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Risk Factors for Oral Cancer in Women[1]

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ABSTRACT

Interviews were obtained from 125 women with oral cavity cancer and 107 female controls to assess the role of mouthwash use as a risk factor for oral cancer in women. In addition to detailed information on mouthwash use throughout adult life, information was obtained regarding smoking, alcohol consumption, general oral hygiene practices, and occurrence of nonmalignant conditions of the oral cavity. Mouthwash use was not associated with increased oral cancer risk in terms of frequency, duration of use, dilution, or rinsing practices. Among mouthwash users, cases reported taking more mouthfuls of mouthwash at each use compared with controls. Again among mouthwash users, cases were significantly more likely than controls to give as a reason for using mouthwash "to disguise the smell of tobacco" and "to disguise the smell of alcohol," whereas similar proportions of cases and controls reported using mouthwash to "disguise the smell of onions, garlic, etc." and "to disguise breath odors due to mouth infections or dental problems." These first two reasons for using mouthwash were strongly associated with smoking and drinking, respectively, and appear to be proxies for these exposures. Smoking, drinking, having 10 or more missing teeth, and religious background (non-Jewish *versus* Jewish) were significantly associated with oral cancer.

INTRODUCTION

In a previous study of risk factors for oral cavity cancer, we noted an apparent association of daily mouthwash use with oral cancer in women (1). This association appeared to be independent of smoking and drinking, the two strongest risk factors. However, we had only limited information on mouthwash use and no information on reasons for using mouthwash, general oral hygiene practices, or occurrence of nonmalignant conditions of the oral cavity. We, therefore, undertook a further study of oral cancer which included information on these items. We report here the results of that study.

MATERIALS AND METHODS

Since the original study found an association between mouthwash use and oral cavity cancer in women but not in men, it was decided to restrict this study to women. A brief questionnaire, devised as an addendum to the main questionnaire, included detailed questions on mouthwash use throughout adulthood, reasons for using mouthwash, occurrence of bleeding gums, gingivitis or periodontal disease, fever blisters, missing teeth, use of dentures, and frequency of toothbrushing. Both questionnaires were administered to all women with oral cancer and controls participating in the American Health Foundation's case-control study of tobacco-related cancers between 1983 and 1987. All cases had to be diagnosed within the year preceding interview, and the lesion had to have histological confirmation. Controls were patients with cancers, benign neoplasms, and nonneoplastic conditions thought not to be related to smoking or drinking. We interviewed 125 oral cancer cases and 107 controls.

The distribution of cancer by subsite within the oral cavity was: tongue, 32%; floor of mouth/gums/gingiva, 30%; buccal mucosa, 2%; palate, 15%; tonsil, 6%; retromolar trigone, 6%; and pharynx, 8%. Among the controls, 38% had cancers thought not to be related to smoking or drinking, 6% had benign neoplastic conditions, and 56% had nonneoplastic conditions.

"Mouthwash use" was defined as the regular use for at least 1 year of a commercial product designed to freshen one's breath. Subjects were asked whether they had ever used mouthwash; age of starting use; whether they were using it at time of diagnosis; if they had stopped, how many years ago they stopped; frequency of mouthwash use in the year preceding diagnosis as well as 10 years earlier; brand used for longest period; dilution; rinsing; and number of mouthfuls. They were also asked, as an open-ended question, their main reason for using mouthwash. This question was followed by the question: "Have you ever used mouthwash to disguise breath odors caused by (*a*) cigarettes or tobacco, (*b*) beer or alcohol, (*c*) onions, garlic, or other strong food, or (*d*) mouth infections or dental problems?"

Smoking was examined in terms of smoking status (never smoked, current smoker, former smoker) and cpd.[3] A current smoker was defined as someone who had smoked cigarettes within the year preceding diagnosis and an exsmoker as someone who had smoked cigarettes (at least 1 cpd for at least 1 year) in the past but had quit more than 1 year prior to diagnosis. Never-smokers were defined as those who had never smoked as much as 1 cigarette/day for a period of 1 year.

Alcohol exposure was quantified in terms of ounces per day of alcohol (in whiskey equivalents) from beer, wine, and hard liquor.

Based on comparisons of categorical variables between cases and controls, simple ORs and their 95% CI were calculated using Miettinen's method (2). For each factor of interest, both unadjusted and adjusted ORs are given in Table 1. Adjusted ORs were obtained from unconditional logistic regression models containing the factor of interest as well as potential confounding variables. For smoking, these included alcohol (never–occasional, 1–3 oz/day, 4 + oz/day), age at diagnosis (continuous), and religion (non-Jewish/Jewish). For alcohol, adjustment factors were smoking (never smoked cigarettes, 1–20 cpd, 21+ cpd), age at diagnosis, and religion. All other factors were adjusted for smoking, drinking, age, and religion. An interaction term was also included in the form of the cross-product of never/ever smoked and never/ever drank. Since the interaction was not significant in the presence of the main effects of smoking and drinking, this interaction term was not included in the final model. Mouthwash use was entered as ever/never (1/0); number of mouthfuls of mouthwash taken on each occasion as none, 1, 2+ (00, 01, 10); and number of missing teeth as none, 1–9, 10+ (00, 01, 10).

RESULTS

There were only slight differences between cases and controls in age, years of schooling, occupational level, and marital status. Cases and controls were similar in terms of race (87% of cases and 89% of controls were white). There were proportionately fewer Jews and more Catholics among cases (4.8 and 48.0%, respectively) compared with controls (17.8 and 36.5%, respectively). Religion, included as a potential confounding variable (non-Jewish/Jewish) in the logistic regression analysis, remained significant in all models.

Unadjusted and adjusted ORs for risk factors for oral cancer are presented in Table 1. Being a present smoker was significantly associated with oral cancer risk (OR_u = 2.77; CI, 1.50–5.14), but being an ex-smoker was not (OR_u = 1.03; CI, 0.52–2.04). When ever-smokers were examined by amount smoked,

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[3] The abbreviations used are: cpd, number of cigarettes smoked per day; OR, odds ratios; CI, confidence intervals.

Table 1 *Unadjusted and adjusted odds ratios for risk factors for oral cancer*

Variable	Cases	Controls	OR_u[a]	95% CI	OR_a[b]	95% CI
Cigarette smoking						
Never	33	43	1.00		1.00	
Present	66	31	2.77	1.50–5.14	2.01	1.01–4.00
Ex-	26	33	1.03	0.52–2.04	0.99	0.47–2.06
Cigarette amount						
0	33	43	1.00		1.00	
1–20	52	43	1.58	0.86–2.89	1.43	0.75–2.75
21+	40	21	2.48	1.24–4.96	1.60	0.74–3.45
Alcohol oz/day (in whiskey equivalents)						
Never	37	42	1.00		1.00	
Occasionally	35	44	0.90	0.48–1.69	0.80	0.41–1.57
1–3	24	15	1.82	0.83–3.97	1.36	0.59–3.13
4+	28	6	3.41	1.26–9.22	2.94	0.98–8.82
Frequency of mouthwash use (1 yr prior to diagnosis)						
Never	65	53	1.00		1.00	
<1/day	23	19	0.99	0.49–2.01	0.92	0.38–2.08
≥1/day	36	35	0.84	0.46–1.51	0.65	0.34–1.22
Frequency of mouthwash use (10 years ago)						
Never	65	53	1.00		1.00	
<1/day	25	24	0.85	0.44–1.66	0.94	0.39–2.28
≥1/day	34	30	0.92	0.50–1.70	0.74	0.40–1.40
Dilute						
Yes	32	21	1.00		1.00	
No	26	32	0.53	0.25–1.14	0.61	0.27–1.38
Rinse						
Yes	45	34	1.00		1.00	
No	14	19	0.56	0.24–1.27	0.68	0.29–1.60
No. of mouthfuls						
1	23	34	1.00		1.00	
2+	35	20	2.59	1.21–5.53	2.94	1.31–6.60
Keep in mouth						
Few seconds	41	36	1.00		1.00	
Longer	18	18	0.88	0.40–1.95	0.86	0.37–1.96
Reasons[c]						
Reason 1						
No	32	39	1.00		1.00	
Yes	26	12	2.64	1.16–6.00	3.30	1.24–8.75
Reason 2						
No	43	46	1.00		1.00	
Yes	15	5	3.21	1.11–9.29	3.25	1.03–10.30
Reason 3						
No	34	25	1.00		1.00	
Yes	24	26	0.68	0.32–1.45	0.66	0.30–1.43
Reason 4						
No	46	38	1.00		1.00	
Yes	12	13	0.76	0.31–1.87	0.72	0.27–1.94
Fever blisters						
No	78	77	1.00		1.00	
Yes	45	30	1.48	0.85–2.59	1.45	0.80–2.64
Bleeding gums						
No	89	77	1.00		1.00	
Yes	35	28	1.08	0.60–1.94	1.12	0.85–1.47
Gingivitis or periodontal disease						
No	98	86	1.00		1.00	
Yes	25	20	1.10	0.57–2.12	1.12	0.55–2.27
Missing teeth						
None	17	23	1.00		1.00	
1+	108	84	1.74	0.88–3.45	1.19	0.52–2.74
Missing teeth						
None	17	23	1.00		1.00	
1–9	37	46	1.09	0.51–2.34	0.89	0.37–2.11
10+	68	37	2.49	1.19–5.19	1.62	0.66–4.02
Dentures						
None	45	39	1.00		1.00	
Partial	35	35	0.87	0.46–1.64	0.64	0.32–1.26
Complete	33	25	1.14	0.58–2.25	0.66	0.31–1.39
Toothbrushing						
2+/day	62	64	1.00		1.00	
≤1/day	43	27	1.64	0.91–2.98	1.56	0.82–2.94

[a] OR_u, unadjusted odds ratio.

[b] OR_a, odds ratio adjusted for cigarette smoking (never, 1–20 cpd, 20+ cpd), drinking (never–occasional, 1–3.9 oz/day in whiskey equivalents, 4+ oz/day in whiskey equivalents), age (continuous), and religion (non-Jewish/Jewish).

[c] "Have you ever used mouthwash to disguise breath odors caused by: (Reason 1) cigarettes or tobacco; (Reason 2) beer or alcohol; (Reason 3) onion, garlic, or other strong food; or (Reason 4) mouth infections or dental problems."

the OR for lighter smokers (1–20 cpd) was 1.58 (CI, 0.86–2.89) and that for heavier smokers (21+ cpd) was 2.48 (CI, 1.24–4.96). Adjustment for drinking and other confounders reduced the magnitude of these ORs.

No cases and only one control reported ever having chewed tobacco; one case and one control reported ever using snuff.

Alcohol intake was positively associated with oral cancer risk, and the OR increased with increased amount. Drinkers of 4 oz or more of whiskey equivalents of alcohol had an OR_u of 3.41 (CI, 1.26–9.22). Adjustment for smoking and other confounders reduced the OR to 2.94 (CI, 0.98–8.82).

Contrary to the results of the earlier study, mouthwash use was not associated with increased oral cancer risk in terms of frequency, duration of use, dilution, or rinsing practices. Cases did, however, report taking more mouthfuls of mouthwash at each use compared with controls. For those habitually taking two or more mouthfuls, compared with those taking one mouthful, the unadjusted OR was 2.59 (CI, 1.21–5.53) and the adjusted OR was 2.94 (CI, 1.31–6.60).

To the initial open-ended question "What is your main reason for using mouthwash?" almost all users responded "to freshen my breath," or the equivalent. On the subsidiary question about specific motivations for using mouthwash, cases were significantly more likely than controls to give as a reason for using mouthwash "to disguise the smell of tobacco" ($OR_u = 2.64$; CI, 1.16–6.00; $OR_a = 3.30$; CI, 1.24–8.75) and "to disguise tthe smell of alcohol" ($OR_u = 3.21$; CI, 1.11–9.29; $OR_a = 3.25$; CI, 1.03–10.30), whereas similar proportions of cases and controls reported using mouthwash to "disguise the smell of onions, garlic, etc." and to "disguise breath odors due to mouth infections or dental problems." When reason 1 was entered together with smoking in the logistic model, the OR for smoking was greatly reduced (OR for smokers of 21+ cpd = 1.10; CI, 0.34–3.48); the same occurred with reason 2 and drinking (OR for drinkers of 4+ oz/day = 1.54; CI, 0.52–4.55). This suggests that these reasons function as proxies for smoking and drinking.

Twenty-nine cases and 37 controls were lifetime nonsmokers and never–occasional drinkers. Of these, 19 cases (66%) and 23 controls (62%) reported never having used mouthwash; 8 cases (28%) and 7 controls (19%) reported using mouthwash daily (OR = 1.38, CI, 0.42–4.55).

Having missing teeth was associated with increased oral cancer risk (OR for those having any missing teeth relative to those having no missing teeth = 1.74; CI, 0.88–3.45). Those having 10 or more missing teeth had an OR of 2.49 (CI, 1.19–5.19) relative to those having no missing teeth. Adjustment for confounders reduced the OR for those missing 10 or more teeth to borderline statistical significance, 1.78 (CI, 0.97–3.26). Among those with any missing teeth, the mean number of missing teeth was 17.4 for cases and 13.3 for controls ($P = 0.0001$).

Elevated but nonsignificant ORs were seen for those with a history of fever blisters and for those brushing their teeth once or less per day. No association was seen with bleeding gums or gingivitis/periodontal disease.

DISCUSSION

Our first study of mouthwash use and oral cancer was carried out to confirm the observation of Weaver *et al.* (3) that, of 11 nonsmoking nondrinking patients with squamous cell carcinoma of the head and neck, 10 were long term mouthwash users. It seemed plausible that prolonged exposure to certain constituents of commercial mouthwashes could increase the risk of oral cancer. Most commonly used brands of mouthwash contain ethanol in a percentage ranging from 7% to 27%. In addition, they contain artificial sweeteners, flavoring agents, and artificial coloring. Some mouthwashes contain essential oils such as clove oil or extracts of essential oils such as thymol, eucalyptol, and menthol.

The results of this study do not support a causal association between mouthwash use and oral cancer risk. Except for the number of mouthfuls habitually taken, cases and controls showed no differences in mouthwash use. In contrast, in univariate analyses smoking and drinking both showed significant and dose-related associations with oral cancer. In the logistic regression analyses, heavy drinking, being a present smoker of cigarettes, and religion (non-Jewish *versus* Jewish) showed a significantly increased risk of oral cancer.

In the earlier study we hypothesized that women may tend to use mouthwash to disguise the smell of alcohol on their breath and that they may also tend to underreport their alcohol consumption. In the present study, however, cases did not report a higher frequency of mouthwash use compared with controls, and the reasons given by mouthwash users for using the product are strongly associated with exposure to tobacco or alcohol. The χ^2 for independence, with Yates' correction, for smoking was 4228 ($P < 0.0001$) and for alcohol was 8.69 ($P < 0.01$).

Poor dentition is a suspected risk factor for oral cancer (4–6), and our results show a weak association of missing teeth with oral cancer risk after adjustment for other risk factors. However, there was no apparent difference in the use of dentures (either partial or complete) between cases and controls. It is interesting to note that, relative to cases, a somewhat greater proportion of controls who had lost any teeth were fitted for dentures (60 of 84 controls *versus* 68 of 108 cases; $P = 0.11$). Also, among those with any number of dentures, cases had a greater mean number of missing teeth compared with controls (20.4 *versus* 16.4; $P = 0.0001$). This may reflect a difference in general health consciousness between cases and controls.

The weak association of a history of fever blisters with oral cancer is interesting in light of previous studies showing high titers to herpes simplex virus antibody in oral cancer cases, compared with controls (7). The OR, however, is only slightly elevated and not statistically significant and could be due to biased recall or chance.

It is difficult to explain the discrepancy between the results of this study and those of our previous study. The frequency of daily mouthwash use in the earlier study was 56% among female cases and 35% among female controls; in the present study the corresponding percentages are 29 and 33% (most recent period) or 27% and 28% (frequency as of 10 years prior to diagnosis). The greatest difference was in the frequency of use among cases.

One explanation is that the two study populations differ in variables that affect mouthwash use. Little difference is seen in the proportions of cases who are smokers and drinkers between the two studies or in the proportions of drinkers among the controls. The proportion of ever-smokers among the controls, however, increased from 39% in the earlier study to 60% in the present study. Most of this change is due to an increased proportion of exsmokers (from 12% to 31%). This difference, however, cannot explain the different frequencies of mouthwash use in the two case series.

A second explanation is that, in the original study, the initial mouthwash use question was worded in a biased manner. Instead of first being asked "Have you ever used mouthwash on a regular basis?" as was done in the later study, patients were

simply asked "How frequently do you use mouthwash?" This may have led to biased reporting.

The number of cases in the present study is relatively small, reflecting the low frequency of oral/pharyngeal cancer in women; 9700 new cases were estimated for the whole United States in 1988 (8). Nevertheless, the study had moderate power (63%) to detect an OR of 2.0, with $\alpha = 0.05$, for a factor like mouthwash use to which 33% of the controls reported daily exposure and high power to detect an OR of 2.5 (87%).

Since it is possible that systematic errors in coding, or misinterpretation of codes, could produce a spurious result, we rechecked the computerized record for key variables against the original questionnaire data. We are confident that errors in coding or in processing the data did not affect the results of either study.

It is worth reviewing the four published studies of mouthwash use as a potential risk factor in oral cancer to assess the consistency of their findings.

The issue of mouthwash use as a potential risk factor for oral cancer was originally raised by Weaver *et al.* (3), who reported that, of 11 patients with squamous cell carcinoma of the head and neck who abstained from all alcohol and tobacco, 10 had used mouthwash several times daily for at least 20 years. Nine of the 10 cases were women. Although the comparison group selected by the authors was not comparable to the case group, the apparently heavy use of mouthwash in the nonsmoking/nondrinking cases was sufficiently striking to warrant confirmation.

Our study (1) carried out in response to this report showed an association of daily mouthwash use with oral cancer in women but not in men. An effect of mouthwash use was observed in the total female group (OR for daily users, 2.79; CI, 1.67–4.66) and in the subgroup of women who had never smoked or drunk alcohol (OR for daily users, 3.63; CI, 1.48–8.92). No clear trend was seen with duration of use. In logistic regression analyses which included smoking and drinking as predictors, daily mouthwash use was of borderline statistical significance.

Blot *et al.* (9) recontacted 206 female oral cancer cases and 352 controls from an earlier study of snuff-dipping and oral cancer in order to obtain information on mouthwash use and related factors. Where the patient had died, next-of-kin were queried on the subject's habits. The overall OR for use of mouthwash adjusted for smoking and snuff use was 1.15 (CI, 0.8–1.7), but among those abstaining from tobacco and alcohol the OR was 1.94 (CI, 0.8–4.7). No dose-response relationship was observed for duration of use.

In a study of 95 male oral cancer cases and 913 controls, Mashberg *et al.* (10) found no effect of mouthwash use either before or after adjustment for smoking, drinking, and age (overall OR for users *versus* nonusers, 0.82; CI, 0.53–1.25). This study does not directly contradict the results of the previous three studies since those studies noted an association in women who were nonsmokers and nondrinkers. In the study of Mashberg *et al.* there were no never-smokers in the case group.

While the present study cannot rule out the possibility that chronic mouthwash use may contribute to oral cancer risk in women, our results are consistent with the null hypothesis of no effect.

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