Prospective Study of Alcohol Consumption and Risk of Oral Premalignant Lesions in Men

Nancy Nairi Maserejian,[1,3,5] Kaumudi J. Joshipura,[1,3,6] Bernard A. Rosner,[4] Edward Giovannucci,[1,2,4] and Athanasios I. Zavras[3]

Departments of [1]Epidemiology and [2]Nutrition, Harvard School of Public Health; [3]Department of Oral Health Policy and Epidemiology, Harvard School of Dental Medicine; [4]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston; [5]New England Research Institutes, Watertown, Massachusetts; and [6]Division of Dental Public Health, School of Dentistry, University of Puerto Rico Medical Science Campus, San Juan, Puerto Rico

Abstract

Recent case-control studies indicate that alcohol increases the risk of oral premalignant lesions (OPL) among tobacco users, but the independent association between alcohol and OPL remains unclear. We prospectively evaluated the association between alcohol consumption and the incidence of OPL. Participants were 41,458 men in the Health Professionals Follow-up Study. Alcohol consumption was assessed every 4 years using validated food frequency questionnaires. We confirmed clinically or histopathologically diagnosed OPL events occurring between 1986 and 2002 by medical record review (193 cases). Multivariate-adjusted relative risks of OPL were calculated from Cox proportional hazards models. With detailed control for tobacco and other variables, multivariate relative risks (95% confidence intervals) were 1.7 (0.9-3.2) for drinkers of 0.1 to 14.9 g/d, 2.9 (1.5-5.6) for 15 to 29.9 g/d, and 2.5 (1.3-5.1) for ≥30 g/d, compared with nondrinkers. Approximately one additional drink per day (12.5 g) was associated with a 22% increase in risk ($P < 0.001$). The associations did not vary by beverage type, frequency, or consumption with meals. Results were similar when restricted to cases of oral epithelial dysplasia. Alcohol increased OPL risk in never-users of tobacco as well as in past or current users. An interaction between alcohol and tobacco was apparent by their more-than-additive joint effects. Alcohol is an independent risk factor for OPL, regardless of beverage type or drinking pattern. Recommendations to reduce alcohol intake have the potential to reduce incidence of OPL in non-smokers and smokers alike. (Cancer Epidemiol Biomarkers Prev 2006;15(4):774–81)

Introduction

Oral cancer remains one of the 10 most frequent forms of malignancy in the U.S., with considerable morbidity and mortality (1). Virtually all oral squamous cell carcinomas arise from premalignant precursor lesions, which are often clinically defined as leukoplakia or erythroplakia (2, 3). Thus, a better understanding of what causes oral premalignant lesions (OPL) is important for the prevention of malignant lesions.

Alcohol has been found to increase the risk of OPL in the presence of tobacco (4, 5), but the independent association between alcohol and OPL remains unclear. After adjustment for tobacco use, some case-control studies observed a 2- to 3-fold greater risk of leukoplakia (6), oral submucous fibrosis (7), erythroplakia (8), and oral epithelial dysplasia (OED; ref. 9), whereas others found no independent associations between alcohol and OPL (5, 10-13). Studies of specific types of alcoholic beverages also vary; wine is particularly controversial, as it has shown no relation to OPL (9), but also a lower risk (11, 14). Drinking pattern, such as drinking with meals or concentrated drinking over a few days per week, may play a role as well (15, 16), but no data regarding drinking pattern and OPL risk have been published.

A difficulty that all studies of alcohol and OPL must deal with is that the exact mechanism of alcohol in carcinogenesis is uncertain. The field cancerization theory posits that several molecular alterations with distinct genetic changes occur frequently, and multiple events or ''hits'' accumulate until malignant transformation occurs (17-19). The multistage theory of oral carcinogenesis considers exposures to have more distinct roles, such as tumor initiators or promoters (20). Results from a recent case-control study support the theory that alcohol is a promoter rather than an initiator, as it was unrelated to the occurrence of leukoplakia, but doubled the risk of malignant transformation (13). Indeed, there is strong evidence that alcohol is an independent risk factor for oral cancer (4, 21-27). Conflicting results in case-control studies of alcohol and OPL may be the result of methodologic shortcomings, such as recall bias, insufficient control for tobacco, and selection bias. Prospective cohort studies of alcohol and OPL, which minimize such limitations, are lacking.

Considering that ~65% of the adult U.S. population drinks alcohol (28) and that the prevalence of tobacco use is decreasing in the U.S. and other developed countries, the independent role of alcohol becomes increasingly important to understand. To clarify the independent role of alcohol in the development of OPL, we prospectively assessed alcohol consumption in a large cohort of men in the U.S., and examined whether associations varied by beverage type, drinking patterns, and tobacco use.

Materials and Methods

Study Population: Health Professionals Follow-up Study. The Health Professionals Follow-up Study is an ongoing prospective cohort study of 51,529 U.S. male health professionals (58% dentists, as well as optometrists, osteopaths, pharmacists, podiatrists, and veterinarians) who were aged 40 to 75 years when the study was initiated in 1986. At baseline, these men completed detailed questionnaires assessing dietary intake, life-style factors, and medical history. Follow-up questionnaires were mailed to participants every 2 years to update exposure information and ascertain newly diagnosed

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Requests for reprints: Nancy Maserejian, New England Research Institutes, 9 Galen Street, Watertown, MA 02472. Phone: 617-923-7747, ext. 229. E-mail: nmaserej@post.harvard.edu

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disease. Loss to follow-up occurred among 1.74% of participants. This study received institutional approval by the Human Subjects Committee at the Harvard School of Public Health.

We excluded participants from analyses if they reported an implausible daily energy intake or omitted 70 or more of the 131 dietary questions asked at baseline (~3% of men). In addition, we excluded men with any of the following diagnoses prior to the baseline date of January 1986: cirrhosis of the liver (1%), alcohol dependence problem (0.75%), an OPL (0.04%), or any cancer other than non–melanoma skin cancer (4%). After exclusions, 41,458 men remained in the study.

Assessment of OPLs. A specific question on the lifetime occurrence of leukoplakia or any other oral precancerous lesion was first included in the 1996 survey, and any new oral precancer diagnoses were reported on subsequent questionnaires. Participants who reported receiving a professional diagnosis of leukoplakia, or any other OPL between 1986 and 2002, were mailed an additional questionnaire to confirm the diagnosis and release dental records and pathology reports.

Primary outcome definition was based on a clinical diagnosis to reflect routine clinical practice. Lesions meeting one of the diagnosis criteria described in Appendix A were included. Lesions on the external lip vermilion, which are likely to resemble skin cancer in etiology, and lesions of the oropharynx were excluded from analyses. Oral malignancies that were not first diagnosed as premalignancies were included because they likely developed from premalignant precursors (2, 3); omitting these cases would have resulted in selective exclusion of premalignancies, particularly those with greater malignant potential. Also, participants whose medical records indicated oral squamous cell carcinoma *in situ* were considered cases because severe OED is consistent with carcinoma *in situ*. During follow-up, we verified a total of 193 new OPL events. A clinical diagnosis term had been recorded for 95 cases (49%), the most common being leukoplakia (72% of clinical diagnoses). Of the 131 cases that had undergone biopsy (68%), 84 (64%) had dysplasia present. Nondentist participants who attested to their OPL on the additional questionnaire to substantiate the biennial self-report, but for whom dental/medical records were unobtainable, were considered ''probable'' OPL cases. The diagnosis remained as ''probable'' for 21% of the men and ''confirmed'' for 79% of the men, most often confirmed by dental and pathology records (72%).

The main analyses were conducted including all OPL events (193 events), and then repeated with various restrictions to verify overall findings. First, we conducted an analysis with only confirmed OPL cases (152 events). Then, to further minimize potential misclassification and detection bias, we restricted the entire sample of participants to the 23,920 men who were dentists by profession (89 events). We also ran analyses excluding 18 cases diagnosed as oral lichen planus (leaving 175 events) or 43 cases that were first diagnosed as oral cancer upon detection (leaving 150 events). An analysis aiming to examine a longer induction period also served to ensure the prospective quality of the investigation; here, we included only the 97 OPL events that occurred after 1996, which was the first year the diagnosis appeared on a Health Professionals Follow-up Study questionnaire. Finally, because the clinical definition of OPL is prone to subjectivity and is waning in popularity, we analyzed the outcome of histologically confirmed OED or cancer (84 events). Because results were similar across these various restricted analyses, the results we report are from analyses including all the probable OPL events, unless otherwise specified.

Assessment of Alcohol Intake. The semiquantitative food frequency questionnaire, which was completed at baseline in 1986 and every 4 years thereafter, asked questions on the frequency of consumption of 131 food items, including beer, red wine, white wine, and liquor, over the past year. We standardized alcohol portions as a 12 oz (355 mL) bottle or can of beer, a 4 oz (118 mL) glass of wine, and a shot of liquor. We calculated total alcohol intake in grams per day by multiplying the number of servings of each beverage type by the grams of ethanol per serving (beer, 12.8 g; light beer, 11.3 g; wine, 11.0 g; and liquor, 14.0 g per serving) and then summing all alcoholic beverages. Former drinkers were defined at baseline as men who consumed no alcohol in 1986 but reported that they had decreased their alcohol intake in the 10 years prior. In 1994, we asked drinkers the proportion of alcoholic beverages consumed with meals (<25%, 25-49%, 50-74%, or ≥75%). This method of assessing alcohol has been shown to be valid (r = 0.86 compared with two 1-week diet records; predicts a 0.3 mg/dL increase in serum high-density lipoprotein concentration per gram of alcohol intake, r = 0.35) and reproducible (r = 0.92 for food frequency questionnaires completed 1 year apart) in this cohort (29).

Data Analysis. Each eligible participant contributed person-time of follow-up from the date of return of the baseline questionnaire to the month of diagnosis of an oral premalignant or malignant lesion, death, or the end of follow-up (January 31, 2002), whichever occurred first. Participants who reported an OPL or oral cancer, or who died, were excluded from subsequent follow-up.

We calculated cumulative incidence curves for the total cohort and stratified by baseline alcohol consumption using the Kaplan-Meier method. We used multivariate Cox proportional hazards models with time-dependent covariates to calculate hazard ratios and 95% confidence intervals (CI) as estimates of relative risk (RR). To assess linear relationships and test for trend, we entered into the model a single ordinal variable, which we evaluated by the Wald test (30). We examined the proportional hazards model assumptions by including interaction terms with time variables; nonsignificant interaction terms indicated no violation of proportional hazards. All nonnutrient covariates were updated in the analysis using simple updating for each 2-year period, and missing variables were assigned their values from the previous questionnaire. Multivariate models adjusted for age (months), time period (2-year intervals), cigarette use (never, former, current), age at start smoking (<15, 15-19, 20-29, ≥30 years old), quantity smoked during years of active smoking (1-4, 5-14, 15-24, 25-34, 35-44, or ≥45 cigarettes/d), time since quitting among past smokers (<10 or ≥10 years), pipe or cigar use (never, former, current), ever use of chewing tobacco (yes/no), former drinker status at baseline (yes/no), total energy intake (quintiles), fruit intake (quintiles), and profession (dentist versus nondentist). We also included the following factors and assessed change in estimates and CIs, but they did not have an effect on the results and so were not included as confounders in the final multivariate analyses: race/ethnicity, family history of cancer, having had a recent physical exam, number of natural teeth, vegetable intake, vitamin C–rich fruit and vegetable intake, multivitamin intake, total intake of vitamins E, C, A, or folate, and an interaction term between folate and alcohol consumption. Additional analyses excluded men who were former drinkers at baseline, to verify that our main analysis was not confounded by past heavy alcohol use among nonusers.

We examined whether OPL risk differed according to type of alcoholic beverage by simultaneously entering into the model terms for the amount (g/d) of wine, beer, and liquor consumed. To assess drinking patterns, we evaluated whether OPL risk was associated with drinking frequency or drinking with meals, controlling for alcohol intake.

To best represent long-term alcohol intake and to reduce within-person variation, the main analysis used the cumulative average daily intake from all available questionnaires up

to the start of each 2-year follow-up interval (31). If participants were diagnosed with an alcohol dependence problem or cancer during follow-up, intake was not updated after the beginning of the interval in which they developed the diagnosis. Because the induction period for any relationship between alcohol and OPL is not known, additional analyses examined the possibility of a long latency for OPL development, first by using only the baseline (1986) intake, and then by using only baseline intake and applying a 10-year lag in follow-up (beginning at disease follow-up in 1996). We also explored the possibility of short-term effects, by simply updating alcohol intake every 4 years.

Results

At baseline, increased alcohol consumption was positively associated with tobacco use and multivitamin use, and negatively associated with fruit intake (Table 1). Among men who drank >30 g/d, beer and liquor were consumed in greater quantities than wine. Liquor was most closely correlated to drinking outside of meals, whereas wine was positively associated with drinking with meals (Spearman correlation coefficients: −0.12 for liquor, 0.23 for wine, −0.05 for beer; $P < 0.0001$ for all). Men who consumed the majority of their alcohol outside of meals also tended to consume more alcohol per day.

We verified 193 cases of OPL during follow-up. Cumulative incidence rates for both the total cohort and stratified by baseline alcohol consumption are shown in Fig. 1. Cumulative average alcohol consumption was significantly associated with OPL events, increasing risk by ~22% with each additional drink per day (12.5 g/d increase; RR, 1.22; 95% CI, 1.10-1.35, $P = 0.0002$; Table 2). Results were similar when we used only baseline (1986) or recent (0-4 year lag, data not shown) intake levels. When we examined a longer induction period, by using alcohol intake levels in 1986 to examine disease risk after 1996, the RRs were generally stronger. For example, men who consumed ≥30 g/d in 1986 had more than three times the risk of OPL 10 or more years later, compared with nondrinkers in 1986 (RR, 3.43; 95% CI, 1.15-10.21; $P = 0.02$). Results were confirmed in analyses of OED events. Here, an additional 12.5 g/d had a slightly greater risk of OED as compared with any OPL (OED; RR, 1.29; 95% CI, 1.10-1.50), although fewer OED events contributed to wider CIs. Results were also similar when we excluded lesions that were first diagnosed as oral cancer or when we restricted the entire analysis to participants who were dentists by profession (data not shown).

Men who were former drinkers in 1986 (12% of the baseline population) were at increased risk for OPL (RR, 1.59; 95% CI, 0.74-3.39; $P = 0.23$) and were thus included as a category in the multivariate models. In additional analyses, we excluded these former drinkers, and results were similar to the main analysis (data not shown).

Drinking Patterns. After adjustment for the amount of alcohol consumed on drinking days, frequency of drinking was not statistically significant (RR, 1.05; 95% CI, 0.98-1.12; $P = 0.15$). However, drinking frequency and amount were highly correlated (Spearman correlation coefficient, 0.73; $P < 0.0001$), thereby limiting our ability to separate their effects.

Of the men who reported their alcohol intake with respect to meals in 1994, 40% consumed <25% of their overall intake with meals, 20% consumed 25% to 74% with meals, 22% consumed >75% with meals, and 18% did not drink. No clear associations emerged between the percentage of alcohol consumed with meals and risk of OPL. Adjusting for amount of alcohol consumed per day, the RR of OPL for men who consumed the majority of their alcohol with meals, compared with men who primarily drank outside of meals, was 1.47 (95% CI, 0.85-2.52; $P = 0.17$, for drinking >75% versus <25% with meals).

Type of Alcoholic Beverage. We observed similar increases in OPL risk with consumption of wine, beer, or liquor, although the association with wine was not statistically significant (wine $P_{trend} = 0.27$; beer $P_{trend} = 0.02$; liquor $P_{trend} = 0.05$;

Table 1. Characteristics of 41,458 men in the Health Professionals Follow-up Study, by alcohol consumption, at baseline (1986)

	Baseline alcohol consumption				
	0 g/d (n = 9,417)	0.1-4.9 g/d (n = 10,189)	5.0-14.9 g/d (n = 11,522)	15.0-29.9 g/d (n = 5,565)	≥30 g/d (n = 4,765)
Age, mean in years	54.0	53.1	53.6	53.7	55.2
Amount of alcohol consumed (g/d)					
Total, mean	0	2.5	9.7	20.1	45.9
As beer	0	0.6	3.3	5.9	16.6
As wine	0	1.1	3.0	6.7	7.8
As liquor	0	0.6	3.3	7.4	22.1
Consumed <25% of alcohol with meals (%)*	0	28	37	36	43
Days per week alcohol was consumed (mean no.)	0	0.9	3.0	5.0	6.3
Cigarette smoking status and quantity †					
Never (%)	61	51	43	36	25
Past (%)	30	38	45	53	54
Current (%)	6	6	7	8	17
≥35 cigarettes/d (%)	15	16	15	16	18
<10 y since quit smoking (%)	32	29	29	31	35
<15 y of age at start of smoking (%)	4	5	6	8	10
Chewing tobacco ever-user (%)	4	3	4	4	7
Pipe or cigar user (%)	4	5	7	9	11
Recently had a routine physical exam (%) ‡	51	53	54	54	51
Multivitamin user (%)	40	41	43	44	44
Fruit intake (servings/d)	2.5	2.5	2.4	2.3	1.8
Dentist by profession (%)	56	57	59	60	57

NOTE: All measurements were taken at baseline (1986), except for the percentage of alcohol consumed with meals (1994) and recent physical exam (1988). Except for age, all variables were adjusted by direct standardization to the age distribution of the entire study population.

*The percentage of alcohol consumed with meals was asked in the 1994 questionnaire.

†Quantity smoked was calculated among current smokers only. Years since quit smoking was calculated among past smokers only. Age at start smoking was calculated among past and current smokers. Categories of smoking status do not add up to 100% due to rounding and missing data.

‡Recent physical exam was asked in the 1988 questionnaire.

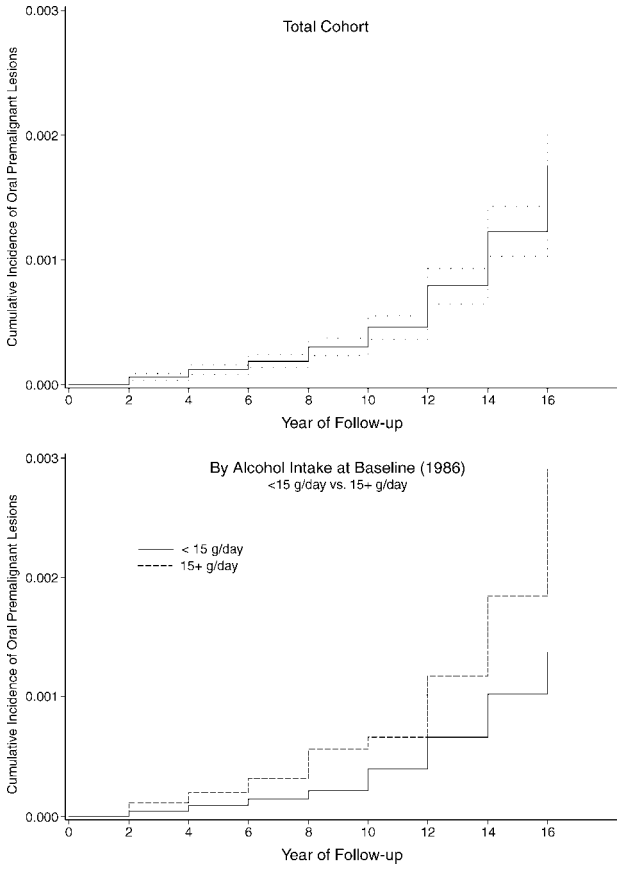

Figure 1. Cumulative incidence of OPLs among 41,458 Health Professionals, from 1986 to 2002, total cohort and stratified by baseline alcohol intake. Total cohort analysis, 95% CIs. Test for homogeneity across strata of baseline alcohol intake ($P < 0.0001$).

Table 3). We examined the association for red and white wine separately, but due to the absence of appreciable differences in OPL risk, we present results for overall wine consumption. When we restricted the analysis to men who drank alcohol mostly outside of meals, wine was strongly associated with OPL risk (controlling for liquor and beer intake, 12.5 g/d increase in wine, compared with nondrinkers of wine; RR, 1.87; 95% CI, 1.02-3.41; $P = 0.04$). In contrast, among men who consumed the majority of their alcohol with meals, no association with wine was apparent, although power was low to assess the relative effect of each beverage type by pattern of consumption with meals.

Modification of Effects by Tobacco Use. Tobacco use, in the form of cigarette, cigar, pipe, or chewing tobacco, was strongly associated with increased risk of OPL. Compared with never users of any tobacco, past users of tobacco had approximately twice the risk of OPL (age-adjusted RR, 1.90; 95% CI, 1.32-2.74; multivariate, including alcohol RR, 1.75; 95% CI, 1.21-2.54), and current users had approximately six times the risk of OPL (age-adjusted RR, 6.63; 95% CI, 4.48-9.81; multivariate RR, 5.73; 95% CI, 3.82-8.60).

A joint analysis revealed a significantly increased OPL risk for men who have a history of past or current tobacco use and consume moderate-to-high amounts of alcohol (Table 4). Men who currently use tobacco and drink ≥15 g/d had >10 times the risk as men who never used tobacco and drink <15 g/d (RR, 10.2; 95% CI, 6.03-17.1; $P < 0.0001$). Positive interactions between alcohol and past or current tobacco use were apparent on the additive scale (i.e., $RR_{\geq 15\ g/d\ alcohol\ and\ current\ tobacco} > RR_{<15\ g/d\ alcohol,\ current\ tobacco} + RR_{\geq 15\ g/d\ alcohol,\ never\ tobacco} - 1.0$), but not on the multiplicative (i.e., $RR_{\geq 15\ g/d\ alcohol\ and\ current\ tobacco} < RR_{<15\ g/d\ alcohol,\ current\ tobacco} \times RR_{\geq 15\ g/d\ alcohol,\ never\ tobacco}$) scale. For example, on the additive scale, the risk estimate for current smoking and drinking >15 g/d (RR, 10.2) was greater than the sum of the estimates for exposure to either risk factor (RR, 2.16 + 6.40 − 1.0 = 7.56; 10.2 > 7.56).

When we separately examined never, past, and current tobacco users, alcohol was associated with an elevated risk of OPL for all groups. The multivariate RR associated with an additional drink per day (12.5 g ethanol) was strongest for men who never used tobacco, attesting to the independence of alcohol as a risk factor for OPL (never tobacco RR, 1.61; 95% CI, 1.30-1.99; $P < 0.0001$; past tobacco RR, 1.09; 95% CI, 0.91-1.31; $P = 0.34$; current tobacco RR, 1.20; 95% CI, 1.03-1.40; $P = 0.02$). For never and past smokers, results were similar using baseline (1986), cumulative average, or recent intake levels. For current smokers, recent intake levels increased OPL risk to

Table 2. Multivariate RR and 95% CI of OPLs, by average daily alcohol intake

	RR (95% CI) per category of intake					RR (95% CI) with additional 12.5 g/d (~1 drink)	P value, test for trend ≥30 g/d
	0 g/d	0.1-4.9 g/d	5.0-14.9 g/d	15.0-29.9 g/d	≥30 g/d		
Any OPL (n)	21	46	47	46	33		
Cumulative average intake*	1.00	1.72 (0.93-3.17)	1.69 (0.88-3.22)	2.89 (1.49-5.60)†	2.52 (1.25-5.07)†	1.22 (1.10-1.35)	0.0002
Baseline 1986 intake*	31	33	53	36	40		
	1.00	1.28 (0.63-2.60)	1.70 (0.86-3.37)	2.28 (1.12-4.65)‡	2.36 (1.15-4.84)‡	1.19 (1.08-1.31)	0.0003
Baseline 1986 intake with lag-time of 10 to 16 years§	14	12	32	15	24		
	1.00	1.23 (0.40-3.84)	2.69 (0.94-7.67)	2.53 (0.83-7.74)	3.43 (1.15-10.21)‡	1.20 (1.06-1.37)	0.006
OED, cumulative average intake (n)‖	12	21	16	17	18		
	1.00	1.16 (0.50-2.71)	0.83 (0.33-2.09)	1.63 (0.65-4.13)	2.19 (0.85-5.63)	1.29 (1.10-1.50)	0.001
OED, Baseline 1986 intake‖	15	13	22	14	20		
	1.00	0.83 (0.31-2.20)	1.18 (0.47-2.96)	1.56 (0.58-4.15)	2.17 (0.83-5.67)	1.28 (1.12-1.46)	0.0004

NOTE: Risks are adjusted for age, follow-up cycle, pipe/cigar smoking status, chewing tobacco use, cigarette smoking status, years since quitting among past smokers, cigarettes smoked per day among current smokers, age at start of smoking, total energy intake, fruit intake, former drinker at baseline, and dental profession. The reference group includes nondrinkers (0 g/d). Cumulative average intake incorporates intake through 16 years (1986-2002) of follow-up. Baseline intake uses only 1986 intake levels to assess risk from 1986 to 2002. A single alcoholic beverage contains 11.0 to 14.0 g of alcohol.

*Analysis included 193 oral premalignant lesion events among 41,458 participants.

†$P < 0.01$.

‡$P = 0.02$.

§Analysis used baseline 1986 alcohol consumption to assess disease risk from 1996 to 2002, and included 97 events among 41,458 participants.

‖Oral epithelial dysplasia analysis included only the 84 events with confirmed dysplasia among 41,395 participants, after excluding men with an oral premalignant lesion that did not undergo biopsy.

Table 3. RR and 95% CI of OPLs, by type of alcoholic beverage consumed, cumulative average intake from 1986 to 2002

	RR (95% CI) by category of alcohol intake from specific beverages			RR (95% CI) with additional 12.5 g/d (~1 drink)	*P* value, test for trend
	0 g/d	0.1-9.9 g/d	≥10 g/d		
Wine					
Median intake (g/d)	0	1.6	14.9		
Cases of OPL (*n*)	74	109	7		
Person-years	202,640	400,728	40,664		
	1.0	1.32 (0.89-1.96)	1.37 (0.73-2.56)	1.17 (0.88-1.56)	0.27
Beer					
Median intake (g/d)	0	1.8	12.8		
Cases of OPL (*n*)	55	105	31		
Person-years	231,236	346,054	65,096		
	1.0	1.01 (0.69-1.49)	1.46 (0.89-2.41)	1.20 (1.02-1.41)	0.02
Liquor					
Median intake (g/d)	0	1.7	17.0		
Cases of OPL (*n*)	58	96	39		
Person-years	265,952	285,064	92,638		
	1.0	1.29 (0.88-1.89)	1.26 (0.79-2.01)	1.16 (1.00-1.34)	0.05

NOTE: Risks are adjusted for intake of other types of alcoholic beverages and the covariates listed in Table 2. The alcohol content per serving is ~12.8 g for regular beer (12 oz can or bottle), 11.3 g for light beer, 11.0 g for wine (4 oz glass), and 14.0 g for liquor (shot).

a greater extent than did intake in 1986 (e.g., recent intake, ≥30 g/d; RR, 9.06; 95% CI, 2.07-39.6; baseline intake, ≥30 g/d; RR, 3.55; 95% CI, 0.46-27.2). When we modeled these two highly correlated variables together in current smokers, the association between baseline intake and OPL substantially weakened, but recent intake remained significantly associated with increased risk among current smokers. Overall, however, current smokers were less affected by each additional drink per day than were never-users of tobacco, most likely as a consequence of tobacco's strong independent association with OPL.

Discussion

In this prospective study of 41,458 men with detailed control for tobacco use, alcohol consumption was consistently associated with a greater risk of OPLs, regardless of the frequency of drinking, proportion consumed with meals, timing of the alcohol assessment, type of beverage, or tobacco use history. The association was most apparent in never-users of tobacco, indicating that alcohol is an independent risk factor for OPL.

Our results are compatible with previous case-control studies of OPL, which have found similar increases in risk with alcohol consumption among nonsmokers (6, 9). A study of 927 cases and 47,773 matched controls in India found that ever-drinking was associated with 1.5 times the risk of leukoplakia (95% CI, 1.3-1.9), and when the analysis was restricted to nonsmokers or nonchewers, the estimated odds ratios were greater (e.g., nonsmokers odds ratios, 2.1; 95% CI, 1.3-3.4; ref. 6). Risks of oral submucous fibrosis (170 cases) and erythroplakia (100 cases) were also similarly elevated by alcohol consumption in this population after adjustment for tobacco use (7, 8). A study of OED among men in New England found a higher risk than we observed for OED (odds ratios, 2.4; 95% CI, 1.2-4.8; restricted to noncurrent smokers odds ratios, 2.1; 95% CI, 0.7-6.7; ref. 9). The difference in risk may partly be due to residual confounding by tobacco in the case-control study, which adjusted only for current cigarette smoking status (yes/no). In our study, we found that additional control for chewing tobacco, pipe and cigar use, in addition to lifelong cigarette smoking details, importantly reduced the estimates associated with alcohol use and effectively controlled for much of tobacco's confounding effects.

Proposed mechanisms of alcohol in the development of OPL and oral carcinogenesis include the following: alcohol increases the penetration of carcinogens through the oral mucosa by increasing their solubility and the permeability of oral mucosa (32); chronic consumption causes oral mucosal atrophy and hyper-regeneration, thereby making the epithelium more susceptible to chemical carcinogens (33); alcohol potentiates the genotoxicity of carcinogenic agents; alcohol inhibits DNA repair capacity; alcohol has systemic effects such as malnutrition and immunosuppression; and metabolism of ethanol to acetaldehyde, which is a carcinogen (34). Although pure ethanol itself has not been shown to be carcinogenic in laboratory experiments (35), acetaldehyde, the primary metabolic product of ethanol, is mutagenic (36, 37). In the first phase of the metabolization process (34), alcohol is oxidized to acetaldehyde, primarily through the enzyme alcohol dehydrogenase. Acetaldehyde is then destroyed by the action of aldehyde dehydrogenase, which converts it to acetate. Single nucleotide polymorphisms at alcohol dehydrogenase and aldehyde dehydrogenase genes alter the metabolization of alcohol and may act as modifiers of alcohol's effects among drinkers (38, 39). In the final metabolization phases, acetate is oxidized to create carbon dioxide, fatty acids, and water (34). Although most of the process of metabolizing alcohol is done in the liver, alcohol is also metabolized in the oral mucosa by alcohol dehydrogenase. Interestingly, the activity of aldehyde dehydrogenase is lacking in the oral mucosa, which could lead to the accumulation of acetaldehyde in oral tissues (40).

Table 4. Multivariate RR and 95% CI of OPLs, in the joint analysis of tobacco use (chewing tobacco, cigarette, pipe, cigar) and cumulative average alcohol consumption

	Never tobacco, alcohol (<15 g/d)	Never tobacco, alcohol (≥15 g/d)	Past tobacco, alcohol (<15 g/d)	Past tobacco, alcohol (≥15 g/d)	Current tobacco, alcohol (<15 g/d)	Current tobacco, alcohol (≥15 g/d)
RR (95% CI)	1.0	2.16 (1.10-4.22)	1.90 (1.21-2.97)	3.12 (1.91-5.11)	6.40 (3.89-10.53)	10.2 (6.03-17.1)
P	reference	0.02	0.005	<0.0001	<0.0001	<0.0001

NOTE: Risk estimates are adjusted for age, follow-up cycle, total energy intake, fruit intake, former drinker at baseline, and dental profession.

Because the exact mechanisms of alcohol's potential carcinogenic effects are unknown, we explored two additional methods of assessing alcohol consumption—baseline intake and updated recent intake—as well as the cumulative average updated intake through 16 years of follow-up. Results were similar for all methods, with an exception among current tobacco-users, for whom recent intake levels were associated with a 2- to 4-fold greater risk compared with baseline intake levels. One interpretation may be that alcohol has roles in both earlier and later stages of OPL development for all men, and current smokers who concomitantly drink have even greater risk. Case-control studies of cessation of alcohol drinking and risk of oral or pharyngeal cancer support this interpretation, as they have observed elevated cancer risks remaining several years after drinking cessation (41, 42). Alternatively, consumption at baseline is highly correlated to later consumption, and it is difficult to disentangle the effects of alcohol at distinct time points.

We observed similar increases in OPL risk for liquor, beer, or wine, but the associations were significant only for beer and liquor (borderline significance), which were the predominant alcoholic beverages consumed in this population. Our findings, which are consistent with previous case-control studies of OPL (9, 43), support the hypothesis that the beverage most widely consumed in a given population is most likely to be associated with disease risk, and the overall amount of ethanol consumed is most critical (27, 44, 45). Correlates of beverage choice, particularly among smaller samples of drinkers of less commonly consumed beverages, may explain the different beverage-specific RRs between study populations (44, 46). For example, in parts of Europe where wine is the most commonly consumed alcohol, studies have found wine to be more significantly associated with oral cancer risk, and at much greater magnitudes than beer or liquor (27, 47, 48). Suggested inverse associations between wine and oral cancer risk in a prospective study conducted in Denmark (24) may be due to residual confounding (49, 50). In areas such as Denmark and the U.S., where wine is a somewhat selective type of beverage, wine drinkers are more likely to have other healthy life-style habits, which may decrease the risk of oral lesions (50-52). The potential effects of uncontrolled confounding were confirmed in our study; adjustment for tobacco and other factors in the multivariate model weakened the risks associated with beer and liquor, but increased the risks associated with wine intake.

We found that an additional factor that may modify analyses of beverage type is the pattern of consumption with respect to meals. Although we saw no significant associations with pattern of consumption with meals or frequency of intake in the main analysis, results from exploratory subanalyses suggested that drinking patterns may affect the risk estimates for certain beverages. Specifically, wine—the only beverage failing to achieve statistical significance in the main analysis—was strongly associated with OPL risk when we restricted the analysis to men who drank most of their alcohol outside of meals. One interpretation is that wine is indeed associated with OPL risk, but because wine drinkers often consume the beverage with meals, an ''alcohol washing effect'' occurs by food consumption, thereby reducing the effect of ethanol and its carcinogenic metabolites on the oral mucosa (16, 26, 53). Thus, the potential effects of wine in our analyses may have been weakened by food absorption. The sum of the evidence indicates that alcohol concentration, rather than specific compounds in various beverages, may be the critical determinant of OPL risk.

We observed an interaction between alcohol and tobacco use that showed a departure from risk-difference additivity, whereby the joint effects of drinking and smoking were greater than that expected, considering the independent effects of each exposure. The possibility of strong joint effects is clear: tobacco contains high levels of the carcinogen acetaldehyde (54), and when coupled with the acetaldehyde resulting from alcohol metabolization, a synergistic increase in salivary tissue acetaldehyde levels results (55, 56). Experimental studies have also found lingering effects of tobacco in the oral mucosa (55-58). A recent study compared *in vivo* salivary acetaldehyde concentrations in nonsmokers and smokers who had not actively smoked for 3 days (56), and found that after ethanol intake, the acetaldehyde concentration in smokers was two times higher when not smoking ($P = 0.02$) and seven times higher when they resumed active smoking, compared with nonsmokers ($P < 0.001$).

Despite our detection of positive additive interactions, we observed that RR with increasing alcohol consumption was higher in never smokers than in current smokers. This statistical finding is not surprising, given the high baseline risk associated with tobacco use. Indeed, when examining the joint effects of a strong risk factor (e.g., smoking) with a potentially weaker risk factor (e.g., alcohol), there is a tendency toward a negative multiplicative interaction, partly because the maximum absolute risk associated with exposure to any risk factor cannot exceed 100% (59). That is, the strength of an association based on a relative measure is a function of the relative prevalence of other risk factors; in smokers, it is likely that the majority of cases are explained by smoking, thereby lessening the apparent effect of alcohol. Our findings are consistent with most previous studies exploring the relationship between alcohol and tobacco in OPL (6, 8, 14) or oral cancer (24, 46, 60-62), which failed to find positive multiplicative interactions, but often observed more-than-additive interactions. Findings suggestive of positive multiplicative interactions for OED and oral cancer are likely to be related to residual confounding by smoking intensity within categories of alcohol consumption (9, 63). A common problem with assessing the interaction is low power, particularly because few people fall into the category of nondrinker and current smoker. Future studies should include larger numbers of never, past, and current users of tobacco to clarify the nature of interactions with alcohol. In the meantime, the observed positive additive interaction with tobacco takes precedence over suggestive multiplicative interactions, in terms of defining high-risk groups to target preventative measures and reduce the incidence of OPL.

A disadvantage of the asymptomatic nature of OPL is that some cases may have been missed. We addressed this issue by restricting the main analysis to 58% of the participants who were dentists by profession. Dentists are highly likely to be aware of the health of their oral cavity, including the presence of oral lesions, thereby minimizing disease misclassification. In our study, participants who were dentists were indeed significantly more likely to have their diagnosis followed up with a biopsy. Results in the dentist-only analysis were similar to the main analysis, and we further confirmed results in the analysis of OED. Although the participants from the Health Professionals Follow-up Study have levels of alcohol consumption that are slightly lower than that of the general U.S. population, their consumption rates are similar to rates for men with higher education degrees (64), and our results are internally valid.

In conclusion, increased alcohol consumption was independently associated with a greater risk of OPLs in this prospective study of men. The association did not vary by type of alcoholic beverage, timing of alcohol assessment, or frequency of use. Elevated risks were apparent in men who never used tobacco as well as in past or current smokers. Our results advance the current body of knowledge of the relationship between alcohol and oral cancer by indicating that alcohol may act in the early, precursor lesion stages of oral carcinogenesis, with long-lasting consequences. Recommendations to decrease alcohol intake have the potential to reduce the frequency of oral premalignancies and malignancies alike.

Appendix A Eligible Oral Lesions for Case Definition

Lesion	Definition
Leukoplakia	a white patch or plaque that does not rub off, and cannot be characterized clinically or pathologically as any other disease
Erythroplakia	a red patch that cannot be clinically or pathologically diagnosed as any other condition
Erythroleukoplakia	an area of leukoplakia that has red patches, also known as ''speckled leukoplakia'' or ''leukoerythroplakia''
Lichen planus	chronic dermatologic disease that also affects the mucosa of the mouth, of either reticular (interlacing white lines) or erosive (ulceration in center) type
OED	histopathologically verified abnormality of development, in pathology, alteration in size, shape and organization of adult cells
Oral squamous cell carcinoma	histopathologically verified malignant neoplasm characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize; virtually all arise from premalignant precursor lesions

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