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ORIGINAL PAPER

Alcohol and tobacco, and the risk of cancers of the upper aerodigestive tract in Latin America: a case–control study

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Abstract
Background Cancers of the upper aerodigestive tract (UADT; including oral cavity, pharynx, larynx and oesophagus) have high incidence rates all over the world, and they are especially frequent in some parts of Latin America. However, the data on the role of the major risk factors in these areas are still limited.
Methods We have evaluated the role of alcohol and tobacco consumption, based on 2,252 upper aerodigestive squamous-cell carcinoma cases and 1,707 controls from seven centres in Brazil, Argentina, and Cuba.
Results We show that alcohol drinkers have a risk of UADT cancers that is up to five times higher than that of never-drinkers. A very strong effect of aperitifs and spirits as compared to other alcohol types was observed, with the ORs reaching 12.76 (CI 5.37–30.32) for oesophagus. Tobacco smokers were up to six times more likely to develop aerodigestive cancers than never-smokers, with the ORs reaching 11.14 (7.72–16.08) among current smokers for hypopharynx and larynx cancer. There was a trend for a decrease in risk after quitting alcohol drinking or tobacco smoking for all sites. The interactive effect of alcohol and tobacco was more than multiplicative. In this study, 65% of all UADT cases were attributable to a combined effect of alcohol and tobacco use.
Conclusions In this largest study on UADT cancer in Latin America, we have shown for the first time that a prevailing majority of UADT cancer cases is due to a combined effect of alcohol and tobacco use and could be prevented by quitting the use of either of these two agents.

Keywords Upper aerodigestive tract · South America · Tobacco · Alcohol · Cancer

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Abbreviations

UADT	Upper aerodigestive tract
SCC	Squamous-cell carcinoma
OR	Odds ratio
CI	Confidence interval

Introduction

Cancers of the upper aerodigestive tract (UADT) comprise cancers of the oral cavity, oropharynx, hypopharynx and larynx, frequently referred to as head and neck cancers, as well as cancers of the oesophagus. It is estimated that over one million new UADT cancer cases appeared worldwide in the year 2002 and that these types of cancers were responsible for over 680,000 deaths. There is a striking geographical variation in the incidence of UADT cancers worldwide, with some parts of South America (Brazil, especially south and south-east Brazil, Uruguay and Argentina) ranking among the high-risk areas for all UADT sites [1].

The major risk factors for UADT cancers in Europe and both Americas are alcohol drinking and tobacco smoking, with evidence of an interaction between them [2–4]. Smoking alone is responsible for about 41% of head and neck cancers in men and about 15% in women worldwide [4]. Both alcohol and tobacco, combined with a low intake of fresh fruits and vegetables, are also causally associated with squamous-cell carcinoma (SCC) of the oesophagus; however, the relative contribution of these risk factors varies between different geographical areas. In Western countries, alcohol and tobacco are estimated to be responsible for 90% of all oesophageal SCCs, whereas in developing countries, other factors, such as viral infections, may have an important role. However, only one study so far has estimated the proportion of upper aerodigestive cancer cases attributable to tobacco and alcohol in developing countries of South America and it was devoted exclusively to cancer of the oesophagus [5].

In this study, we assessed the role of tobacco and alcohol consumption as well as their interactions in the development of squamous-cell carcinomas of the four sites of the upper aerodigestive tract in high-risk populations in Latin America.

Materials and methods

The study and subjects

An international multicentre hospital-based case–control study of upper aerodigestive cancers was initiated in 1998 in seven centres in high UADT cancer risk areas in Latin America (São Paolo, Goiania, Rio de Janeiro, Pelotas, and Porto Alegre in Brazil, Buenos Aires in Argentina, and La Havana in Cuba). These high-risk areas were identified based on age-standardised incidence rates reported in the Globocan database [1]. Cases and potential controls were identified by study coordinators from hospital admission records or from the relevant clinical wards; the exact procedures varied by centre but were consistent between cases and controls within each centre. Cases were patients with UADT cancers, newly diagnosed in one of the participating hospitals or referred to one of these hospitals for primary therapy, with no prior treatment, either local or systemic. All cases were histologically confirmed by a pathologist in each of the participating hospitals. Controls were recruited from in- or outpatients at the same hospitals as the cases, frequency-matched on sex, age and centre. Only patients with a recent diagnosis from a defined list of diseases not related to tobacco or alcohol were included in the control group. The main disease groups were diseases of the digestive system (22.7%), injuries, poisoning and certain other consequences of external causes (14.3%), diseases of musculoskeletal system and connective tissue (14.0%), diseases of the genitourinary system (13.8%) and disease of the circulatory system (13.0%). None of the remaining disease groups constituted more than 5% of the control group.

Potential participants were first contacted by the medical staff of the wards and then approached by the interviewers; 2,479 incident cancer cases and 1,825 controls were initially recruited, with the response rate of 95% for the cases and 86% for the controls. Informed consent was obtained from all study subjects, and ethical approvals were obtained from relevant ethical committees. Each individual answered a detailed lifestyle questionnaire, including basic demographic characteristics and the history of tobacco and alcohol use, that was administered face-to-face in the hospital by a trained interviewer. Cases and controls were identified and interviewed in parallel by the same interviewers. All interviewers were trained in a standardised fashion and closely supervised by local study coordinators. Cases were interviewed within days or weeks from the date of diagnosis. And 227 non-eligible cases were excluded from the study. These were patients with cancers of the salivary glands, tumours with an unknown site, in situ tumours and carcinomas other than squamous cell. Furthermore, 118 controls were excluded due to diagnosis thought to be potentially related to alcohol and/or tobacco consumption. A total of 2,252 cases and 1,707 controls were included in the final analysis. The cases were grouped into three main tumour site categories on the basis of the ICD-O classification [6]:

(1) oral cavity and oropharynx, including floor of the mouth, tongue, other parts of oral cavity, oral cavity

NOS, oropharynx, overlapping tumours with the origin in the oral cavity (overlapping oral cavity–oropharynx–hypopharynx NOS) (C00.3-C00.8, C01.9, C02.0-4, C02.8-9, C03.0-1, C03.9, C04.0-1, C04.8-9, C05.0-2, C05.8-9, C06.0-2, C06.8-9, C09.0-1, C09.8-9, C10.0-4, C10.8-9, C14.0, C14.2 and C14.8)

(2) hypopharynx and larynx (C12.9, C13 and C32)

(3) oesophagus (C15)

Tumours overlapping more than one of the above categories were kept as a separate category.

Oesophageal cancer cases were available only from two of the centres in Brazil (Pelotas and Goiania), so controls from other centres were excluded from the analyses for that site. Similarly, no oral cases were available from Cuba, so controls from this centre were excluded from the analyses for that site.

Statistical analysis

The sections of the questionnaire concerning alcohol drinking and tobacco smoking contained detailed information on age at which regular drinking or smoking began and stopped, periods in which the subjects drank or smoked by age, the quantity and type of alcohol drunk or the number and type of tobacco products smoked during each period, and any period of not drinking or not smoking.

Ever-drinkers were defined as having ever consumed alcoholic drinks at least once a month. Individuals who quit drinking more than a year before the interview (for controls) or the diagnosis date (for cases) were considered to be former drinkers. The intervals were calculated in years. Alcohol amounts were presented as ethanol-grams per day, with the assumption that beer contains approximately 5% of ethanol in volume, wine 12% and spirits 40% [2]. Cumulative consumption (gram-years) was estimated by multiplying average grams of ethanol per day by the years of alcohol consumption.

Ever-smokers were defined as having smoked on average one cigarette, one cigar or one pipe fill a day for at least 1 year. Individuals who quit smoking more than a year before the interview (for controls) or the diagnosis date (for cases) were considered to be former smokers. The intervals were calculated in years. Overall, tobacco use was estimated by combining the number of cigarettes, cigars and pipes smoked, quantified into cigarette-equivalents per day with the assumption that one cigar is equivalent to four cigarettes and one pipe to three and a half cigarettes [4]. Pack-years of smoking were calculated by multiplying the number of packs smoked per day (assuming 20 cigarettes or cigarette-equivalents per pack) by the number of years the subject smoked.

To estimate the risk of upper aerodigestive cancers associated with tobacco and/or alcohol consumption, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated by unconditional multivariate logistic regression using Stata Intercooled, version 8.0, with adjustment for sex, age (continuous), centre, education, and fruit and cruciferous consumption (the last three categorised as shown in Table 1), as well as for cumulative alcohol or tobacco consumption (alcohol gram-years or tobacco pack-years) as appropriate, with the exclusion of the missing values. The ORs for quitting of the habit were additionally adjusted for average alcohol or tobacco consumption accordingly. p Values for the dose–effect relationships were assessed by including the continuous variable in the logistic regression model. Continuous variables, such as cumulative tobacco smoking, were analysed in categories; additional analyses were conducted to test for linear trend across categories by using discrete variables with equal increments among categories. The cut-offs for quartiles (Q1–Q4) and tertiles (T1–T3) were obtained from the distribution of controls.

Interactions between alcohol and tobacco were assessed by likelihood ratio test, comparing the fit of an unconditional regression model including terms for ever alcohol and tobacco consumption with the model including also an interaction term. Furthermore, the interaction was assessed for average daily alcohol and tobacco consumption categories (using tertiles of average alcohol-grams per day and four categories of average cigarette-equivalents per day) using ordinal terms and a cross-product of these terms. Attributable fractions were calculated using the Levin's formula for polytomous exposure level as described by Hanley [7].

Results

Detailed characteristics of the study subjects and tumours are presented in Table 1. The largest number of cases was from São Paolo and Goiania. The age and sex distribution as well as education levels were similar between cases and controls. Over three quarters of the study subjects were men.

Alcohol drinking

Alcohol drinkers had an increased risk of developing cancer, with adjusted odds ratios (ORs) ranging from 2.50 (95% confidence interval, CI: 1.91–3.26) for hypopharynx and larynx to 4.41 for oesophagus (95% CI: 2.41–8.07), and 4.62 for oral cavity and 4.63 for oropharynx (95% CI: 3.39–6.28). For all sites except for oesophagus, the increase in risk was bigger for current than for former drinkers. Dose–effect relationships were evident for alcohol quantity, drinking duration and cumulative alcohol consumption. A protective effect of quitting alcohol drinking was also observed for all the three sites (Table 2). The effect of

Table 1 Characteristics of subjects in the Latin America multicentre study

	Oral cavity + oropharynx (n = 1,030)		Hypopharynx + larynx (n = 997)		Oesophagus (n = 171)		Overlapping sites (n = 54)		All sites (n = 2,252)		Controls (n = 1,707)	
	n	%	n	%	n	%	n	%	n	%	n	%
Centre												
Cuba	0	0%	192	19%	0	0%	1	2%	193	9%	176	10%
Argentina, Buenos Aires	158	15%	113	11%	0	0%	38	70%	309	14%	207	12%
Brazil, Porto Alegre	115	11%	66	7%	0	0%	2	4%	183	8%	157	9%
Brazil, Rio de Janeiro	198	19%	215	22%	0	0%	3	6%	416	18%	249	15%
Brazil, Sao Paolo	313	30%	165	17%	0	0%	1	2%	479	21%	422	25%
Brazil, Pelotas	42	4%	66	7%	80	47%	9	17%	197	9%	240	14%
Brazil, Goiania	204	20%	180	18%	91	53%	0	0%	475	21%	256	15%
Age (years)												
<40	39	4%	13	1%	2	1%	1	2%	55	2%	97	6%
40–49	238	23%	162	16%	31	18%	9	17%	440	20%	340	20%
50–59	368	36%	320	32%	60	35%	21	39%	769	34%	554	32%
60–69	262	25%	330	33%	51	30%	16	30%	659	29%	460	27%
70–79	106	10%	157	16%	17	10%	7	13%	287	13%	222	13%
>79	17	2%	14	1%	10	6%	0	0%	41	2%	34	2%
Sex												
Male	849	82%	878	88%	139	81%	51	94%	1,917	85%	1,354	79%
Female	181	18%	118	12%	31	18%	3	6%	333	15%	353	21%
Education												
Illiterate	203	20%	205	21%	54	32%	12	22%	474	21%	301	18%
Primary education	697	68%	659	66%	105	61%	31	57%	1,492	66%	1,123	66%
Secondary education	106	10%	108	11%	11	6%	10	19%	235	10%	205	12%
University education	23	2%	24	2%	0	0%	1	2%	48	2%	76	4%
Fresh fruit consumption												
Not at all or less than once a week	168	16%	176	18%	36	21%	7	13%	387	17%	140	8%
Q1 (1–2 times per week)	247	24%	212	21%	51	30%	9	17%	519	23%	301	18%
Q2 (3–5 times per week)	261	25%	230	23%	45	26%	7	13%	543	24%	451	26%
Q3 (6–7 times per week)	242	23%	227	23%	32	19%	20	37%	521	23%	460	27%
Q4 (>7 times per week)	104	10%	141	14%	7	4%	9	17%	261	12%	352	21%
Cruciferous consumption												
Not at all or less than once a week	489	47%	448	45%	99	58%	36	67%	1,072	48%	685	40%
T1 (1 time per week)	206	20%	185	19%	30	18%	4	7%	425	19%	374	22%
T2 (2 times per week)	150	15%	110	11%	19	11%	7	13%	286	13%	242	14%
T3 (>2 times per week)	178	17%	246	25%	23	13%	5	9%	452	20%	405	24%

The missing values were the following: 1 for age among cases, 2 for sex among cases, 5 for education (3 among cases and 2 among controls), 24 for fruit consumption (21 among cases and 3 among controls), 18 for cruciferous consumption (17 among cases and 1 among controls)

alcohol drinking was apparently stronger for oesophagus than for head and neck cancers combined (all but oesophagus), especially for the highest alcohol consumption categories (data not shown).

Heterogeneity of the risk of ever-drinking effect for upper aerodigestive cancers was observed between centres (test for heterogeneity p value < 0.001), although this was explained by differences in alcohol quantities consumed in each centre (test for heterogeneity using OR per 10 g of ethanol as a continuous unit, p value $= 0.726$).

In the analysis of drinkers of different alcohol types, we compared the effect among pure drinkers. Only 45 cases and 29 controls reported drinking spirits only, so pure drinkers of spirits and aperitifs were combined. A very strong effect was observed for this category as compared to other categories (Table 2). To investigate whether this may

Table 2 Alcohol drinking and the risk of cancer of the upper aerodigestive tract by site

	Oral cavity + oropharynx			Hypopharynx + larynx			Oesophagus		
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*
Status									
Never-drinkers	73	442	1.00 (ref)	116	495	1.00 (ref)	23	174	1.00 (ref)
Ever-drinkers	957	1,089	4.62 (3.39–6.28)	881	1,212	2.50 (1.91–3.26)	148	322	4.41 (2.41–8.07)
Former drinkers	285	396	3.62 (2.58–5.06)	276	432	2.09 (1.55–2.82)	70	138	4.24 (2.26–7.94)
Current drinkers	672	693	5.26 (3.76–7.37)	605	780	2.78 (2.06–3.75)	78	184	4.10 (2.19–7.69)
Alcohol quantity (grams per day)									
Never-drinkers	73	442	1.00 (ref)	116	495	1.00 (ref)	23	174	1.00 (ref)
Q1 (0.1–8.6)	112	274	2.92 (2.02–4.20)	121	301	1.76 (1.26–2.45)	28	105	2.92 (1.42–6.03)
Q2 (8.61–24.8)	136	270	3.39 (2.34–4.92)	140	300	1.87 (1.35–2.59)	22	83	2.79 (1.31–5.97)
Q3 (24.81–68.8)	257	266	6.60 (4.58–9.53)	209	298	2.63 (1.9–3.62)	37	61	7.03 (3.34–14.83)
Q4 (>68.8)	447	268	10.95 (7.6–15.78)	404	302	4.52 (3.31–6.18)	58	71	9.28 (4.4–19.59)
OR-10 continuous			*1.07 (1.05–1.08)*			*1.05 (1.04–1.06)*			*1.06 (1.03–1.09)*
Duration (years)									
Never-drinkers	73	442	1.00 (ref)	116	495	1.00 (ref)	23	174	1.00 (ref)
1–15	58	130	2.64 (1.70–4.09)	57	132	1.98 (1.31–2.99)	8	39	2.14 (0.81–5.69)
16–30	312	399	4.27 (3.03–6.01)	229	428	2.21 (1.62–3.03)	57	136	4.29 (2.18–8.46)
31–40	309	293	5.79 (4.10–8.17)	260	337	2.6 (1.91–3.54)	36	74	4.61 (2.24–9.49)
≥41	273	256	5.65 (3.93–8.13)	328	304	2.8 (2.06–3.81)	44	71	5.74 (2.76–11.94)
OR-10 continuous			*1.41 (1.32–1.50)*			*1.22 (1.15–1.29)*			*1.41 (1.23–1.61)*
Cumulative alcohol consumption (gram-years)									
Never-drinkers	73	442	1.00 (ref)	116	495	1.00 (ref)	23	174	1.00 (ref)
Q1 (0.1–233.6)	109	277	2.74 (1.90–3.94)	118	300	1.84 (1.32–2.55)	23	111	2.26 (1.1–4.65)
Q2 (233.61–765)	137	276	3.64 (2.51–5.29)	126	301	1.78 (1.28–2.48)	25	78	3.33 (1.57–7.07)
Q3 (765.1–2,035.6)	238	262	6.16 (4.27–8.87)	194	299	2.35 (1.7–3.25)	37	66	6.36 (3.01–13.44)
Q4 (>2,035.6)	468	263	11.26 (7.83–16.20)	436	301	4.59 (3.37–6.24)	60	65	9.26 (4.46–19.23)
OR-1,000 continuous			*1.21 (1.17–1.26)*			*1.15 (1.11–1.19)*			*1.18 (1.08–1.29)*
Type of alcohol									
Never-drinkers	73	442	1.00 (ref)	116	495	1.00 (ref)	23	174	1.00 (ref)
Beer only	70	219	2.28 (1.49–3.49)	61	225	1.33 (0.87–2.03)	4	64	0.93 (0.27–3.26)
Wine only	42	65	2.92 (1.61–5.29)	33	66	1.76 (0.95–3.25)	2	10	1.75 (0.32–9.58)
Aperitif or spirits only	190	121	11.38 (7.36–17.59)	169	152	3.90 (2.68–5.69)	56	51	12.76 (5.37–30.32)
*Type of alcohol among ever-drinkers***									
Beer only (ref)	70	219	1.00 (ref)	61	225	1.00 (ref)	4	64	1.00 (ref)
Wine only	42	65	1.69 (0.77–3.71)	33	66	2.05 (0.90–4.67)	2	10	1.45 (0.18–11.77)
Aperitif or spirits only	190	121	3.99 (2.60–6.14)	169	152	2.73 (1.77–4.21)	56	51	12.99 (3.67–46.02)
*Years since quitting drinking****									
Current drinkers	669	692	1.00 (ref)	601	779	1.00 (ref)	77	184	1.00 (ref)
2–4	95	96	0.81 (0.57–1.14)	72	106	0.83 (0.58–1.18)	28	30	2.15 (1.10–4.21)
5–9	82	101	0.63 (0.45–0.90)	64	108	0.57 (0.40–0.82)	15	37	0.89 (0.43–1.85)
10–19	70	116	0.50 (0.35–0.71)	89	124	0.74 (0.54–1.04)	18	39	0.75 (0.36–1.55)
≥20	36	80	0.42 (0.26–0.66)	48	91	0.55 (0.36–0.83)	9	30	0.46 (0.19–1.16)
OR-10 continuous			*0.69 (0.59–0.80)*			*0.81 (0.71–0.92)*			*0.72 (0.54–0.96)*

Q1–Q4 quartiles, *OR-10 (1,000) continuous* OR for an increase in 10 (1,000) units on a continuous scale; * ORs were adjusted by sex, age, centre, education, tobacco pack-years, and fruit and cruciferous consumption; ** ORs for ever-drinkers were additionally adjusted for alcohol gram-years, *** ORs for years since quitting drinking were additionally adjusted for alcohol-grams per day

be due to differences in alcohol consumption between drinkers of different alcohol types, an analysis of drinkers only was conducted, with beer drinkers as a reference category. The strong effect was still observed for pure drinkers of spirits and aperitifs, and additional adjusting for drinking quantity or total alcohol consumption did not change the strength of associations (Table 2). The odds ratios for beer and wine drinking were similar, despite different case–control ratios in these two categories. This was not due to strong confounding from tobacco smoking (data not shown).

The associations were much weaker in never-smokers. The increase in risk observed for never-smoking ever-drinkers was negligible; however, the number of subjects was small (Table 4A) and the effect of alcohol alone was more pronounced for heavy drinkers (Table 5A)

Tobacco smoking

The history of tobacco smoking was associated with an increased risk of cancer for all the three sites, with ORs ranging from 3.14 for oesophagus (95% CI: 1.74–5.67), through 5.49 for oral cavity and oropharynx (95% CI: 4.06–7.41), up to 7.44 for hypopharynx and larynx (95% CI: 5.30–10.45; Table 3). The risks were consistently higher for current than former smokers. No heterogeneity of results as to the never-ever smoking effect was observed between centres (test for heterogeneity p value = 0.200; data not shown). A clear dose–effect relationship was observed for smoking duration for all sites, as well as for smoking frequency and cumulative consumption for head and neck cancers but not for oesophagus (Table 3). A clear protective effect of quitting smoking was observed for all the three subsites. The risk estimates for all head and neck sites combined were similar to those for all UADT sites and higher than those for oesophagus alone, e.g., ever-smokers had an OR of 6.23 (95% CI 4.92–7.90) for head and neck cancer as compared to 5.75 (CI: 4.60–7.20) for upper aerodigestive cancer and 3.14 (CI: 1.74–5.67) for cancer of the oesophagus. Elevated odds ratios for the use of cigarettes only were observed for all sites, with the highest risk for larynx cancer. Estimating the risk associated with smoking other tobacco products was difficult as a vast majority of individuals reported smoking cigarettes only (data not shown). The strength of associations between tobacco smoking and cancer risk was maintained in never-alcohol drinkers for cancers of the hypopharynx and larynx, but not for other sites (Table 4B).

Alcohol–tobacco interaction

A more than multiplicative interactive effect was observed between alcohol and tobacco use for oral cavity with oropharynx (LR test p value < 0.001) and for oesophagus (LR test p value = 0.066) (Table 5A). From 56.7% (hypopharynx with larynx) to 74.3% (oral cavity with oropharynx) of cases were attributable to the combined use of alcohol and tobacco (Table 5A). In an interaction analysis using average daily alcohol and tobacco consumption terms, the risk increased with increasing exposure to both alcohol and tobacco. Alcohol alone had an effect, and the odds ratios were higher for higher quantities of alcohol consumed (Table 5B).

Discussion

The carcinogenic effects of tobacco and alcohol have been recently evaluated by the International Agency for Research on Cancer, and both agents have been classified as carcinogenic to humans [2–4]. A causal association between alcohol and tobacco consumption, and cancers of the upper aerodigestive tract (UADT) was shown by many studies; however, the data on the role of these two carcinogens in developing countries are still quite limited. To date, the most extensively studied region in South America was Uruguay and the most frequently investigated site was oesophagus [5, 8–12]. A few studies have addressed the question in Brazil and/or Argentina [5, 13–17] and one in Cuba [18]; however, most of them were limited to the analysis of one UADT subsite only. To the best of our knowledge, our study is the largest and the most comprehensive study investigating the role of alcohol and tobacco in the development of upper aerodigestive cancers ever conducted in high-risk areas in South America.

Our risk estimates for alcohol drinking were relatively high for all sites. In an analysis of all UADT sites pooled together, alcohol alone had an effect, with the combined OR of 2.77 for the highest alcohol consumption category. This is higher than reported in European studies [19–22], and this is unlikely to be due to the choice of a different cut-off. However, a strong alcohol effect in never-smokers, especially for heavy drinkers, was observed in previous studies from the same area [5, 13, 14]. The fact that we did not observe a strong alcohol effect in never-smokers when analysing each UADT site separately is likely due to small numbers of cases in each category. The close-to-null effect of alcohol in never-smokers could also be a result of exposure misclassification which would mask a weak effect. We confirmed strong dose–effect relationships for alcohol quantity, drinking duration and total alcohol consumption, which were not evident in all of the previous South American studies.

Contrary to European studies [21–23], we observed a strong effect of aperitifs and spirits as compared to other types of alcohol. This difference may be due to different

Table 3 Tobacco smoking and the risk of cancer of the upper aerodigestive tract by site

	Oral cavity + oropharynx			Hypopharynx + larynx			Oesophagus		
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*
Status									
Never-smokers	64	468	1.00 (ref)	42	509	1.00 (ref)	18	158	1.00 (ref)
Ever-smokers	965	1,063	5.49 (4.06–7.41)	955	1,198	7.44 (5.30–10.45)	153	338	3.14 (1.74–5.67)
Former smokers	211	507	2.59 (1.85–3.61)	222	556	3.70 (2.56–5.34)	46	179	1.69 (0.88–3.24)
Current smokers	754	556	8.26 (5.91–11.53)	733	642	11.14 (7.72–16.08)	107	159	4.98 (2.59–9.57)
Duration (*years*)									
Never-smokers	64	468	1.00 (ref)	42	509	1.00 (ref)	18	158	1.00 (ref)
≤20	62	239	1.78 (1.18–2.67)	35	254	1.61 (0.99–2.62)	12	83	1.23 (0.54–2.82)
20 < x ≤ 30	172	213	4.93 (3.45–7.06)	123	234	5.38 (3.60–8.04)	25	58	3.20 (1.49–6.89)
30 < x ≤ 40	347	305	6.69 (4.79–9.35)	311	342	9.02 (6.26–13.01)	42	88	3.06 (1.53–6.10)
40 < x ≤ 50	232	200	8.24 (5.74–11.84)	282	239	10.48 (7.18–15.32)	42	70	4.07 (2.04–8.12)
>50	146	97	11.02 (7.15–17.01)	199	120	14.92 (9.70–22.96)	32	39	5.5 (2.49–12.17)
OR-10 continuous			*1.58 (1.48–1.69)*			*1.61 (0.99–2.62)*			*1.23 (0.54–2.82)*
Frequency (*cigarette-equivalents/day*)									
Never-smokers	64	468	1.00 (ref)	42	509	1.00 (ref)	18	158	1.00 (ref)
≤10	176	329	3.45 (2.45–4.85)	158	353	4.60 (3.15–6.73)	56	114	3.14 (1.66–5.95)
10 < x ≤ 20	437	425	6.85 (4.96–9.47)	379	488	7.83 (5.47–11.21)	57	110	3.5 (1.82–6.73)
20 < x ≤ 30	180	124	8.41 (5.74–12.33)	190	145	11.76 (7.87–17.58)	20	41	3.42 (1.48–7.94)
>30	166	176	5.08 (3.49–7.39)	223	203	9.27 (6.28–13.67)	20	73	1.81 (0.83–3.98)
OR-10 continuous			*1.30 (1.22–1.38)*			*4.60 (3.15–6.73)*			*3.14 (1.66–5.95)*
Total consumption (*pack-years*)									
Never-smokers	64	468	1.00 (ref)	42	509	1.00 (ref)	18	158	1.00 (ref)
Q1 (0–12.5)	105	280	2.60 (1.81-3.75)	80	297	3.09 (2.05–4.66)	30	99	2.19 (1.10–4.39)
Q2 (12.51–27)	211	276	5.35 (3.79–7.55)	175	300	6.46 (4.41–9.48)	46	82	4.26 (2.16–8.42)
Q3 (27.1–44.5)	303	255	7.78 (5.52–10.96)	254	296	8.83 (6.08–12.81)	38	61	4.12 (2.00–8.49)
Q4 (> 44.5)	340	243	8.34 (5.89–11.8)	441	296	12.44 (8.6–17.98)	39	96	2.75 (1.35–5.63)
OR-10 continuous			*1.18 (1.14–1.22)*			*1.21 (1.17–1.25)*			*1.04 (0.98–1.10)*
*Years since quitting***									
Current smokers	753	556	1.00 (ref)	730	642	1.00 (ref)	107	159	1.00 (ref)
2–4	66	85	0.61 (0.42–0.88)	63	94	0.63 (0.44–0.90)	9	31	0.42 (0.18–0.99)
5–9	53	84	0.42 (0.28–0.63)	56	92	0.46 (0.31–0.67)	7	31	0.32 (0.13–0.81)
10–19	42	142	0.21 (0.14–0.31)	56	159	0.29 (0.20–0.41)	17	52	0.45 (0.23–0.89)
≥20	47	194	0.19 (0.13–0.27)	47	209	0.16 (0.11–0.23)	12	65	0.23 (0.11–0.49)
OR continuous unit			*0.56 (0.50–0.63)*			*0.53 (0.47–0.60)*			*0.62 (0.49–0.80)*

Q1–Q4 quartiles; *OR-10 continuous* OR for an increase in 10 units on a continuous scale; * ORs were adjusted by sex, age, centre, education, alcohol gram-years, as well as for fruit and cruciferous consumption; ** ORs were additionally adjusted for cigarette-equivalents per day

drinking patterns and/or different types of alcoholic drinks (different composition and/or alcohol concentration, possible impurities etc.) that are consumed in Latin America as compared to Europe. Three other big studies conducted in the same areas of South America also detected a stronger effect of aperitifs and spirits as compared to other types of beverages. Castellsague et al. reported a strong effect for oesophageal cancer in Brazil, Paraguay, Uruguay and Argentina [5], Garrote et al. for oral and oropharynx cancer in Cuba [18], and Schlecht et al. for head and neck sites in Brazil [17]. The lack of effect reported in other two studies [13, 14] may be due to low power. We might hypothesise that a stronger effect of aperitifs and spirits found in our study could also be a result of reduced misclassification in self-reports of the predominant type of alcoholic beverage with respect to other less regularly consumed types. However, no evidence for a reduced misclassification of self-reports concerning the frequently consumed beverages has ever been described. Moreover, we have found only an over twofold increase in risk associated with the

Table 4 The effect of alcohol drinking or tobacco smoking on the risk of cancer of the upper aerodigestive tract in never-users of the other habit

	Oral cavity + oropharynx ($n = 64$)			Hypopharynx + larynx ($n = 42$)			Oesophagus ($n = 18$)		
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*
A. Alcohol in never-smokers									
Status									
Never-drinkers	33	247	1.00 (ref)	18	268	1.00 (ref)	11	90	1.00 (ref)
Ever-drinkers	31	221	1.12 (0.59–2.12)	24	241	1.29 (0.62–2.67)	7	68	0.94 (0.26–3.52)
Former drinkers	6	71	0.89 (0.33–2.44)	7	74	1.39 (0.52–3.70)	4	28	1.05 (0.23–4.79)
Current drinkers	25	150	1.22 (0.45–3.34)	17	167	1.19 (0.45–3.19)	3	40	0.76 (0.17–3.47)
	Oral cavity + oropharynx ($n = 73$)			Hypopharynx + larynx ($n = 116$)			Oesophagus ($n = 23$)		
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*
B. Tobacco smoking in never-drinkers									
Status									
Never-smokers	33	247	1.00 (ref)	18	268	1.00 (ref)	11	90	1.00 (ref)
Ever-smokers	40	195	1.68 (0.98–2.89)	98	227	6.97 (3.89–12.47)	12	84	1.42 (0.51–3.96)
Former smokers	16	101	1.42 (0.71–2.82)	25	111	3.84 (1.92–7.67)	8	42	1.56 (0.48–5.07)
Current smokers	24	94	2.05 (1.03–4.07)	73	116	9.87 (4.94–19.73)	4	42	1.11 (0.34–3.61)

* ORs were adjusted by sex, age, centre, education, as well as fruit and cruciferous consumption

consumption of aperitifs and spirits in the centre with the highest prevalence of strong alcohol drinkers among controls (La Havana, Cuba, 34%), whereas the highest over 15-fold increase in risk has been found in a centre with a relatively low prevalence of strong alcohol drinkers among controls (Porto Alegre, Brazil, 13%) (data not shown).

With regard to smoking history, we found that ever tobacco use increased the risk three- to eightfold, depending on the site. Our results are comparable with those of a review of 128 tobacco studies from all over the world that were published by June 2002, which reported average relative risks for UADT sites ranging from 2.0 to 10.0, with the weakest effect for oesophagus [24], and also with those of the three studies conducted in the same areas of South America as ours [5, 13, 14], which were not included in the above-mentioned review.

A dose–effect relationship between different smoking parameters and UADT cancer risk has been shown by many studies [4] but the evidence from Latin America was not very consistent. However, in a multicentre study of oesophageal cancer in four countries of Latin America, Castellsague et al. have found dose–effect relationships for smoking duration, quantity and cumulative consumption, with the duration showing the strongest effect [5]. In line with these results, we found a clear dose–effect relationship between smoking duration and the risk of cancer for all sites, as well as between average tobacco amount and cumulative consumption for all sites but oesophagus. The latter could be explained by a linear correlation between alcohol and tobacco consumption.

We have also found that quitting alcohol drinking or tobacco smoking decreases the risk of UADT cancers. Former users of alcohol or tobacco were at lower risk than current users, with an independent protective effect of quitting either of the two habits. A protective effect of smoking cessation has already been reported by others for head and neck cancers in Brazil [16] and for oesophageal cancer in Argentina, Brazil, Paraguay and Uruguay [5].

We have confirmed a more than multiplicative effect of alcohol and tobacco on the upper aerodigestive cancers that was reported by some of the other studies [15]. Alcohol alone had an effect but, with the exception of tobacco smoking in hypopharynx/larynx cancer patients, the associations between alcohol or tobacco consumption and the cancer risk were much weaker in never-users of the other agent. Schlecht et al., in a study of head and neck cancer in Brazil, have also found a more than multiplicative effect of alcohol and tobacco use but, contrary to our results, the effect of alcohol alone did not increase with alcohol consumption [15]. However, in his study, patients suffering form alcohol- or tobacco-related diseases were not excluded from the control group. Only 3–6% of cases in our study were attributable to the use of alcohol alone and 7–26% to the use of tobacco alone, whereas between 57% (hypopharynx with larynx) and 74% (oral cavity with oropharynx) of cases were attributable to the combined use of alcohol and tobacco. The attributable fractions reported in two other studies from South America, both on oesophageal cancer, were higher: 97.2% for a combined tobacco and alcohol use in Uruguay [8], and 90% for ever-

Table 5 Tobacco–alcohol interaction and the risk of cancers of the upper aerodigestive tract

	Oral cancer + oropharynx				Hypopharynx + larynx				Oesophagus				All			
	Cases	Controls	OR (95% CI)*	AF	Cases	Controls	OR (95% CI)*	AF	Cases	Controls	OR (95% CI)*	AF	Cases	Controls	OR (95% CI)*	AF
A. Ever alcohol and tobacco use by site																
Tobacco/alcohol																
No/no	33	247	1.00 (ref)		18	268	1.00 (ref)		11	90	1.00 (ref)		62	268	1.00 (ref)	
No/yes	31	221	1.21 (0.69–2.10)	2.6%	24	241	1.67 (0.87–3.21)	5.6%	7	68	1.52 (0.50–4,64)	5.9%	64	241	1.34 (0.89–2.02)	3.5%
Yes/no	40	195	1.66 (0.98–2.78)	6.8%	98	227	6.08 (3.52–10.49)	26.2%	12	84	1.25 (0.49–3.21)	3.6%	154	227	3.06 (2.14–4.37)	16.6%
Yes/yes	926	868	9.88 (6.47–15.07)	74.3%	857	971	13.17 (7.87–22.04)	56.7%	141	254	6.07 (2.68–13.76)	63.6%	1,972	971	10.17 (7.37–14.02)	64.6%
Total				83.7%				88.5%				76.0%				84.7%
LR test *p* value			<0.001				0.461				0.066				<0.001	

Average alcohol-grams per day	Average cigarette-equivalents per day							
	Never		≤15		>15, ≤30		>30	
	Cases/controls	OR (95% CI)*	Cases/controls	OR (95% CI)*	Cases/controls	OR (95% CI)*	Cases/controls	OR (95% CI)*
B. Alcohol and tobacco average daily consumption, all UADT sites combined								
Never	62/268	1.00 (ref)	65/110	2.39 (1.56–3.68)	65/79	4.33 (2.75–6.82)	23/37	3.52 (1.9–6.52)
T1 (0.001–13.53)	27/126	1.14 (0.68–1.92)	139/125	5.73 (3.85–8.52)	138/114	7.24 (4.83–10.85)	46/35	7.01 (4.04–12.16)
T2 (13.531–46.61)	16/59	1.59 (0.83–3.04)	149/129	6.85 (4.59–10.23)	232/156	9.69 (6.6–14.22)	91/52	10.52 (6.53–16.94)
T3 (>46.61)	21/51	2.77 (1.50–5.12)	276/115	14.23 (9.6–21.1)	614/153	25.72 (17.67–37.45)	262/79	20.6 (13.59–31.22)

AF attributable fraction, *LR* likelihood ratio; * ORs were adjusted for age, sex, centre, education as well as for fresh fruit and cruciferous consumption

T1–T3 tertiles; * ORs were adjusted for age, sex, centre and education, as well as for fruit and cruciferous consumption

use of either of the two or both in Paraguay/Uruguay/Brazil/Argentina [5]. This difference could not be explained by the fact that the previous studies provided estimates for males only or separately for males and females. Our analysis combined the two sexes together due to relatively small numbers of women participating in the study. Restricting our analysis to males increased the attributable fractions for cancers of the hypopharynx and larynx (1%) as well as oesophageal cancers (12%) (data not shown) but even then they did not reach the 90% and over that was reported by Castellsague et al. for oesophagus.

Overall, our results confirm an important role of alcohol and tobacco in the aetiology of UADT cancers in high-risk areas in South America. Other putative risk factors, like HPV infections for oral cancer or mate consumption for oesophageal cancer, have been proposed as important determinants of the UADT cancer incidence in this area. However, the HPV infection in our study cohort was very low and less than 5% overall when measured by either HPV16 serology for E6 or E7 antibodies or HPV16 E7 DNA presence in tumour tissue [25]. In this study population at least, we show that a vast majority of cases is due to a joint effect of alcohol and tobacco and could thus be prevented by reducing exposure to either and preferably both of these two agents.

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