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ORIGINAL CONTRIBUTIONS

Interaction between Tobacco and Alcohol Consumption and the Risk of Cancers of the Upper Aero-Digestive Tract in Brazil

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The authors investigated the joint effects of tobacco and alcohol consumption on the risk of squamous cell carcinomas of the upper aero-digestive tract (UADT) using data from a hospital-based case-control study conducted in southern Brazil, 1986–1989. A total of 784 cases of cancers of the mouth, pharynx, and larynx and 1,578 non-cancer controls matched on age, sex, hospital catchment area, and period of admission were interviewed about their smoking and drinking habits and other characteristics. Using logistic regression, evidence was found for interaction between the cumulative exposures for smoking and alcohol on UADT cancer risk. The joint effects for pharyngeal cancers exceeded the levels expected under a multiplicative model for moderate smokers ($p = 0.007$). There was little statistical evidence, however, for interaction on cancers of the mouth ($p = 0.28$) or larynx ($p = 0.95$). Among never smokers, heavy drinkers had 9.2 times (95% confidence interval 1.7, 48.5) greater risk of cancers of mouth, pharynx, and supraglottis than never drinkers, with a dose-response trend ($p = 0.013$) with cumulative consumption. The authors conclude that the interaction occurring in the pharynx between smoking and alcohol on UADT cancers is not uniform, with varying effects depending on the level of smoking exposure. Alcohol may act as both a promoter for tobacco and as an independent risk factor. *Am J Epidemiol* 1999;150:1129–37.

alcohol drinking; case-control studies; epidemiologic methods; head and neck neoplasms; larynx; mouth; pharynx; smoking

Cancers of the upper aero-digestive tract (UADT) rank as the third most frequent group of neoplasms among males and the fourth most frequent among females in developing countries (1). Incidence and mortality rates of cancers of the oral cavity and pharynx, in particular, are rising in most areas of the world (2).

Tobacco smoking and alcohol drinking have long been identified as the two most important risk factors for UADT cancers (3). Risk is further aggravated by diets deficient in fruits and vegetables (4, 5) and by other environmental and life-style exposures (6, 7). Arguments for an interactive relation between smoking and alcohol on risk have long been proposed (8). The pattern of interaction between alcohol and tobacco also seems to differ with respect to tumor site (9). Some studies have attempted to investigate the separate effects of smoking and alcohol (3, 10), but have been hampered by the highly correlated nature of the two behaviors and the rarity of never smokers and drinkers that are identified in epidemiologic studies (11). The difficulty in gauging the effects of interaction between smoking and alcohol on risk is also aggravated by the inherent multidimensional nature of these variables, with few studies taking into

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Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, 9th Revision; UADT, upper aero-digestive tract.

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account both intensity and duration of exposure to these factors.

We analyzed data from a large hospital-based case-control study of UADT cancers to assess the role of interaction between tobacco and alcohol on disease risk. The study was conducted in populations from Central and Southern Brazil, areas known for their high incidence of UADT cancers (1, 12). We compared the risk of cancer across specific UADT sites and investigated the isolated effect of alcohol among persons with little or no reported smoking exposure.

MATERIALS AND METHODS

Population

Between February 1986 and January 1989, 784 patients with newly diagnosed, histopathologically confirmed carcinomas of the oral cavity (*International Classification of Diseases*, 9th Revision (ICD-9) codes 140–145), pharynx (ICD-9 146–149), and larynx (ICD-9 161) were selected from hospitals in three metropolitan areas of Brazil: São Paulo, Curitiba, and Goiânia. Patients with tumors of the salivary gland (ICD-9 142) or of the nasopharynx (ICD-9 147) were excluded from the investigation. With the exception of the head-and-neck surgery service in São Paulo, which is responsible for approximately 20 percent of all incident cases of the city, the patient accrual in the other two centers approached 100 percent of all incident cases in each area for the period of study.

For each case, two control subjects (n = 1,578) were also selected from the same hospital or from the nearest general hospital by matching on sex, 5-year age group, and quarter of admission. In total, nine cases were eliminated before matching: one refused, seven interviews were interrupted due to physical conditions, and one was excluded when no suitable controls were identified. The underlying causes of hospitalization among control patients could be grouped into 13 diagnostic categories. Digestive system diseases (ICD-9 520–579) represented the most common cause (26 percent), followed by cardiovascular diseases (ICD-9 390–459) (24.9 percent) and trauma and poisoning (ICD-9 800–999) (8.6 percent). Other specified diagnostic categories included pregnancy-related diseases (ICD-9 630–676) (0.3 percent), respiratory system diseases (ICD-9 460–519) (6.1 percent), genito-urinary tract diseases (ICD-9 580–629) (7.5 percent), and ill-defined diagnostic conditions (ICD-9 780–799) (10.5 percent). Patients with neoplastic diseases (ICD-9 140–239) or mental disorders (ICD-9 290–319) were not considered eligible.

Risk factor information

Interviews were carried out before treatment by trained nurses who were blinded to all etiologic hypotheses. The questionnaire-based interviews elicited information on sociodemographic variables, health conditions, environmental and occupational exposures, tobacco and alcohol consumption, diet, and oral hygiene.

Lifetime, cumulative exposure to tobacco was expressed in pack-years, a variable that subsumes both intensity and duration of smoking. One pack-year was defined as the cumulative exposure that corresponds to smoking one pack of cigarettes (20 cigarettes in Brazil) per day for one year. This variable incorporated smoking of manufactured cigarettes, hand-rolled cigarettes, cigars, and pipes. Tobacco doses were calculated as follows: 20 manufactured cigarettes = 4 hand-rolled, black tobacco cigarettes = 4 cigars = 5 pipefuls with regular pipe tobacco = one pack. Data on frequency and volume of alcohol consumption were also gathered for all types of alcoholic beverages, including beer, wine, hard liquor, *cachaça* (a spirit made from sugar cane), and combined into a synthetic index which expressed lifetime consumption of ethanol in kilograms. The doses of ethanol concentration were calculated as follows: beer = 5 percent, wine = 10 percent, and hard liquor and *cachaça* = 50 percent ethanol.

Statistical analysis

We estimated relative risks of disease associated with individual exposures by computing odds ratios and their respective 95 percent confidence intervals (CI) by multivariate logistic regression using conditional maximum likelihood estimation, thus preserving the matching used in the design (13). Analyses were done with MULTLR, a public domain logistic regression software (available at http://www.epi.mcgill.ca) (14). Statistical assessment of interaction (effect modification) was based on a multiplicative model by fitting models containing both main effects (smoking and alcohol consumption) and their cross-product terms. Inference was based on the partial likelihood ratio (deviance) statistic between nested models adjusted for confounders.

Potential empirical confounders were examined from tens of sociodemographic, dietary, occupational, and oral hygiene variables. Assessment of confounding was based on a deviation in odds ratios of 5 percent or greater from the model mutually adjusting for tobacco or alcohol consumption (15). All covariates identified by this method were considered as empirical confounders and were included in all models.

Statistical trend in the dose-risk relationship for a given variable was assessed in models containing the factor treated as an ordinal variable.

RESULTS

Case accrual by city was as follows: 213 (27.2 percent) in São Paulo, 380 (48.5 percent) in Curitiba, and 191 (24.4 percent) in Goiânia. Cases included 373 (47.6 percent) patients with oral cancer, 217 (27.7 percent) with pharyngeal cancer, and 194 (24.7 percent) with laryngeal cancer. In general, sociodemographic characteristics did not differ markedly between cases and controls. The proportion of white patients among cases (85 percent) was slightly higher than among controls (80 percent). There were more illiterate cases than controls (32 percent vs. 27 percent), and a higher percent of cases were Catholic (92 percent vs. 81 percent). Cases had somewhat lower median family income values than controls: US$66 and US$83 per month, respectively. Most subjects (87.1 percent) were men, and the average age of cases and controls was 58 years.

As expected, smoking was more frequently reported by cases than by controls; 28 percent of the controls had never smoked compared with only 4 percent of the cases. Likewise, for alcohol drinking, 25 percent of the controls compared with 9 percent of cases were nondrinkers. The alcohol-adjusted odds ratio contrasting ever versus never smokers was 8.3 (95 percent CI 5.3, 13.0), whereas the crude odds ratio was 9.7 (95 percent CI 6.3, 15.1). The smoking-adjusted odds ratio for alcohol was 2.8 (95 percent CI 1.9, 4.0) and the crude odds ratio was 4.0 (95 percent CI 2.8, 5.8).

The covariates that yielded changes in the adjusted odds ratio for smoking of more than 5 percent in either direction (other than alcohol) were use of wood stove in home (6.4 percent decrease) and temperature of beverages consumed (8.1 percent decrease). The variables that changed the odds ratio for alcohol by more than 5 percent (other than smoking) were race (9.9 percent decrease), religion (6.0 percent decrease), consumption of spicy foods and peppers (7.4 percent decrease), and temperature of beverages consumed (7.0 percent decrease). Interaction between various study factors and tobacco and alcohol consumption was investigated in models containing each factor, terms for tobacco and alcohol, and cross-product terms between the factor and the latter variables. Except for the interaction between tobacco and alcohol (described below), there was no statistical evidence of effect modification with other variables.

Analysis of all sites

Tobacco consumption was based on a baseline category for non-exposure and three exposure categories defined by the tertile cut-off values within exposed controls: 1) never smokers, 2) <1–25 pack-years, 3) 26–60 pack-years, 4) >60 pack-years. Following the same procedure, lifetime exposure to alcohol was defined as: 1) <1 kg, 2) 1–145 kg, 3) 146–932 kg, 4) >932 kg of ethanol. Risk magnitudes for a model assuming effect modification as compared with the baseline model assuming independence of effects are represented in figure 1.

In figure 1A, where independence of effects was assumed, the odds ratios reflect only mutual adjustment. The risk due to alcohol seems to increase somewhat exponentially with levels of tobacco consumption. Figure 1B illustrates the effect after addition of the cross-product terms. With exposure to tobacco, the effect of increasing alcohol consumption was augmented compared with corresponding risks observed in figure 1A. There was borderline statistical evidence of effect modification as judged by the contribution of goodness of fit of nine cross-product terms in addition to a baseline model containing six main effect terms for smoking and alcohol ($p = 0.063$). By omitting the empirical confounders from the latter models, there seemed to be a gain in precision (at the expense of compromising validity) in the assessment of interaction ($p = 0.02$).

Site-specific analysis

The preceding analysis indicated that a more complex nature of effect modification was occurring within the three main sites along the aero-digestive tract: mouth, pharynx, and larynx. To compensate for the reduction in sample size in site-specific analyses, tobacco consumption was reduced to three categories: a baseline group including light smokers of ≤5 pack-years, and two exposure categories defined by the median cutoff value in exposed controls, 6–42 pack-years and >42 pack-years. Lifetime exposure to alcohol was defined as 0–10 kg (baseline), 11–530 kg, and >530 kg of alcohol. Inclusion of very low consumption levels in the categories of non-exposure for smoking and alcohol was necessary to allow enough cases to be classified in the joint baseline category. Table 1 shows the frequency distributions for cases and controls according to the combined categories of both main exposures for each UADT site.

Table 2 shows the odds ratios of mouth cancer for combined categories of tobacco and alcohol consumption. Assuming independence, both smoking and alcohol consumption were considered as independent variables in the model, referring to a baseline category of light smokers and drinkers. By including the cross-product terms for tobacco and alcohol consumption, the odds ratios over levels of exposure did not vary materi-

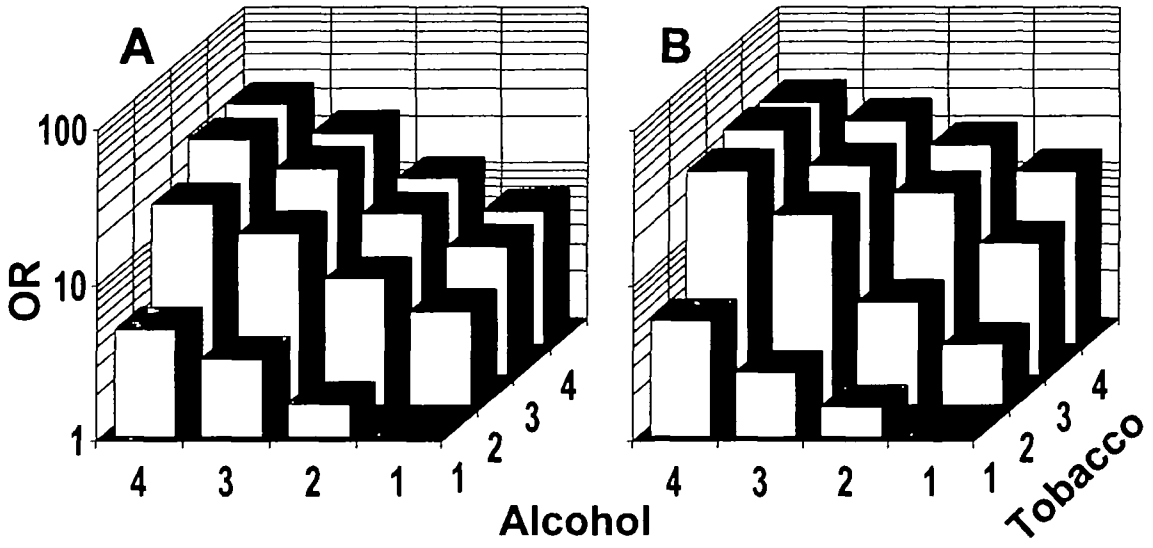

FIGURE 1. Odds ratios for cancer at all sites along the upper aero-digestive tract (UADT) in southern Brazil, 1986–1989, according to joint exposure to tobacco and alcohol consumption. Results by conditional logistic regression (matching variables: age, sex, study location, and admission period) controlling for race, temperature of beverages, religion, use of a wood stove, and consumption of spicy foods. Model A assumes independence of effects. Model B assumes effect modification. Levels of lifetime alcohol consumption: 1) <1 kg; 2) 1–145 kg; 3) 146–932 kg; 4) >932 kg; levels of cumulative tobacco exposure: 1) never smoked; 2) 1–25 pack-years; 3) 26–60 pack-years; 4) >60 pack-years.

TABLE 1. Frequency distributions for cases/controls by upper aero-digestive tract tumor site according to joint categories of lifetime cumulative tobacco and alcohol consumption, southern Brazil, 1986–1989

Tumor site (ICD-9* codes)	Lifetime tobacco consumption (in pack-years)	Lifetime alcohol consumption (in kg)		
		0–10	11–530	>530
Mouth (140–145)	0–5	18/139	8/70	4/30
	6–42	23/54	38/44	84/84
	>42	15/28	44/86	139/134
Pharynx (146–149)	0–5	3/43	4/38	4/20
	6–42	2/65	21/71	59/71
	>42	9/12	26/55	88/94
Larynx (161)	0–5	3/62	1/33	1/12
	6–42	15/31	25/61	34/45
	>42	7/17	28/41	80/84

* ICD-9, *International Classification of Diseases*, 9th Revision.

ally between models, which resulted in a nonsignificant contribution to the overall goodness of fit of the independence model (log likelihood ratio test, $p = 0.284$). When the two main exposures were considered as ordinal variables, significant dose-response trends were observed (both tobacco and alcohol: $p = < 0.0001$). However, the contribution of the cross-product term on the baseline model remained nonsignificant.

Likewise, table 3 shows the odds ratios of pharyngeal cancer for combined levels of tobacco and alcohol. Without the cross-product terms, the odds ratio for moderate tobacco and high alcohol consumption increased to 16.6 (95 percent CI 5.7, 48.5). However, assuming effect modification between smoking and drinking, the joint effect for the same levels of exposures increased fourfold, with a significant contribution by the inclusion of the interaction terms ($p = 0.007$) supporting the model for interaction. The statistical trends for dose-response relationships for smoking and drinking were also significant (both $p < 0.0001$). Assuming effect modification, the increases in risk with alcohol consumption above baseline at all levels of smoking were also higher in the pharynx when compared with the equivalent models for mouth cancer. Comparing odds ratios within the same model for interaction, the combined risks for joint exposure to moderate smoking and moderate to high alcohol consumption were higher than expected as determined by the simple product of the odds ratios for smoking and alcohol in the absence of the other. However, at high levels of smoking, the observed odds ratios were lower than expected for moderate and high alcohol drinking. The effect modification terms therefore contributed both a positive and negative effect on the joint risks of pharyngeal cancer. A model including dichotomous forms of the two variables based on the same baseline category of light smokers and drinkers produced a net sub-multiplicative interaction effect (data not shown).

Table 4 shows the odds ratios of laryngeal cancer for joint categories of smoking and drinking. There was no

TABLE 2. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the mouth according to categories of joint tobacco and alcohol exposure comparing models assuming independence of effects and effect modification, southern Brazil, 1986–1989*

Type of analysis (assumption)	Level of smoking‡	Level of alcohol consumption†					
		1		2		3	
		OR	95% CI	OR	95% CI	OR	95% CI
Independence	1	1.0	(referent)	1.6	0.9, 2.8	3.6	2.0, 6.5
	2	4.8	2.7, 8.7	7.5	3.5, 15.8	17.5	8.2, 37.0
	3	6.7	3.6, 12.5	10.3	4.8, 22.2	24.1	11.4, 51.1
Effect modification	1	1.0	(referent)	1.2	0.4, 3.4	2.3	0.6, 9.1
	2	2.9	1.2, 6.8	6.2	2.7, 14.1	19.5	2.6, 147
	3	7.8	2.9, 21.0	11.2	4.8, 26.3	20.3	9.0, 45.3

* Conditional logistic regression (matching variables: age, sex, study location, and admission period) with adjustment for race, beverage temperature, religion, wood stove use, and consumption of spicy food.
† Levels of lifetime alcohol consumption: 1, 0–10; 2, 11–530; 3, >530 kg.
‡ Levels of cumulative tobacco exposure: 1, 0–5; 2, 6–42; 3, >42 pack-years.

statistical evidence of effect modification ($p = 0.945$). Although the dose-response relationships were significant for both tobacco ($p < 0.0001$) and alcohol ($p = 0.0004$), the effect of alcohol seemed to become pronounced only at the highest consumption level among light smokers.

We used dichotomous forms of the two exposure variables to analyze the joint associations by subsite (table 5). In each combination, there was no statistical evidence of interaction as judged by the contribution to goodness of fit of the one cross-product term in addition to the baseline models. This was primarily due to the small number of cases within each subsite sample. For supra-glottis (ICD-9 161.1), oropharynx (ICD-9 146), and hypopharynx (ICD-9 147), there was indication of enhanced effects for joint exposure to smoking and alcohol due to elevated baseline risks in the models assuming effect modification. In contrast, the effect of fitting models including the cross-product term for oral cavity subsites and for the glottic region (ICD-9 161.0–161.2) was to reduce odds ratio estimates for all exposure levels although the cross-product terms had positive effects on the joint estimates of risk.

Effect of alcohol in nonsmokers

Table 6 shows the odds ratios of combined cancers of the mouth, pharynx, and supra-glottis due to alcohol drinking exclusively among never smokers and for a larger stratum that also included light smokers of ≤5 pack-years. Because this restriction created strong imbalance between cases and controls across all matched sets, a new matching indicator was created to regroup subjects in such a way that no sets were formed

TABLE 3. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the pharynx according to categories of joint tobacco and alcohol exposure comparing models assuming independence of effects and effect modification, southern Brazil, 1986–1989*

Type of analysis (assumption)	Level of smoking‡	Level of alcohol consumption†					
		1		2		3	
		OR	95% CI	OR	95% CI	OR	95% CI
Independence	1	1.0	(referent)	2.0	0.9, 4.6	4.6	2.0, 10.5
	2	3.6	1.6, 8.0	7.4	2.5, 21.7	16.6	5.7, 48.5
	3	5.4	2.4, 12.2	11.0	3.7, 32.4	24.9	8.6, 72.1
Effect modification	1	1.0	(referent)	6.2	0.7, 56.6	22.3	2.1, 238
	2	2.4	0.2, 24.0	21.7	2.6, 180	66.3	1.7, 2,556
	3	69.4	6.9, 694	43.0	4.9, 340	77.3	9.2, 625

* Conditional logistic regression (matching variables: age, sex, study location, and admission period) with adjustment for race, beverage temperature, religion, wood stove use, and consumption of spicy food.
† Levels of lifetime alcohol consumption: 1, 0–10; 2, 11–530; 3, >530 kg.
‡ Levels of cumulative tobacco exposure: 1, 0–5; 2, 6–42; 3, >42 pack-years.

TABLE 4. Odds ratios (OR) and 95% confidence intervals (CI) for cancer of the larynx according to categories of joint tobacco and alcohol exposure comparing models assuming independence of effects and effect modification, southern Brazil, 1986–1989*

Type of analysis (assumption)	Level of smoking‡	Level of alcohol consumption†					
		1		2		3	
		OR	95% CI	OR	95% CI	OR	95% CI
Independence	1	1.0	(referent)	1.5	0.7, 3.0	3.1	1.5, 6.7
	2	11.4	4.0, 32.7	16.5	4.8, 56.8	35.6	10.1, 125
	3	13.5	4.6, 40.0	19.6	0.9, 442	42.3	1.9, 946
Effect modification	1	1.0	(referent)	1.2	0.1, 14.4	5.5	0.4, 71.5
	2	13.5	2.7, 66.8	16.1	3.4, 76.2	36.9	0.7, 1,800
	3	11.4	2.1, 62.0	22.0	4.5, 107	43.1	9.1, 206

* Conditional logistic regression (matching variables: age, sex, study location, and admission period) with adjustment for race, beverage temperature, religion, wood stove use, and consumption of spicy food.
† Levels of lifetime alcohol consumption: 1, 0–10; 2, 11–530; 3, >530 kg.
‡ Levels of cumulative tobacco exposure: 1, 0–5; 2, 6–42; 3, >42 pack-years.

with zero cases. Controls were rematched to cases only by 5-year age group, sex, and study location. In addition, alcohol consumption had to be categorized with different cutpoints to represent the tertiles of exposure above the baseline of lifetime nondrinkers among controls. Two categorical forms for alcohol consumption were used: never drinkers versus ever drinkers, and nondrinkers who had consumed <1 kg of alcohol versus drinkers divided into tertiles of consumption.

Even with the small frequency of never smokers, both crude and adjusted models showed a significant risk elevation with ever drinking. Both models showed statistically significant trends in dose-response relationship with increasing levels of alcohol exposure. As expected, when light smokers were included, there was some gain in precision in gauging the effect of alcohol, both at each level of consumption and as a dose-response trend.

TABLE 5. Site-specific odds ratios (OR) and 95% confidence intervals (CI) for upper aero-digestive tract cancers according to categories of joint tobacco and alcohol exposure comparing models assuming independence and effect modification, southern Brazil, 1986–1989*

Tumor site	Tobacco exposure	OR (95% CI) by model and level of alcohol consumption			
		Independence		Effect modification	
		<1–25 kg	>25 kg	<1–25 kg	>25 kg
Tongue	Never	1.0 (referent)	4.9 (2.0, 12.2)	1.0 (referent)	3.8 (0.7, 20.4)
	Ever	5.1 (1.7, 15.2)	24.7 (6.5, 93.6)	4.3 (1.0, 17.8)	22.3 (5.4, 92.4)
Lip	Never	1.0 (referent)	1.5 (0.5, 3.9)	1.0 (referent)	0.7 (0.1, 10.4)
	Ever	4.2 (1.3, 13.8)	6.2 (1.6, 25.0)	3.1 (0.7, 14.1)	5.1 (1.2, 22.6)
Other mouth	Never	1.0 (referent)	2.5 (1.4, 4.7)	1.0 (referent)	0.5 (0.1, 4.5)
	Ever	5.7 (2.6, 12.6)	14.4 (5.6, 37.5)	3.6 (1.4, 8.9)	10.4 (3.9, 27.3)
Oropharynx	Never	1.0 (referent)	3.2 (1.1, 9.7)	1.0 (referent)	5.2 (0.1, 220.7)
	Ever	10.5 (1.9, 59.1)	34.1 (4.9, 234.2)	14.5 (0.7, 300.9)	46.4 (2.1, 1,015)
Hypopharynx	Never	1.0 (referent)	4.2 (1.6, 11.5)	1.0 (referent)	7.5 (0.5, 109.8)
	Ever	4.6 (1.2, 17.1)	19.4 (4.5, 83.4)	6.8 (0.7, 67.3)	27.6 (3.0, 247.3)
Supraglottic	Never	1.0 (referent)	3.6 (1.3, 10.0)	1.0 (referent)	6.8 (0.3, 146.9)
	Ever	8.9 (1.9, 42.2)	31.7 (5.7, 174.9)	12.4 (1.3, 119.0)	42.4 (4.3, 412.1)
Transglottic	Never	1.0 (referent)	2.1 (1.1, 3.9)	1.0 (referent)	0.9 (0.1, 9.8)
	Ever	7.3 (2.5, 21.1)	15.0 (4.7, 48.4)	5.4 (1.5, 19.3)	11.6 (3.2, 41.8)

* Conditional logistic regression (matching variables: age, sex, study location, and admission period) with adjustment for race, beverage temperature, religion, wood stove use, and consumption of spicy food.

TABLE 6. Odds ratios (OR) and 95% confidence interval (CI) for oral, pharyngeal, and supraglottic cancers in never smokers and light smokers in southern Brazil, 1986–1989*

Smoking exposure	Alcohol consumption	Cases/ controls	Crude		Adjusted†	
			OR	95% CI	OR	95% CI
Never smokers only	Never	10/154	1.0	(referent)	1.0	(referent)
	Ever	18/185	4.5	1.2, 17.2	5.5	1.3, 24.4
	Nondrinker‡	11/157	1.0	(referent)	1.0	(referent)
	1–22 kg	7/63	2.5	0.6, 10.6	1.9	0.4, 9.6
	23–245 kg	3/63	2.0	0.4, 9.5	2.3	0.4, 12.4
	>245 kg	7/56	7.7	1.6, 37.4	9.1	1.7, 48.5
	Trend (*p* value)			0.021		0.013
Never + light smokers§	Never	11/184	1.0	(referent)	1.0	(referent)
	Ever	32/264	5.6	2.0, 15.8	5.1	1.7, 15.0
	Nondrinker‡	13/187	1.0	(referent)	1.0	(referent)
	1–22 kg	11/85	3.2	1.1, 9.2	2.7	0.9, 8.0
	23–245 kg	7/85	2.9	0.9, 9.2	2.8	0.9, 9.2
	>245 kg	12/90	6.6	1.9, 22.3	6.3	1.8, 22.4
	Trend (*p* value)			0.004		0.006

* Conditional logistic regression (matching variables: 5-year age group, sex, and study location).
† Controlling additionally for covariates: race, beverage temperature, religion, wood stove use, and consumption of spicy food.
‡ Includes never drinkers and those with <1 kg lifetime consumption.
§ Includes never smokers and light smokers with a cumulative tobacco consumption of ≤5 pack-years.

DISCUSSION

Before we address the implications of these findings, it is important to consider the limitations of the study. Odds ratios were based on a comparison with hospital controls, with no attempt to exclude tobacco and alcohol-related diseases from the latter group. In consequence, exposure prevalence among controls may have been overestimated, thus leading to conservatively biased odds ratios. The degree of bias is unlikely to have varied geographically. By stratifying the analyses of tobacco and alcohol by study center, we did not observe materially different results concerning the strength of the associations and patterns of effect modification. This indicates that the magnitude and patterns of the joint associations seemed to be invariant with respect to the distribution of diagnostic conditions among hospital controls. It was also reassuring that although case subjects had on average lower incomes and were less educated than controls, the effect from confounding was negligible. Including primary indicators of socioeconomic status into the analyses did not change the magnitude of the odds ratios for the two key exposures.

Misclassification from faulty recall or as a result of the simplifying assumptions we made when constructing the cumulative summary variables may have influenced the results. However, since all interviews were conducted in hospitals and no subjects or interviewers were made aware of the etiologic hypotheses being tested, recall or reporting error would be comparable for cases and controls and likely only underestimated the actual effects. Furthermore, awareness of the hazardous effects of alcohol and smoking on cancer risk is not as widespread in the population studied as compared with developed countries.

Feldman and Boxer (16) found that odds ratios for UADT cancers as an aggregate seem to indicate a higher than multiplicative interaction. In our study, when effect modification was assumed for combined UADT sites, the odds ratios for heavy drinking rose substantially for low to moderate levels of smoking and then reached a maximum for higher levels of smoking where the effect of interaction decreased expected risks. The risks of smoking increased in the absence of alcohol while the effect of alcohol within never smokers remained low. Because evidence of effect modification was borderline over the entire UADT, we suspected that the interaction pattern could vary for different epithelial regions that are in direct contact with both alcohol and tobacco carcinogens versus areas that are not directly exposed to alcohol.

The general approach to studying sites within the UADT in past studies has been to combine mouth and pharyngeal cancers together and keep the larynx and esophagus separate in statistical analyses. The available

evidence has both supported and rejected conclusions of interaction when grouping mouth and pharynx cancers together (3, 17). Franceschi et al. (10) observed an odds ratio of 79.6 for the combined exposures of heavy smoking and drinking in oral cavity and pharyngeal cancers. Blot et al. (3), who also observed a multiplicative effect, found an odds ratio of 37.7 in men for the highest levels of exposure. When we separated oral cavity and pharyngeal cancers, we found similar odds ratios for combined levels of highest exposure assuming the multiplicative model of independence. With effect modification, however, the odds ratio rose to 77.3 within the pharynx, a level that was comparable to that measured by Baron et al. (9) using polychotomous logistic regression to individualize the associations by site. We found an inconsistent pattern of supra-multiplicative association within the pharynx for moderate smokers that increased with alcohol consumption. At higher levels of smoking, the combined risk was lower than expected, although risks for pharyngeal cancer were higher overall, considering all levels of exposure. Contribution from the cross-product term to the risk of mouth cancer was minimal, which may have resulted from the heterogeneity of effects by subsites included (tongue, floor of the mouth, gum, cheek mucosa).

Two studies have investigated tobacco and alcohol interaction in laryngeal cancer (18, 19). When comparing the excess risk of heavy smoking and drinking over light smoking and drinking, these studies identified a mild departure above the multiplicative model. Evidence of separate risk patterns for the supra-glottis versus the intrinsic larynx has been demonstrated (20–23), and the supra-glottic region has been considered as part of the pharynx in terms of etiology and diagnosis (10). Our results support this divergent nature in risk pattern for the larynx. We identified a tendency toward effect modification within the supraglottis that was comparable with that observed in the oropharynx and hypopharynx. The absence of an effect from alcohol among never smokers on cancers of the lip and other parts of the mouth may reflect impedance to carcinogenicity in the epithelium due to the "washing" effects of mastication and deglutition or the lack of prolonged exposure of the epithelium to alcohol.

Saracci (24) stated that, when identified as a risk factor in a more than multiplicative interaction model, alcohol may in fact be carcinogenic only in the presence of tobacco. However, Elwood et al. (17) and LaVecchia and Negri (25) observed among nonsmokers, as we did, that alcohol in fact acts both as an independent risk factor and as a promoter of oral, pharyngeal, and esophageal cancers.

Although the effect of alcohol was lower in cancers of the larynx, tobacco had a pronounced effect, even at low levels of exposure. Furthermore, odds ratios for mouth and pharynx cancers increased rapidly and significantly with greater exposure to both alcohol and tobacco. This supports the hypothesis that anatomical gradients in risk reflect the degrees of exposure and that interaction would only occur in the squamous epithelial areas of the UADT that are exposed to both carcinogens. The mouth is exposed to both alcohol and tobacco, as is the pharynx, but the larynx, especially intrinsic areas such as the transglottis, is exposed more to cigarette smoke than to alcohol.

No reference to a biologic model is required to support a statistical evaluation of independence and interaction (26, 27). Plausible hypotheses do exist, however, to explain the synergy between tobacco and alcohol on the risk of UADT cancers. Tobacco smoke substances are known carcinogens which act primarily during the initiation process. The likely effect of alcohol, however, is more easily understood as a cancer promoter via one or more of the following mechanisms: 1) increased permeability of mucosal cells to tobacco smoke carcinogens due to solubilization by alcohol; 2) presence of low levels of carcinogenic substances in alcoholic beverages; or 3) cellular injury produced by ethanol metabolites (28). Therefore, it is hardly surprising that, when combined with other cancer-causing agents, such as cigarette smoke, the risk of cancer in the UADT should increase significantly. The dramatic added cancer morbidity and subsequent mortality associated with smoking and drinking provides a strong argument for targeting public health campaigns to curb the effect of both exposures simultaneously.

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REFERENCES

1. Parkin DM, Oisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993;54:594–606.
2. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from 18 major cancers in 1985—implications for

prevention and projections of future burden. Int J Cancer 1993;55:891–903.
3. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282–7.
4. Franceschi S, Bidoli E, Barón AE, et al. Nutrition and cancer of the oral cavity and pharynx in north-east Italy. Int J Cancer 1991;47:20–5.
5. Franco EL, Kowalski LP, Oliveira BV, et al. Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer 1989; 43:992–1000.
6. Blot WJ, McLaughlin JK, Devesa SS, et al. Cancers of the oral cavity and pharynx. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press, 1996:666–80.
7. Pintos J, Franco EL, Oliveira BV, et al. Mate, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in Southern Brazil. Epidemiology 1994;5:583–90.
8. Rothman KJ, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chronic Dis 1972;25:711–16.
9. Baron AE, Franceschi S, Barra S, et al. A comparison of the joint effects of alcohol and smoking on the risk of cancer across sites in the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 1993;2:519–23.
10. Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in Northern Italy. Cancer Res 1990;50:6502–7.
11. Morabia A, Stellman SD, Wynder EL. Smoking prevalence in neighborhood and hospital controls—implications for hospital-based case-control studies. J Clin Epidemiol 1996;49: 885–9.
12. Muir C, Waterhouse J, Mack T, et al. Cancer incidence in five continents. Vol V. IARC Scientific Publications no. 88. Lyon: International Agency for Research on Cancer, 1987.
13. Breslow NE, Day NE. Statistical methods in cancer research, Vol 1. The analysis of case control studies. IARC Scientific Publications no. 32. Lyon: International Agency for Research on Cancer, 1980:248–79.
14. Campos-Filho N, Franco EL. A microcomputer program for multiple logistic regression by unconditional and conditional maximum likelihood methods. Am J Epidemiol 1989;129: 439–44.
15. Robins JM, Greenland S. The role of model selection in causal inference from nonexperimental data. Am J Epidemiol 1986; 123:392–402.
16. Feldman JG, Boxer P. Relationship of drinking to head and neck cancer. Prev Med 1979;8:507–19.
17. Elwood JM, Pearson JC, Skippen DH, et al. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Cancer 1984;34:603–12.
18. Flanders WD, Rothman KJ. Interaction of alcohol and tobacco in laryngeal cancer. Am J Epidemiol 1982;115:371–9.
19. Tuyns AJ, Esteve J, Raymond L, et al. Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 1988;41:483–91.
20. Brugere J, Guenel P, Leclerc A, et al. Differential effects of tobacco and alcohol in cancer of the larynx, pharynx, and mouth. Cancer 1986;57:391–5.
21. Guenel P, Chastang J-F, Luce D, et al. A study of the interaction of alcohol drinking and tobacco smoking among French cases of laryngeal cancer. J Epidemiol Community Health 1988;42:350–4.
22. Maier H, Dietz A, Gewelke U, et al. Tobacco and alcohol and the risk of head and neck cancer. Clin Investigator 1992; 70:320–7.
23. Sancho-Garnier H, Theobald S. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. II. Pharynx and larynx cancer. Eur J Cancer 1993;29A:273–6.
24. Saracci R. The interactions of tobacco smoking and other agents in cancer etiology. Epidemiol Rev 1987;9:175–93.
25. LaVecchia C, Negri E. The role of alcohol in oesophageal cancer in nonsmokers and of tobacco in nondrinkers. Int J Cancer 1989;43:784–5.
26. Miettinen O. Confounding and effect-modification. Am J Epidemiol 1974;100:350–3.
27. Rothman KJ, Greenland S, Walker AM. Concepts of interaction. Am J Epidemiol 1980;112:467–70.
28. Hsu TC. Alcohol: a cocarcinogen in head and neck malignancies. In: Newell GR, Hong WK, eds. The biology and prevention of aerodigestive tract cancers. New York: Plenum Press, 1992:35–7.