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ORIGINAL PAPER

Smoking and drinking in relation to oral cancer and oral epithelial dysplasia

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Abstract
Objective Risks associated with smoking and drinking are not necessarily constant over the multistage pathway to oral cancer. We investigated whether smoking and drinking patterns differ for persons with oral cancer (OC) relative to those with oral epithelial dysplasia (OED), a precancerous condition.
Methods Incident cases of OC and OED were interviewed using a questionnaire containing questions on smoking and drinking. Odds ratios (ORs) compared the odds of smoking and drinking among persons with OC relative to OED.
Results No adjusted ORs for smoking achieved statistical significance; however, most were <1.0. The odds of OC relative to OED increased with drinking level; the adjusted OR for 19+ drinks/week was 3.03 (1.56–5.87). Age drinking began and years of drinking were not notably different for OC and OED cases; a higher proportion of OC cases reported discontinuing alcohol for 9+ years before diagnosis.
Conclusions The relationship between smoking and OED was at least as strong as that for smoking and OC, suggesting that smoking may have its greatest impact on oral carcinogenesis prior to malignant transformation. Drinking was more strongly associated with OC than OED, particularly at elevated consumption levels; the role of alcohol does not appear limited to a late-stage effect.

Keywords Tobacco smoking · Alcohol drinking · Oral cancer · Oral dysplasia · Mouth neoplasms

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Introduction

Worldwide, it is estimated that there were approximately 274,300 new cases of and 127,500 deaths attributed to cancer of the oral cavity during 2002 [1]. Most oral cancers are squamous cell carcinomas, and the vast majority of oral squamous cell carcinomas are preceded by precursor lesions that can present as either leukoplakia, erythroplakia, or erythroleukoplakia [2, 3]. Microscopically, these lesions may exhibit oral epithelial dysplasia (OED), a histopathologic diagnosis characterized by cellular changes

and maturational disturbances indicative of developing malignancy [4]. A diagnosis of OED is important because reported malignant transformation rates among persons diagnosed with OED are as high as 36% [5]. As a consequence, the presence or absence of OED in a biopsy specimen is often an important indicator in determining how closely a lesion should be followed and whether treatment should be initiated.

Smoking and drinking are independently and synergistically associated with an increased risk of oral cancer, and the risks tend to increase with an increased frequency of exposure [2, 6–8]. In a previous study, we also found that OED risk was positively associated with smoking and drinking in an independent, dose-dependent fashion, with evidence of a synergistic joint effect [9]. Despite the similarity of these findings, however, it does not necessarily follow that the risks associated with these preventable exposures are constant over the multistage pathway to oral cancer. While smoking tobacco is associated with an increased risk of oral leukoplakia [10–15], follow-up studies of persons with leukoplakia have often reported that smokers have a lower transformation rate to oral cancer than do non-smokers [5, 16–18]. Further, while alcohol consumption is clearly a risk factor for oral and pharyngeal cancer, the role of alcohol is more equivocal in terms oral leukoplakia, with some investigations revealing weak to moderate associations [11, 19, 20] but others finding no relationship [12, 13, 15, 21]. Moreover, in a recent report from Taiwan, smoking, but not drinking, was found to be an important risk factor in the development of oral leukoplakia, while drinking was more important than smoking in the malignant transformation of oral leukoplakia [21].

In order to evaluate whether the risks associated with smoking and drinking differ for OED and oral cancer, we conducted a case–control study in which the cases were defined as persons diagnosed with an invasive oral cancer, and the controls were persons diagnosed with OED. Using this approach, we compared smoking and drinking exposure profiles for individuals with oral cancer relative to OED while controlling for other covariates. Since differences in exposure frequency, duration of use, age at initiation, years of cessation, and total lifetime consumption could be important determinants in differentiating persons with OED from those with oral cancer, we investigated each of these components. In so doing, we sought not only to highlight differences in exposure patterns among cases of OED and oral cancer, but also to shed additional light on which aspects of smoking and drinking may be associated with the transformation of OED to oral cancer.

Materials and methods

Sample

Incident cases of histologically-confirmed oral cancer and OED were identified by reviewing pathology reports generated via oral pathology laboratories at the University of Florida College of Dentistry, the New Jersey Dental School, and the University of Connecticut School of Dental Medicine. These pathology laboratories serve primarily community-based general dentists and oral and maxillofacial surgeons as well as other dental specialists. Cases were eligible for inclusion in the study if they were aged 30–79 years at diagnosis, had been diagnosed with an invasive squamous cell carcinoma or epithelial dysplasia of the oral cavity excluding the lip and major/minor salivary glands (eligible site codes: ICD-0-3 C 01.9 through C06.9) [22], could provide reliable information, and could speak and read English. Persons diagnosed with carcinoma in situ were classified as having dysplasia while individuals whose pathology report read "superficial invasion" were classified as having an invasive oral carcinoma. In order to minimize the possible inclusion of prevalent OED and oral cancer cases in the study, we excluded all persons with a history of OED or oral cancer from the OED series and all persons with a previous diagnosis of oral cancer from the cancer series.

After obtaining surgeon permission, study personnel contacted potential subjects, first via mail and subsequently by telephone. Consenting individuals were interviewed over the telephone by trained interviewers who used a standardized, structured questionnaire and were blinded to both the study hypotheses and each respondent's diagnostic status. Surrogate interviews were not conducted, and subjects were compensated 20 dollars for the time required to participate. All interviews were completed during the period spanning January, 1994 through December, 2000.

Tobacco & alcohol use

Smoking tobacco use was defined in terms of cigarettes, pipes, and cigars. An "ever smoker" of cigarettes was defined as an individual who reported smoking at least 100 cigarettes during his or her lifetime while an ever smoker of a pipe or cigars was defined as an individual who reported having smoked such a product for six months or more. A "current smoker" was defined as an individual who reported smoking within the calendar year prior to the diagnosis date while an "ex-smoker" was defined as an ever smoker who had discontinued the habit more than one calendar year prior to the diagnosis date. Cigarette equivalents were calculated using the conversion factor 1 cigarette = 1/2 pipe = 1/4 cigar [9].

The consumption of alcoholic beverages was obtained in terms of beer, wine, and hard liquor, with a drink being defined as 12 ounces of beer, 4 ounces of wine, and 1.5 ounces of hard liquor [8, 9]. A "never drinker" was defined as a person who reported drinking fewer than 12 drinks of each alcoholic beverage type over his or her lifetime. Among "ever drinkers," the total number of drinks consumed per week was calculated by summing the average number of drinks of beer, wine, and hard liquor reportedly consumed per week. On an a priori basis, total alcohol consumption was dichotomized at less than seven drinks/week and seven or more drinks/week [9, 23]. For subjects interviewed after April 28, 1996, the questionnaire included questions regarding whether and when the drinking of each alcoholic beverage type had been discontinued. Based upon those responses, a "current drinker" was defined as an individual who reported drinking any type of alcoholic beverage within the calendar year prior to the diagnosis date while an "ex-drinker" was defined as an ever drinker who had discontinued all drinking for more than one calendar year prior to the diagnosis date. For those subjects who reported discontinuing all alcohol use, the last year of any alcohol consumption was used to calculate the total number of years of alcohol cessation before diagnosis. The lifetime number of drinks consumed was estimated based upon the average number of drinks/week and the years of alcohol consumption.

Odds ratios (ORs) and their 95% confidence intervals were obtained using unconditional logistic regression [24]. All reported ORs compare oral cancer relative to OED. As used in this paper, odds ratios can be interpreted as the odds of exposure among the oral cancer cases relative to the odds of exposure among the OED cases. ORs greater than 1.0 indicate that the odds of exposure are higher in the cancer series than in the OED series, while ORs less than 1.0 indicate that the odds of exposure are higher in the OED series.

Where indicated, odds ratios were adjusted for gender, age (30–49, 50–59, 60–69, 70–79 years), education (≤high school, some post-high school training, college degree or more), pathology laboratory, and either smoking (pack-year equivalents 0, >0–<20, 20–<50, 50+) or drinking (<1, 1–<6, 6–<19, 19+ drinks/week). We also investigated a number of other variables as potential confounders, including the Body Mass Index (BMI), mouthwash use, denture use, and for the 84% of subjects who returned food frequency questionnaires, the intake of fruits and vegetables; the addition of these variables to the adjusted model did not notably impact the reported ORs and were excluded from the final models. Tests of linear trend were conducted by adding the relevant, ordinally defined variable as a variate into the next lower order model and evaluating the statistical significance of that addition using the likelihood ratio statistic. Interactions between smoking and drinking were evaluated on an exploratory basis.

The study protocol was reviewed and approved by the applicable institutional review boards.

Results

Descriptive characteristics of the sample

In order to recruit the sample of subjects included in this analysis, a total of 354 surgeons were approached for permission to contact their patients. Of these surgeons, 330 (93%) could be contacted regarding the study, and of these, 92% (304/330) assisted with the project.

A total of 824 potentially eligible subjects were identified. Of these subjects, 76 were too ill to participate or had died prior to being contacted regarding the study. An additional 61 subjects were not contacted based upon the wishes of the clinician who performed the biopsy, and letter or telephone could not reach 118 cases. Among the individuals who could be contacted by telephone, 80% (455/569; i.e., OED: 80%, 273/340, oral cancer: 79%, 182/229) agreed to participate in the study. Among participating subjects, one refused to answer questions regarding drinking frequency and was excluded from the analysis.

Table 1 presents demographic characteristics of the 454 study subjects included in the analysis. About 60% had a diagnosis of OED; the gender, age, and race/ethnicity distributions were similar across diagnoses, and the majority of cases were diagnosed at the University of Florida.

Smoking tobacco

Table 2 presents odds ratios for smoking associated with oral cancer relative to OED. In each analysis, the crude ORs suggested little consistent difference in the odds of smoking among cancer cases relative to cases of OED, and no stratum-specific differences were statistically significant. As with the crude ORs, no adjusted ORs achieved statistical significance; however, most adjusted OR point estimates fell modestly below 1.0. In Table 2, the adjusted OR for current, relative to never smoking is reported as 0.65 and can be interpreted, as the odds of smoking among cancer cases are 35% lower than the odds of smoking among OED cases.

When the sample was stratified by drinking (current, former/never) and smoking (current, former) status, adjusted OR point estimates again generally fell below 1.0, but statistical significance was only rarely achieved (Table 3).

Table 1 Distribution of demographic variables by cancer/OED status

Variable	Cancer *n* (%)	OED *n* (%)
Gender		
Males	97 (53.6)	143 (52.4)
Females	84 (46.4)	130 (47.6)
Age		
30–49	32 (17.7)	53 (19.4)
50–59	44 (24.3)	57 (20.9)
60–69	52 (28.7)	80 (29.3)
70–79	53 (29.3)	83 (30.4)
Mean (SD)	61.5 (11.4)	61.4 (12.0)
Race/Ethnicity		
White, non-Hispanic	169 (93.4)	258 (94.5)
Black, non-Hispanic	7 (3.9)	6 (2.2)
Hispanic	1 (0.6)	3 (1.1)
Asian, American Indian or Alaskan Native	1 (0.6)	2 (0.8)
Mixed/Other	2 (1.1)	3 (1.1)
No response	1 (0.6)	1 (0.4)
Laboratory of diagnosis		
University of Florida	68 (37.6)	136 (49.8)
University of Connecticut	81 (44.8)	62 (22.7)
New Jersey	32 (17.7)	75 (27.5)
Total	181	273

Alcohol

Table 4 presents ORs for drinking associated with oral cancer relative to OED. Using the a priori definition for total alcohol consumption (i.e., 7+ vs. <7 drinks/week), the adjusted OR for oral cancer relative to OED was 1.87 (95% CI: 1.18–2.96). When we defined levels of drinking based upon the distribution of alcohol consumption in the OED series (approximate quartiles), the odds of oral cancer relative to OED increased with each successive level of drinking (linear trend $P = 0.001$); the adjusted OR was 3.03 (1.56–5.87) for the highest category of alcohol consumption (19+ drinks per week). Prior to adjusting for the reported level of alcohol consumption, odds ratios for oral cancer relative to OED were also modestly elevated for each defined category of age at which regular drinking began, across levels of drinking duration, and for both current and former drinkers, in each case relative to never drinkers; however, these ORs regressed toward or below 1.0 after also adjusting for the level of drinking. On the other hand, adjusted ORs for increasing levels of drinking were not notably affected when the adjusted model also controlled for the age at which drinking began, drinking duration, and current/former drinking status. As with the average level of alcohol consumption, adjusted ORs increased with the estimated lifetime alcohol consumption (linear trend $P = 0.001$).

When we conducted analyses of alcohol use stratified by smoking (current, former, never) and drinking status (current, former), we again observed a generalized increase in the odds of oral cancer relative to OED with successively higher levels of reported alcohol consumption (Table 5). Further, when alcohol consumption was classified by product type, ORs for beer and hard liquor tended to increase with higher levels of intake while for wine, ORs consistently fell below 1.0.

Since cancer cases were more likely than cases of OED to drink 19+ drinks/week, we conducted further analyses restricted to these heavy drinkers (Table 6). Among heavy drinkers, oral cancer cases reported drinking, on average, more drinks/week of beer (28.6 vs. 23.1, $p = 0.21$), hard liquor (28.9 vs. 19.5, $p = 0.08$) and wine (7.1 vs. 4.8, $p = 0.28$) (data not shown). Neither the age at which drinking began nor the total duration of alcohol consumption was notably different for persons with oral cancer relative to OED. In terms of alcohol cessation, most heavy consumers were current drinkers; however, a notably higher proportion of cancer cases than OED cases (17% vs. 7%, $p = 0.08$) reported having stopped all alcohol consumption for nine or more years prior to their diagnosis. Among those persons who were long-term ex-drinkers (9+ years), the mean reported alcohol consumption was significantly higher among cancer (100 drinks/week) relative to OED cases (40 drinks/week; $p = 0.001$).

No smoking-drinking interactions approached or attained statistical significance. When we fitted an interaction term for current smoking (yes/no) and alcohol consumption (four levels) to the adjusted model (referent category; never/ex-smokers, <1 drink/week; interaction $p = 0.51$), ORs were highest for drinkers of 19+ drinks/week. Among current smokers, the OR for heavy drinking was 2.41 (1.02–5.68) while for never/ex-smokers the OR was 3.66 (1.55–8.64).

Discussion

Oral epithelial dysplasia represents a relatively late phase in the multistage process of oral carcinogenesis; however, longitudinal studies have consistently reported that most persons with a diagnosis of OED do not transform to oral cancer [5, 16, 25]. While a growing number of biomarkers have been evaluated in relation to one or another stage of oral carcinogenesis or as predictors of malignant transformation [26–30], surprisingly little is known about the role that tobacco and alcohol play during the latter stages of oral carcinogenesis despite the fact that these exposures are clearly implicated in the overall genesis of invasive oral cancer [2, 6–8, 31, 32].

Table 2 Odds ratios for smoking associated with oral cancer relative to OED

Exposure	Cancer (*n*)	OED (*n*)	OR[a]	95% CI	ORadj[b]	95% CI
Never smoked	32	49	1.0	–	1.0	–
Ever smoked	149	224	1.02	0.62–1.67	0.84	0.41–1.25
Ex-smoker	59	92	0.98	0.57–1.71	0.80	0.43–1.49
Current smoker	90	132	1.04	0.62–1.76	0.65	0.36–1.19
Current smoking						
No	91	141	1.0	–	1.0	–
Yes	90	132	1.06	0.73–1.54	0.76	0.49–1.18
Pack-year equivalents of smoking[c]						
0	32	49	1.0	–	1.0	–
>0–<20	40	56	1.09	0.60–2.00	1.01	0.52–1.96
20–<50	56	101	0.85	0.49–1.48	0.58	0.31–1.08
50+	53	67	1.21	0.68–2.15	0.66	0.34–1.29
Trend *P*			0.71		0.09	
Average cigarette equivalents per day [c]						
0	32	49	1.0	–	1.0	–
1–19	38	63	0.92	0.51–1.68	0.82	0.43–1.58
20–39	69	116	0.91	0.53–1.56	0.64	0.35–1.17
40+	42	45	1.43	0.77–2.64	0.76	0.37–1.56
Trend *P*			0.32		0.30	
Years since stopped smoking						
Never smoker	32	49	1.0	–	1.0	–
20+ years	29	38	1.17	0.61–2.25	1.08	0.52–2.25
2–19 years	30	54	0.85	0.45–1.60	0.63	0.31–1.27
Current smoker	90	132	1.04	0.62–1.76	0.64	0.35–1.18
Trend *P*			0.99		0.08	
Age started smoking						
Never smoker	32	49	1.0	–	1.0	–
>0–<17	61	68	1.37	0.78–2.41	0.85	0.45–1.62
17–19	44	76	0.89	0.50–1.58	0.68	0.35–1.30
20+	44	80	0.84	0.47–1.50	0.65	0.34–1.22
Trend *P*			0.20		0.13	

[a] Crude OR

[b] OR adjusted for age (four levels), gender, alcohol consumption (four levels), education (three levels), pathology laboratory

[c] Pack-year and average cigarette equivalents for pipe and cigar smokers based on 1 cigarette = 1/2 pipe = 1/4 cigar

Much of what is known regarding lifestyle differences among persons with an invasive oral cancer relative to those with a premalignant lesion is based upon follow-up studies of persons with oral leukoplakia. Early reports suggested that nonsmokers were more likely to undergo malignant transformation than were smokers [5, 17, 18], while the role of alcohol in transformation received little attention [33]. More recently, an investigation from Taiwan using a case–control approach, concluded that alcohol intake, but not smoking, was strongly associated with the transformation of oral leukoplakia to oral cancer [21], while a study conducted in the Netherlands reported no association between alcohol consumption and the malignant transformation of oral leukoplakia, but a statistically significant increased risk of transformation among non-smoking, relative to smoking, females [16].

Tobacco

Smoking tobacco is associated with an increased risk of oral and pharyngeal cancer [2, 6–8, 31], OED [9], and oral leukoplakia in general [10–15], with risks increasing in a dose-dependent fashion and declining with the duration of smoking cessation. In the current study, which directly relates the exposure odds of oral cancer to the odds of OED, we did not find clear evidence that cases of oral cancer and OED were significantly different as regards their smoking patterns or history. Nevertheless, it is notable

Table 3 Adjusted odds ratios for smoking associated with oral cancer relative to OED stratified by drinking and smoking status[a]

	Drinking status	
	Current (n = 290)	Former/Never (n = 108)
Pack-year equivalents		
0	1.0	1.0
>0–<20	0.80 (0.32–1.98)	0.91 (0.24–3.41)
20–<50	0.37 (0.16–0.89)	0.54 (0.15–1.95)
50+	0.49 (0.20–1.20)	0.52 (0.13–2.14)
Trend P	0.06	0.29
Smoking status		
Never	1.0	1.0
Ex-smoker	0.50 (0.21–1.17)	1.15 (0.32–4.13)
Current smoker	0.52 (0.23–1.20)	0.44 (0.13–1.45)
Trend P	0.25	0.15
	Smoking Status	
	Current (n = 222)	Former (n = 151)
Pack-year equivalents		
<20	1.0	1.0
20– < 50	0.37 (0.15–0.92)	0.79 (0.34–1.85)
50+	0.52 (0.19–1.39)	0.57 (0.21–1.56)
Trend P	0.50	0.27

[a] OR adjusted for age (four levels), gender, alcohol consumption (four levels), education (three levels), and pathology laboratory

that adjusted ORs for various measures of smoking status, including ever, ex-, and current smoking, as well as pack-year equivalents and average cigarette-equivalents smoked, generally fell modestly below 1.0 (oral cancer relative to OED). Similar findings related to smoking were also observed when we stratified on current and former/never drinkers as well as when current and former smokers were considered separately. Therefore, while previous U.S. studies of oral cancer and OED have reported generally similar patterns of increased risk with higher levels of smoking and decreased risk with duration of smoking cessation [8, 9], our findings suggest that on a comparative basis, and for a given measure of smoking, the association between smoking and OED is at least as strong as the association between smoking and oral cancer.

Previous follow-up studies of oral leukoplakia have reported evidence that non-smokers are at a higher risk of developing invasive cancer than smokers [5, 16–18]. While the current study cannot directly address that issue, it is notable that the adjusted OR for current smoking was 0.65 (0.36–1.19) for oral cancer versus OED suggesting that the risk of oral cancer associated with current smoking may be somewhat lower than the risk of OED. If that is the case, and if the vast majority of oral squamous cell cancers pass through a dysplastic phase in a clinically identifiable pre-cancerous lesion, it follows that the impact of current smoking on OED transformation to cancer may be attenuated relative to the role of smoking during OED development and earlier stages of oral carcinogenesis.

In toto, while previous epidemiologic studies are consistent in identifying smoking tobacco as an important risk factor for oral cancer, our current analysis suggests that smoking may have its greatest impact during stages of oral carcinogenesis that precede malignant transformation, a finding that should be investigated in future studies.

Alcohol consumption

Previous U.S. studies of oral cancer and OED, as well as a prospective study, which included various potentially premalignant oral lesions and invasive squamous cell carcinomas as outcome events, have reported a frequency-response relationship between drinking and the risk of both oral cancer and precancer, and some [8, 9, 34], but not all [32, 35] have reported a stronger frequency-response trend for beer and hard liquor than for wine intake.

Our current results, which were highly robust, extend findings from earlier U.S. studies by providing evidence that alcohol intake is an important factor in differentiating cases of oral cancer from persons with OED, particularly at higher consumption levels and primarily for beer and hard liquor drinkers. Moreover, heavy drinking was more strongly associated with oral cancer than OED among both current and never/ex-smokers and did not appear to be a function of a longer duration of alcohol consumption or the age at which regular drinking began. Although we previously reported that increasing alcohol consumption was associated with an increased risk of OED, particularly at

Table 4 Odds ratios for drinking associated with oral cancer relative to OED

Exposure	Cancer (*n*)	OED (*n*)	OR[a]	95% CI	ORadj[b]	95% CI
Drinks/week						
<7	70	143	1.0	–	1.0	–
7+	111	130	1.74	1.19–2.56	1.87	1.18–2.96
No. drinks/week (quartiles) All alcohol combined						
<1	34	72	1.0	–	1.0	–
1–<6	33	63	1.11	0.62–1.99	1.31	0.70–2.46
6–<19	40	70	1.21	0.69–2.13	1.50	0.80–2.84
19+	74	68	2.30	1.36–3.90	3.03	1.56–5.87
Trend *P*			0.001		0.001	
Age started regular drinking[c]						
Never drinkers	12	25	1.0	–	1.0[d]	–
<19	57	87	1.37	0.64–2.93	1.11	0.42–2.96
19–22	60	82	1.52	0.71–3.28	1.21	0.47–3.11
23+	52	78	1.39	0.64–3.00	1.06	0.41–2.74
Trend *P*			0.53		0.99	
Note: When not adjusted for level of alcohol consumed[b], ORs: 1.0 (ref), 1.63, 1.64, 1.42 (Trend *P* = 0.78)						
Duration of drinking[c,e]						
Never drinkers	11	20	1.0	–	1.0[d]	–
>0–<31	51	68	1.36	0.60–3.10	0.81	0.29–2.32
31–<43	44	71	1.13	0.49–2.57	0.70	0.24–2.06
44+	61	71	1.56	0.69–3.52	1.38	0.47–4.01
Trend *P*			0.36		0.26	
Note: When not adjusted for amount consumed[b], ORs: 1.0 (ref), 1.38, 1.16, 2.08 (Trend *P* = 0.14)						
Years since quit alcohol[e]						
Never drinkers	11	20	1.0	–	1.0[d]	–
Quit 9+ years	20	23	1.58	0.61–4.08	0.95	0.31–2.93
Quit 2–8 years	13	21	1.13	0.41–3.09	0.64	0.19–2.16
Current drinkers	123	167	1.34	0.62–2.90	0.95	0.35–2.56
Trend *P*			0.72		0.91	
Note: When not adjusted for amount consumed[b], ORs: 1.0 (ref), 1.58, 1.25, 1.52 (Trend *P* = 0.49)						
Lifetime alcohol consumption (drinks)[c,e]						
Never drinkers	11	20	1.0	–	1.0	–
>0–<6,000	34	72	0.86	0.37–1.99	1.05	0.43–2.58
6,000–<30,000	43	70	1.12	0.49–2.56	1.57	0.62–4.00
30,000+	79	68	2.11	0.95–4.72	3.10	1.19–8.06
Trend *P*			0.001		0.001	

[a] Crude OR

[b] OR adjusted for age (four levels), gender, pack-year equivalents of smoking (four levels), education (three levels), and pathology laboratory

[c] Limited to those subjects who answered questions regarding the age at which regular alcohol consumption began

[d] OR adjusted as in 'b' as well as level of alcohol consumption

[e] Limited to those subjects who were asked questions regarding their discontinuance of alcohol

higher levels of consumption [9], our current findings suggest that the trend is stronger for oral cancer.

The mechanism or mechanisms by which alcoholic beverages increase the risk of OED and oral cancer are not clearly understood and complicated by the fact that ethanol per se does not appear to be carcinogenic in experimental animals. It is known, however, that ethanol can be metabolized to acetaldehyde, and acetaldehyde is carcinogenic. The alcohol dehydrogenase 3 gene (ADH3) is involved in the alcohol–acetaldehyde pathway, and a growing number of molecular epidemiologic studies have evaluated the role of ADH3 in oral cancer risk, but with

Table 5 Odds ratios for drinking associated with oral cancer relative to OED stratified by smoking and drinking status and type of alcoholic beverage

No. drinks/week (quartiles) (all alcohol combined)	Smoking status		
	Current (n = 222)	Former (n = 151)	Never (n = 81)
<1	1.0[a]	1.0[a]	1.0[b]–
1–<6	1.44 (0.50–4.85)	2.20 (0.70–6.91)	0.93 (0.25–3.52)
6–<19	2.20 (0.75–6.47)	1.65 (0.54–5.07)	1.57 (0.23–10.87)
19+	3.80 (1.25–11.57)	5.36 (1.66–17.31)	7.71 (0.83–72.03)
Trend P	0.009	0.01	0.14
	Drinking status		
No. drinks/week (quartiles) (all alcohol combined)	Current (n = 290)	Former (n = 77)	
<1	1.0[a]	1.0[c]	
1–<6	1.21 (0.51–2.89)	–	
6–<19	2.13 (0.91–5.03)	–	
19+	3.51 (1.42–8.69)	4.13 (1.00–17.08)	
Trend P	0.002	0.05	
	Type of alcoholic beverage		
Drinking quartiles[d]	Beer	Wine	Hard Liquor
1	1.0[e]–	1.0[e]–	1.0[e] –
2	1.43 (0.72–2.84)	0.50 (0.26–0.95)	1.51 (0.76–2.99)
3	2.56 (1.34–4.89)	0.58 (0.31–1.07)	1.55 (0.78–3.06)
4	2.67 (1.35–5.25)	0.64 (0.37–1.14)	2.44 (1.21–4.94)
Trend P	0.003	0.18	0.02

[a] OR adjusted for age (four levels), gender, pack-year equivalents of smoking (four levels), education (three levels), and pathology laboratory

[b] OR adjusted for age (four levels), gender, education (three levels), and pathology laboratory

[c] OR adjusted as in 'a,' referent category: <19 drinks/week

[d] Categorical levels of drinks/week for beer: 0, >0–<0.5, 0.5–<7.5, 7.5+; for wine: 0, >0–<0.25, 0.25–<1.50, 1.5+; and hard liquor: 0, >0–<1.0, 1.0–<6.0, 6.0+

[e] OR adjusted as in 'a' as well as for each other type of alcoholic beverage (four levels)

mixed results [2]. Another possible mechanism by which alcoholic beverages may increase the risk of cancer is the potential for such beverages to contain various carcinogenic congers and contaminants. In addition, alcohol may (a) interfere with nutritional intake or bioavailability, (b) enhance the penetration of carcinogens within the oral mucosa, (c) reduce immune function, (d) potentiate the genotoxicity of or activate carcinogenic agents, (e) interfere with DNA repair and (f) inhibit the detoxification of carcinogens [36–39].

In the current study, the consumption of beer and hard liquor, but not wine, was more strongly associated with oral cancer than OED. This observation may result from the fact that beer and hard liquor intake far exceeded wine consumption and thereby contributed a large proportion of the total ingested ethanol. Previous studies of oral cancer

Table 6 Odds ratios for drinking associated with oral cancer relative to OED, drinkers of 19+ drinks/week only

Exposure	Cancer (n)	OED (n)	OR[a] (95% CI)	ORadj[b] (95% CI)
Age started regular drinking				
<19	31	33	1.0	1.0 –
19–22	28	23	1.30 (0.62–2.71)	1.27 (0.56–2.89)
23+	15	12	1.33 (0.54–3.29)	1.28 (0.44–3.73)
Trend P			0.47	0.57
Duration of drinking (years)[c]				
>0–<31	25	21	1.0 –	1.0 –
31–<43	18	22	0.69 (0.29–1.61)	1.04 (0.33–3.32)
44+	27	16	1.42 (0.61–3.31)	1.17 (0.30–4.49)
Trend P			0.44	0.82
Years since quit alcohol[c]				
Quit 9+ years	12	4	1.0 –	1.0 –
Quit 2–8 years	8	8	0.33 (0.08–1.49)	0.36 (0.07–1.78)
Current drinkers	50	47	0.36 (0.11–1.18)	0.42 (0.12–1.52)
Trend P			0.14	0.26

[a] Crude OR

[b] OR adjusted for age (four levels), gender, pack-year equivalents of smoking (four levels), education (three levels), and pathology laboratory

[c] Limited to those subjects who were asked questions regarding their discontinuance of alcohol

risk have suggested that ethanol per se is the constituent in alcoholic beverages most likely associated with oral cancer risk, and consequently the most frequently consumed alcohol-containing beverages in a given population contribute both the highest total volume of ethanol and the highest oral cancer risk [40]. It is also possible, however, that differences in the exposure-odds observed for wine in comparison to beer and hard liquor reflect differences in the constituent composition of the various beverage types [38], meal consumption patterns associated with the ingestion of the different types of alcoholic beverages [32, 41, 42], or differences in the underlying characteristics of populations that consume the various beverage types [43, 44].

Some U.S. studies have suggested that alcohol consumption is a more important risk factor for oral cancer than smoking [8, 35], and when we compared persons with oral cancer to those with OED, our findings were consistent with that premise, particularly in terms of heavy drinking. Based upon our current and past study results, however, it is possible that tobacco use may be a more important risk factor than alcohol in the development of OED, while heavy drinking may more clearly define those individuals with the greatest risk of developing an invasive intraoral cancer.

Over the years, it has not been clear when, during the multistage model of oral carcinogenesis, alcohol exerts its effect [38, 39]. As in the current study, a number of previous investigations of oral and pharyngeal cancer have reported the lack of a clear trend in risk with the age at which regular drinking began, a finding consistent with a late-stage effect of alcohol [7, 8, 45–47]. In the current study, however, nearly 13% (20/156) of all ever drinking and 17% (12/70) of the once heavy drinking oral cancer cases reported complete alcohol abstinence for at least nine years prior to their diagnosis with oral cancer. Among these cases, alcohol may have had an early or intermediate-stage effect on oral carcinogenesis, but assuming that the self-reports were valid, alcohol could not have had a late effect. In addition, relatively recent reports from case–control studies of oral cancer have revealed an alcohol-associated excess risk of oral cancer that persists long after all alcohol cessation [6, 31, 46], an observation which is not in keeping with a purely late-stage effect [47]. In sum, these findings are consistent in suggesting that the effect of alcohol in oral carcinogenesis is not solely a late stage phenomenon. Consequently, while the results of the current analysis suggest that oral cancer is more strongly associated with heavy drinking than is OED, our findings also caution against assuming that heavy drinking acts only through a late effect.

Study limitations should be considered when interpreting our findings. All exposures were measured by self-report, and some degree of exposure misclassification may have occurred. The potential for recall bias, however, is mitigated by the fact that neither the study subjects nor the interviewers were aware of the study hypotheses and because both case groups were comprised of individuals with documented oral pathoses.

It is possible that some study subjects could have altered their smoking and/or drinking habits based upon the results of an earlier oral biopsy. Concerns that cancer or OED cases would be differentially effected are reduced, however, in that persons in both case groups could have received previous biopsies with histologic diagnoses that would not preclude subject inclusion in the study (e.g., hyperkeratosis with atypical cells), but which could conceivably have led to a modification in risk exposures.

Similarly, signs and symptoms of the disease could have led some subjects to change their smoking or drinking patterns prior to diagnosis. While both the OED and oral cancer subjects had an intraoral lesion that could have elicited a change in smoking or drinking, the cancer cases may have been more likely to have symptoms associated with their disease. Notably, however, all cases were identified via pathology laboratories serving primarily dentists and dental specialists, and evidence suggests that such practitioners are far more likely than their medical counterparts to identify oral cancers in asymptomatic patients [48]. Therefore, limiting our ascertainment of study subjects to persons diagnosed through oral pathology laboratories reduced the potential for pre-diagnosis symptoms among the study cancer subjects, and consequently attenuated the potential for a differential change in smoking or drinking habits among the cancer, relative to OED, subjects. It is further noteworthy that despite the possible reasons for modifying risk exposure prior to diagnosis, the vast majority of ever smokers and drinkers did not discontinue those habits during the years preceding the diagnosis that led to their inclusion in the study.

Although disease status was based upon histopathologic diagnoses generated by board-certified oral pathologists, some disease misclassification could have occurred, particularly as regards OED. Further, it is possible that some prevalent cases were inadvertently included in our OED or cancer series although that possibility was minimized by excluding (a) all persons with a previous history of OED or oral cancer from the OED series and (b) all persons with a previous diagnosis of oral cancer from the cancer series.

In this study, random misclassification of exposure or disease would tend to have biased our results toward finding no difference between the OED and cancer cases while nonrandom misclassification could have biased our findings either toward or away from the null.

When interpreting our findings, we made the assumption that the majority of oral cancers derive from clinically

visible oral precancerous lesions containing OED. It is possible, however, that some oral cancers arise from normally appearing mucosa or progress rapidly through the clinically apparent precancerous stage thereby escaping detection and biopsy [49]. If these oral cancer cases are inherently different in terms of their associated risk factors and represent more that a minority of oral cancer cases, our assumption may not be valid and could lead to biased estimates, conceivably in either direction.

It is also possible that some uncontrolled confounding may have influenced the observed relationships. On the other hand, we did adjust for a number of covariates in our final model and evaluated other variables, including the BMI, mouthwash use, denture use, and fruit and vegetable intake, as potential confounders; however, their inclusion had no meaningful effect on the reported findings.

In summary, we compared smoking and drinking patterns for individuals diagnosed with oral cancer relative to persons diagnosed with OED. Our findings suggest that the association between smoking and OED is at least as strong as the association between smoking and oral cancer, suggesting that smoking may have its greatest impact on oral carcinogenesis in stages prior to OED transformation to cancer. We also found evidence that drinking is more strongly associated with oral cancer than OED, particularly at higher consumption levels and for beer and hard liquor drinkers. However, the impact of alcohol on oral carcinogenesis does not appear to be limited to a late-stage effect. In toto, our study results suggest that tobacco use may play its greatest role in oral carcinogenesis prior to OED transformation to oral cancer, while a history of heavy drinking may more strongly predict those cases of OED with the greatest risk of developing an invasive intraoral cancer.

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