associated with regular mouthwash use. The excess was greater in females (60%) than males (40%) but not stronger among abstainers from tobacco and alcohol. Risks varied in proportion to dose, tending to increase with increasing duration and frequency of mouthwash use and according to the alcohol concentration of the mouthwash. Thus, the findings confirm initial reports that regular users of mouthwash are at increased risk of oral cancer and that the association is stronger among women than men.

Whether mouthwash use *per se*, or factors related to mouthwash use or its reporting, accounts for the association with oral cancer is not clear. We could rule out any sizable confounding due to smoking and drinking, the major determinants of oral cancer. Smokeless tobacco use was relatively uncommon and did not influence the mouthwash findings. It is possible that mouthwash users, perhaps more so for women, tend to underreport consumption of alcoholic beverages or tobacco, but the misclassification would have to be considerably greater for cases than controls to account for the observed excess risks. It also may be possible that some individuals wrongly reported use of mouthwash by not recalling accurately whether they ever used mouthwash at least once/week for 6 months or more and that the frequency of incorrect recall was different for cases than controls. Although misclassification of mouthwash use patterns may have occurred, serious bias from differential recall seems unlikely, since mouthwash use was a common event, *i.e.*, usually daily for long periods of adult life. Because of the large study size and relatively stable risk estimates, chance is also an improbable explanation for the finding of increased risk among mouthwash users.

A causal interpretation seems biologically plausible because some commercial mouthwashes contain an oral carcinogen, alcohol, and drinking alcoholic beverages is a well-recognized cause of oral cancer (1, 10). The dose-response trends we observed with duration and frequency of mouthwash use also are consistent with a causal interpretation. Mouthwashes often contain coloring, flavoring, or sweetening (such as saccharin) agents, but the association with brands having a high alcohol content suggests that alcohol may be responsible, at least in part. Since pure alcohol (*i.e.*, ethanol) has not been shown to be carcinogenic in laboratory animals, the mechanism by which alcoholic beverages induce oral cancer is unknown but probably involves topical exposure, perhaps with a solvent action that enhances penetration of tobacco and other carcinogens (10). Oral swishing with a mouthwash containing 25% ethanol might provide a local mucosal tissue exposure similar to drinking a 100-proof (50% ethanol) alcoholic beverage diluted with equal parts of water or other mixers, although quantitative comparisons are not available. An effect from ingestion of alcohol is unlikely, because few persons reported swallowing mouthwash. The ORs for mouthwash use tended to be elevated in all smoking categories, but the statistical power to discriminate between alternative mathematical models for interaction was weak and hindered evaluation of whether mouthwash and to-

bacco smoking combine synergistically as do alcoholic beverages and tobacco in enhancing oral cancer risk (1). Further study is needed to quantify exposures and risks from alcohol and possibly other ingredients in mouthwash.

Poor oral hygiene and dentition have long been associated with increased risk of oral cancer, although it has often been difficult to eliminate confounding by smoking and alcohol (11–17). In the one investigation that included a dental examination of oral cancer patients and controls, inadequate dentition was associated with a 3-fold increase in risk after controlling for drinking and smoking (13). Another study reported 2- to 3-fold increases in risk among persons who lost 10 or more teeth regardless of whether they wore dentures (16). However, after tobacco and alcohol intake and socioeconomic status were controlled, we found no strong associations between tooth loss, wearing dentures, or having problems with dentures. Except for an intriguing association between gum cancer and denture wearing, our findings are consistent with the lack of association with denture wearing seen in a recent case-control study in Brazil, where dentures are common (17).

Viruses may be involved in oral cancer etiology, although information is limited. Human papillomavirus antigens have been detected in oral papillomas and leukoplakias, with type 16 found especially among patients with oral cancer (18, 19), but its role is unclear since prototypes of human papillomavirus 16 may be common in normal oral tissue (20). Herpes simplex virus has been suggested as a possible risk factor (21), and experimental animals exposed to snuff were found to develop oral tumors when also infected with herpes simplex virus type 1 (22). Although no measures of viral antigens or antibodies were available in this study, the lack of association with herpes-induced cold sores or with canker sores is noteworthy. We did find a strong link to leukoplakia, self-reported by about 6% of the cases and 1% of the controls, but leukoplakias may have been underestimated, since clinical surveys among adult Americans older than 35 years indicate exposure prevalences of about 4% in males and 2% in females (23). Nevertheless, the data are consistent with the consensus view that leukoplakia predisposes to oral cancer. Erythroplasias may pose an even higher risk of malignant transformation (24) but were rarely reported in the present study.

Ionizing radiation has been reported to increase risk of salivary gland cancers (25), but its link to other oral tumors has seldom been examined. We found that oral cancer cases reported fewer dental X-rays than controls. This negative association seems likely to be a reflection of less frequent visits by the cases for dental care.

In summary, this large population-based case-control study, while showing little effect of oral hygiene factors, suggests that the regular use of mouthwash with high alcohol content contributes to oral cancer risk. Although the findings are consistent with the well-established risk associated with alcohol drinking, further research is needed to clarify the relationships observed with mouthwash use.

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