Cancer Therapy Vol 2, 99-106, 2004

Comparison between hypopharyngeal and laryngeal cancers: I-role of tobacco smoking and alcohol drinking

Research Article

Eduardo De Stefani[1*], Paul Brennan[2], Paolo Boffetta[2,3], Alvaro L. Ronco[1], Hugo Deneo-Pellegrini[1], Pelayo Correa[4], Fernando Oreggia[5] and María Mendilaharsu[1]

[1]Registro Nacional de Cáncer, Montevideo, Uruguay.
[2]Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France.
[3]Division of Clinical Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany.
[4]Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana, USA.
[5]Academia Nacional de Medicina, Montevideo, Uruguay.

***Correspondence:** Dr. Eduardo De Stefani, Avenida Brasil 3080 dep. 402, Montevideo, Uruguay; Tel.: (598) 2 708 23 14; Fax: (598) 2 402 08 10; E-Mail: estefani@adinet.com.uy

Key Words: hypopharyngeal and laryngeal cancers, tobacco smoking and alcohol drinking,

Abbreviations: Age-standardized (World Population) incidence rates, (ASR's); food frequency questionnaire, (FFQ); International Classification of Diseases for Oncology, (ICD-O); odds ratios, (OR's); tobacco-specific nitrosamines, (TSNA)

Received: 20 April 2004; Accepted: 30 April 2004; electronically published: May 2004

Summary

In the period 1997-2003, a case-control study on risk factors for hypopharyngeal and laryngeal cancers was conducted in Montevideo, Uruguay. The study included 320 cases and 640 controls and was restricted to males. The main objectives of the study was to compare the relative risks by tumor site for tobacco smoking, alcohol drinking and diet. In this first report, the role of smoking and drinking will be examined by tumor site. Tobacco smoking was a strong risk factor for hypopharyngeal and laryngeal cancers. Nevertheless, odds ratios (OR's) for laryngeal carcinomas were much higher in comparison with hypopharyngeal lesions. On the contrary, alcohol drinking displayed a stronger effect among cancer of the hypopharynx in comparison with larynx carcinomas. The differences by tumor site were statistically significant. These findings suggest that, concerning the effect of tobacco and alcohol, hypopharyngeal and laryngeal cancers could be different epidemiologic entities.

I. Introduction

Cancers of the hypopharynx and larynx has been analized as a sigle entity in several studies (Tuyns et al, 1988; Cattaruzza et al, 1996). According to the International Classification of Diseases for Oncology (ICD-O) (WHO, 1976), hypopharyngeal lesions includes tumors of sinus pyriform, postcricoid region, aryepiglottic fold, posterior wall of hypopharynx and cancers of hypopharynx not elsewhere classified. Accordind to the same classification, laryngeal tumors are divided in glottis lesions, supraglottis tumors, subglottic tumors and lesions of larynx not elsewhere classified (WHO, 1976). Previous studies divided laryngeal cancers in extrinsic and intrinsic (Wynder et al, 1976; Tuyns et al, 1988). Most of the tumors (99.5 %) arising in both sites are squamous cell carcinomas (Austin and Reynolds, 1996).

Hypopharyngeal and laryngeal cancers are very frequent among Uruguayan men (Parkin et al, 1997). According to international comparisons between registries in the Americas, both sites are in first place, followed by Blacks in United States (Parkin et al, 1997). Age-standardized (World Population) incidence rates (ASR's) were of 3.3 per 100,000 men for hypopharyngeal carcinomas, whereas the rate for laryngeal cancer were of 12.2 per 100, 000 men (Parkin et al, 1997).

Tobacco smoking and alcohol drinking are the major risk factors for both sites (Wynder et al, 1976; Tuyns et al, 1988; Austin and Reynolds, 1996; Cattaruzza et al, 1996). Also diet has received particular attention in recent studies (Estève et al, 1996; Riboli et al, 1996; World Cancer Research Fund, 1997). Therefore, we decided to conduct a case-control study in order to compare the risks for smoking and drinking by tumor site in the high-risk population of Uruguay. The a priori hypothesis was that

hypopharyngeal and laryngeal are different epidemiological entities. The role of diet will be analyzed in a companion report.

II. Materials and methods

A. Selection of cases

In the time period 1997-2003 all newly diagnosed and microscopically verified squamous cell carcinomas of the hypopharynx and larynx which occurred in men, were considered eligible for this study. Three-hundred and twenty eight (328) of cases were identified in the four major hospitals in Montevideo. Eight patients were excluded from the cases due to phonation problems, leaving a final number of 320 patients (response rate 97.5 %). After careful endoscopic examination by one of the authors (F.O.), the cases we classified as follows: A. hypopharyngeal carcinomas (85 cases, 26.6 %) and B. laryngeal carcinomas (235, 73.4 %). Most of hypopharyngeal tumors were located in the sinus pyriform (78 patients), whereas laryngeal cancers were distributed as follows: glottic lesions (49 cases), supraglottis lesions (67 cases) and transglottis lesions (119 cases). The term transglottis refers to lesions which involved both supraglottis and glottis.

B. Selection of controls

In the same time period and in the same hospitals, 1235 men which were hospitalized for diseases not related with tobacco smoking, alcohol drinking and without recent changes in their diets were considered eligibles for the study. Thirty five patients refused the interview, leaving a final number of 1200 potential controls (response rate 97.2 %). From this pool of patients, 640 men were frequency matched with cases on age (in ten year intervals) and residence (Montevideo, other counties). The resulting case-control ratio was 1:2. Controls presented the following diseases: abdominal hernia (146 patients, 22.8 %), eye disorders (135, 21.1 %), fractures (70, 10.9 %), injuries (62, 9.7 %), skin diseases (56, 8.8 %), acute appendicitis (52, 8.1 %), hydatid cyst (32, 5.0 %), varicose veins (32, 5.0 %), urinary stones (27, 4.2 %), blood disorders (19, 3.0 %) and osteoarticular diseases (9, 1.4 %).

C. Interviews and questionnaire

Both series of participants (cases and controls) were interviewed in the hospitals by two trained social workers. The interviews were performed shortly after admittance to the hospitals. No proxy interviews were accepted. The patients were administered with a questionnaire which included the following sections: (A) sociodemographics, (B) a complete occupational section based in job titles and its duration, (C) history of cancer among first degree relatives, (D) self-reported height and weigh five years before the date of the interview, (E) a complete history of tobacco smoking (age at start, age at quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation), (F) a complete history of alcohol drinking (age at star, age of quit, number of glasses drunked per day; this was repeated for the main alcoholic beverages consumed in Uruguay: beer, wine and hard liquor), (G) a complete history of maté drinking (maté is the folk name of a local tea prepared by infusion of the herb Ilex paraguariensis; this beverage is usually drunk hot or very hot) and (H) a food frequency questionnaire (FFQ) on 64 food items. This FFQ is considered as representative of the usual diet of Uruguayan population and, although it was not validated, it was tested for reproducibility with reasonably good results. Furthermore, the FFQ allowed the consumption of total energy. All queries on foods referred to the consumption two years before the date of the interview or before the date of the first symptom.

D. Definitions of tobacco and alcohol variables

Patients who smoked less than 100 cigarettes in their lifetime were considered never smokers. Smokers who used cigarettes at the time of the interview or who had quitted one year before the interview were defined as current smokers. The remaining patients were defined as former smokers. Regarding type of tobacco, patients were divided into pure smokers of blond or black tobacco when they had smoked each type of tobacco during more than 85 % of their lifetimes. The remaining patients were defined as mixed smokers. Patients who had drunk occasionally or less than monthly were considered never drinkers. Participants who drunk alcohol beverages at the date of the interview or who quitted one year before the interview were defined as current drinkers. The remaining patients were included in the category of former drinkers. Binge drinkers, that is periodic heavy drinkers, were not identified according to the questionnaire. The amount of alcohol drunk was expressed as mililiters of ethanol per day, according to the following calculations: beer-6 % of ethanol per liter, wine-12 % of ethanol per liter and hard liquor-46 % of ethanol per liter. Among types of wine, red wine is almost exclusively consumed by Uruguayan population, in particular the low socioeconomical population (Comisión Honoraria de Lucha contra el Cáncer, 1993). Regarding hard liquor, Uruguayan population consumes grappa (hard liquor derived fron grapes) and caña (hard liquor from sugarcane) (Comisión Honoraria de Lucha contra el Cáncer, 1993).

E. Statistical analysis

Relative risk, approximated by the odds ratio (OR) and corresponding ninety five per cent confidence intervals (95 % CI) were estimated by unconditional multiple logistic regression (Breslow and Day, 1980). Comparisons between hypopharyngeal and laryngeal cancers were carried out using multinomial (polytomous) regression (Hosmer and Lemeshow, 1989; Rothman and Greenland, 1998). Comparisons between hypopharyngeal and laryngeal cancers were carried out using multinomial (polytomous) regression (Hosmer and Lemeshow, 1989; Rothman and Greenland, 1998). OR's for tobacco smoking variables were obtained after fitting the following model: age (categorical, 6 strata), residence (ordinal, 2 strata), urban/rural status (ordinal, 2 strata), education (categorical, 3 strata), body mass index (categorical, 4 strata) and alcohol drinking (categorical, 5 strata). The model fitted for alcohol variables was similar, replacing alcohol drinking by tobacco smoking (pack years, categorical, 5 strata).

Test for trend were performed after entering categorical variables as ordinal (continuous) in the same model. Departure from the multiplicative model was determined by assessing the likelihood ratio test statistic. An alpha of 0.05 was used as the indicator of statistical significance and, accordingly 95 % Ci s were reported. All Ps were derived from two-sided statistical tests. All the calculations were done with the STATA programme (Stata Reference Manual, 1999).

III. Results

Distribution of cases and controls by sociodemographic variables, body mass index and total calories are shown in **Table 1**. As result of the frequency matched design, age, residence and urban/rural status were rather similar. Also education and monthly income were similar. High body mass index was associated with a

Table 1. Distribution of controls and cases by sociodemographic variables and selected risk factors.

		Cases		Controls		
Variable	**Category**	**Nº**	**%**	**Nº**	**%**	**OR 95 % CI**
Age (years)	30-39	2	0.6	4	0.6	
	40-49	31	9.7	66	10.3	
	50-59	97	30.3	187	29.2	
	60-69	115	35.9	233	36.4	
	70-79	65	20.3	130	20.3	
	80-89	10	3.1	20	3.1	Not applicable
Residence	Montevideo	103	32.2	248	38.7	
	Other counties	217	67.8	392	61.3	Not applicable
Urban/rural	Urban	251	78.4	493	77.0	
	Rural	69	21.6	147	23.0	Not applicable
Education (yrs)	0-2	87	27.2	168	26.3	1.0
	3-5	123	38.4	216	33.7	1.1 0.7-1.6
	6+	110	34.4	256	40.0	0.9 0.6-1.3
Income (Dollars)	<=142	182	38.1	250	39.0	1.0
	143+	130	40.6	241	37.7	1.1 0.8-1.6
	Missing	68	21.3	149	23.3	- -
Body mass index	<=23.0	125	39.1	160	25.0	1.0
	23.1-24.9	97	30.3	162	25.3	0.8 0.5-1.1
	25.0-27.2	56	17.5	156	24.4	0.4 0.3-0.6
	27.3+	42	13.1	162	25.3	0.3 0.2-0.5
Total energy	<=1835	39	12.2	250	25.0	1.0
	1836-2164	54	16.9	250	25.0	1.3 0.8-2.0
	2165-2580	88	27.5	250	25.0	2.2 1.4-3.5
	2581+	139	43.4	250	25.0	3.5 2.3-5.4
Nº patients		320	100.0	640	100.0	

1-Education, income, body mass index and total calories are adjusted for each other.

significant reduction in risk (OR 0.3, 95 % CI 0.2-0.5). On the contrary, cases consumed significant higher amounts of energy compared with controls (OR 3.6, 95 % CI 2.3-5.5). It should be taken into account that this estimation includes alcohol energy plus non-alcoholic sources of energy.

Odds ratios of hypopharyngeal and laryngeal carcinomas for tobacco smoking are shown in **Table 2**. Although the smoking pattern was characterized by higher risks among laryngeal cancers compared with hypopharyngeal carcinomas, the differences between both sites were non significant. Current smokers were associated with an increased risk among laryngeal carcinomas (OR 10.7, 95 % CI 4.3-26.4), whereas the same category of smokers displayed an OR of 6.7 (95 % CI 1.5-30.9, p-value for heterogeneity=0.96). Ex-smokers showed a higher reduction in risk among hypopharyngeal cancers (OR 3.2, 95 % CI 0.6-15.6) compared with laryngeal carcinomas (OR 6.2, 95 % CI 2.5-15.7). Variables which measured the smoking intensity (number of cigarettes/day and number of cigarettes/day among current smokers) were associated with much higher increase in risk among laryngeal tumors compared with hypopharyngeal carcinomas (p-value for heterogeneity=0.12). The same fact was observed for variables which measured smoking duration (years of smoking and years since quit). It should be pointed out that smoking intensity was associated with higher risks compared with smoking duration. This was observed both for hypopharyngeal and laryngeal carcinomas. Cumulative exposure to tobacco smoking (pack years) was associated with an elevated risk in laryngeal carcinomas (OR for heavy smokers 21.3, 95 % CI 8.4-54.3). On the other hand, hypopharyngeal cancers displayed less impressive risk (OR for heavy smokers 9.2, 95 % CI 1.9-44.2). The differences between both locations were close to statistical significance (p-value for heterogeneity=0.07). The effect of type of tobacco yielded non-significant results. More precisely, smokers of black tobacco were associated with a modest increase in risk, more evident in carcinomas of the hypoharynx (reference category: smokers of blond tobacco). On the other hand, smokers of hand-rolled cigarettes were associated with a significant increase of risk of 1.9 (95 % CI 1.3-2.8) among carcinomas of the larynx (reference category: smokers of manufactured cigarettes). The effect of hand-rolling was less marked and not formally significant in squamous cell carcinomas of the hypopharynx. Lifelong users of filter cigarettes were associated with a reduction in risk of 0.6 in both sites and the differences were not significant. Finally, inhalers displayed an increase in risk in hypopharynx and larynx, being the effect higher in laryngeal carcinomas.

Odds ratios of hypopharyngeal and laryngeal carcinomas for alcohol drinking variable are shown in **Table 3**. Current drinkers displayed an OR of 6.0 (95 % CI 2.0-18.0) for hypoharyngeal cancers, whereas the risk

Table 2. Odds ratios of hypopharyngeal and laryngeal cancers for tobacco smoking variables (1)

	Hypopharynx			Larynx	
Variable	**Controls**	**Cases**	**OR 95 % CI**	**Cases**	**OR 95 % CI**
Smoking status					
Never smokers	132	2	1.0	6	1.0
Former smokers	193	18	3.2 0.6-15.6	67	6.2 2.5-15.7
Current smokers	315	65	6.7 1.5-30.9	162	10.7 4.3-26.4
Ever smokers	508	83	5.4 1.2-24.5	229	8.7 3.6-21.2
	p-value for trend		0.0006		<0.0001
	Heterogeneity		0.96		
Number of cigarettes/day					
Never smokers	132	2	1.0	6	1.0
1-9	92	5	1.9 0.3-11.1	7	1.8 0.5-5.7
10-19	153	9	1.7 0.3-8.9	29	3.7 1.4-9.8
20-29	133	33	7.1 1.5-33.8	78	12.5 4.9-31.9
30+	130	36	7.7 1.6-36.8	115	19.3 7.6-49.4
	p-value for trend		<0.0001		<0.0001
	Heterogeneity		0.12		
Years smoked					
Never smokers	132	2	1.0	6	1.0
1-29	96	9	2.6 0.5-13.9	23	4.5 1.7-12.3
30-39	118	19	4.0 0.8-19.9	50	7.4 2.8-19.0
40-49	169	34	5.3 1.1-25.7	75	7.8 3.1-19.7
50+	125	21	5.9 1.2-29.5	81	11.6 4.6-29.5
	p-value for trend		0.009		<0.0001
	Heterogeneity		0.51		
Years since quit					
Current smokers	315	65	1.0	162	1.0
1-9	80	13	0.75 0.37-1.49	45	0.98 0.63-1.54
10-19	64	2	0.19 0.04-0.82	11	0.34 0.17-0.69
20+	49	3	0.43 0.12-1.55	11	0.43 0.20-0.90
Never smokers	132	2	0.15 0.03-0.73	6	0.10 0.04-0.25
	p-value for trend		0.0009		<0.0001
	Heterogeneity		0.93		
Pack years					
Never smokers	132	2	1.0	6	1.0
1-26	183	8	1.6 0.3-8.3	17	2.0 0.7-5.5
27-45	130	25	5.4 1.1-25.6	50	7.1 2.8-18.1
46-67	108	24	6.9 1.4-33.8	70	12.8 5.0-32.6
68+	87	26	9.2 1.9-44.2	92	21.3 8.4-54.3
	p-value for trend		<0.0001		<0.0001
	Heterogeneity		0.07		
Type of tobacco					
Blond	375	55	1.0	157	1.0
Black	133	28	1.4 0.8-2.4	72	1.2 0.8-1.7
	Heterogeneity		0.51		
Type of cigarette					
Manufactured	246	29	1.0	74	1.0
Hand-rolled	160	54	1.6 0.9-2.8	155	1.9 1.3-2.8
	Heterogeneity		0.55		
Filter use					
Plain	248	54	1.0	129	1.0
Mixed	195	21	0.47 0.26-0.84	83	0.84 0.58-1.21
Filter	65	8	0.61 0.25-1.50	17	0.67 0.35-1.28
Never smokers	132	2	0.17 0.04-0.77	6	0.13 0.05-0.31
	p-value for trend		0.001		<0.0001
	Heterogeneity		0.62		

Inhalation				
Never smokers	132 2	1.0	6	1.0
No	107 7	1.8 0.3-9.6	18	2.7 0.9-7.2
Yes	401 76	4.9 1.1-21.6	211	8.1 3.4-19.3
	p-value for trend	0.007		<0.0001
	Heterogeneity	0.95		

1-Adjusted for age (categorical), residence, urban/rural status, education (categorical), body mass index (categorical), and total ml. of ethanol of alcohol drinking (categorical).

Table 3. Odds ratios (and 95 % CI) of hypopharyngeal and laryngeal cancers for alcohol drinking

		Hypopharynx	**Larynx**	
Variable	**Controls Cases**	**OR 95 % CI**	**Cases**	**OR 95 % CI**
Alcohol status (1)				
Never drinkers	191 4	1.0	32	1.0
Former drinkers	88 15	5.8 1.7-19.3	44	1.8 1.0-3.3
Current drinkers	361 66	6.0 2.0-18.0	159	1.6 0.9-2.5
Ever drinkers	449 81	6.0 2.0-17.7	203	1.6 1.0-2.6
	p-value for trend	0.002		0.15
	Heterogeneity	0.02		
Beer (2)				
Beer abstainers	560 75	1.0	205	1.0
1-60	45 8	0.8 0.3-1.9	14	0.6 0.3-1.2
61+	35 2	0.2 0.1-1.1	16	0.8 0.4-1.6
	p-value for trend	0.08		0.26
	Heterogeneity	0.31		
Red wine (3)				
Wine abstainers	234 9	1.0	44	1.0
1-60	212 20	2.3 0.9-5.5	45	0.9 0.5-1.6
61-120	104 29	5.2 2.2-12.4	80	2.8 1.7-4.7
121+	90 27	4.5 1.9-10.8	66	2.3 1.4-3.9
	p-value for trend	0.0001		<0.0001
	Heterogeneity	0.35		
Hard liquor (4)				
Liquor abstainers	468 45	1.0	145	1.0
1-60	102 12	0.9 0.4-1.9	35	0.9 0.5-1.4
61-120	31 10	2.2 0.9-5.2	24	1.5 0.8-2.8
121+	39 18	3.3 1.6-6.8	31	1.5 0.8-2.6
	p-value for trend	0.0008		0.14
	Heterogeneity	0.03		
Total alcohol (1)				
Never drinkers	191 4	1.0	32	1.0
1-60	175 10	2.3 0.7-8.1	31	0.8 0.4-1.5
61-120	116 23	7.6 2.3-24.4	45	1.5 0.8-2.7
121-240	88 17	5.6 1.7-18.6	68	2.4 1.4-4.2
241+	70 31	12.8 4.0-41.2	59	2.5 1.4-4.5
	p-value for trend	<0.0001		<0.0001
	Heterogeneity	0.03		
Years of drinking (1)				
Never drinkers	191 4	1.0	32	1.0
1-29	107 17	5.1 1.5-17.4	36	1.5 0.8-2.9
30-39	131 19	3.9 1.2-12.9	51	1.4 0.8-2.5
40-49	127 27	8.2 2.5-26.5	66	1.9 1.1-3.4
50+	84 18	7.9 2.3-27.8	50	1.6 0.9-3.0
	p-value for trend	0.0005		0.06
	Heterogeneity	0.02		
Alcohol cessation (1)				
Current drinkers	361 66	1.0	159	1.0

1-4	34 8	1.35 0.57-3.22	27	1.94 1.06-3.57
5-9	19 4	1.30 0.40-4.30	9	1.19 0.48-2.94
10+	35 3	0.43 0.12-1.53	8	0.47 0.20-1.13
Never drinkers	191 4	0.16 0.05-0.49	32	0.64 0.39-1.04
	p-value for trend	0.0007		0.04
	Heterogeneity	0.03		
Alcohol years (1)				
Never drinkers	191 4	1.0	32	1.0
1-37	159 3	0.7 0.1-3.6	21	0.6 0.3-1.2
38-80	118 24	7.7 2.4-24.9	43	1.4 0.8-2.6
81-145	94 26	8.8 2.8-28.4	62	2.2 1.2-3.8
146+	78 28	10.8 3.3-35.0	77	2.8 1.6-4.9
	p-value for trend	<0.0001		<0.0001
	Heterogeneity	0.03		
Alcohol pattern (1)				
Never drinkers	191 4	1.0	32	1.0
Pure beer	7 1	4.3 0.4-49.0	1	0.5 0.1-4.8
Pure wine	233 37	5.6 1.8-17.1	96	1.6 0.9-2.7
Pure liquor	31 4	4.8 1.0-22.0	10	1.2 0.5-2.9
Mixed drinkers	178 39	6.9 2.2-21.3	96	1.7 1.0-2.9
	p-value for trend	0.001		0.06
	Heterogeneity	0.05		

1-Adjusted for age (categorical), residence, urban/rural status, education (categorical), body mass index (categorical), and tobacco smoking (pack years categorical).
2-Adjusted for age (categorical), residence, urban/rural status, education (categorical), body mass index (categorical), tobacco smoking (pack years categorical), wine (categorical) and hard liquor (categorical).
3-Adjusted for age (categorical), residence, urban/rural status, education (categorical), body mass index (categorical), tobacco smoking (pack years categorical), beer (categorical) and hard liquor (categorical).
4-Adjusted for age (categorical), residence, urban/rural status, education (categorical), body mass index (categorical), tobacco smoking (pack years categorical), beer (categorical) and wine (categorical) .

among laryngeal carcinomas was only of 1.6 (95 % CI 0.9-2.5, p-value for heterogeneity 0.02). The number of beer drinkers among Uruguayan males is extremelly low (10 cases among hypopharynx lesions and 30 among laryngeal cancers). Thus, it is not surprising that resulting OR's were non-significant. On the other hand, red wine is the preferred alcoholic beverage in Uruguay. Although red wine intake was associated with higher OR´s among patients with hypopharyngeal cancers compared with cancers of the larynx, the differences were non-significant. Hard liquor consumption displayed an increased risk among hypopharyngeal carcinomas (OR 3.3, 95 % CI 1.6-6.8), whereas laryngeal cancers showed a modest elevation in risk of 1.5. The test for heterogeneity was statistical significant (p-value=0.03). Total alcohol consumption, years of drinking alcohol, years of cessation alcohol drinking and lifelong consumption of alcohol (alcohol years) were directly associated with elevated risk for patients with hypopharyngeal carcinomas (OR for heavy drinkers of alcohol 12.8, 95 % CI 4.0-41.2, p-value for trend <0.0001). On the other hand, cancers of the larynx displayed less impressive effects (OR for heavy drinkers of alcohol 2.5, 95 % CI 1.4-4.5). All the variables above mentioned showed significant differences between both sites (p-value for heterogeneity=0.03 for total alcohol drinking). Finally, pattern of consumption of alcoholic beverages displayed an OR of 6.9 for mixed drinkers (95 % CI 2.2-21.3) among hypopharyngeal lesions compared with 1.7 (95 % CI 1.0-2.9, p-value for heterogeneity=0.05) in the same category among laryngeal carcinomas.

Joint effects of tobacco smoking (cigarettes/day) and alcohol drinking for hypopharyngeal and laryngeal cancers are shown in **Table 4**. Both sites displayed independent effect for tobacco smoking and alcohol drinking (see marginals). Whereas the effect of alcohol drinking was much higher in patients with hypopharyngeal lesions, tobacco smoking displayed higher effect in laryngeal cancer. These differences by site were statistical significant (p-value for heterogeneity=0.04 for tobacco and 0.02 for alcohol drinking). Curiously joint effects for heavy smokers and heavy drinkers were rather similar in both sites (OR ~43). Whereas this high risk was due to alcohol in hypopharyngeal cancers, joint OR's should be attributed to tobacco smoking in laryngeal lesions. The results followed a multiplicative model.

IV. Discussion

According to our results, tobacco smoking is a major risk factor for laryngeal cancer, whereas alcohol drinking displayed significant increases in risk among hypopharyngeal carcinomas. Moreover, whereas the effect of tobacco smoking is not significant different between both tumor sites (although cigarettes per day and pack years were much higher in laryngeal carcinoma compared with hypopharyngeal lesions), alcohol drinking displayed significant heterogeneity. These results replicates the findings of Tuyns et al. in the large multicenter study of

IARC (Tuyns et al, 1988). In this study, results for hypopharynx and epilarynx carcinomas are compared with endolaryngeal lesions (Tuyns et al, 1988). These authors strongly suggested that 68 % of the hypopharyngeal cancers versus 28 % of the endolaryngeal cancers are attributable to alcohol drinking. Other studies (Brugere et al, 1986; Barón et al, 1993) reported an elevated risk of hypopharyngeal carcinomas for alcohol drinking, after controlling for tobacco smoking.

Concerning the mechanisms of tobacco smoking, it is clear that this risk factor is a rich source of carcinogens (IARC, 1986). In particular, tobacco contains high amounts of tobacco-specific nitrosamines (TSNA). These compounds have been implicated in the carcinogenesis of lung, oral cavity, pharynx, larynx, esophagus and urinary bladder (Hecht, 2002). In particular, air-cured tobacco (black tobacco) has greater concentrations of TSNA compared with flue-cured tobacco (blond tobacco). In discordance with previous studies (Benhamou et al, 1985; De Stefani et al, 1987; De Stefani et al, 1988, 1993; Boffetta, 1993; Sancho-Garnier and Theobald, 1993), the present study failed to show a significant increase in risk among smokers of black tobacco. This could be the results of the decline in the sales of black tobacco in the Uruguayan market (De Stefani et al, 1994). On the other hand, in the present study, hand-rolled cigarettes were associated with a significant increase in risk for squamous cell laryngeal carcinomas, and, in a lesser degree for hypopharyngeal carcinoma. Our results replicates findings from previous studies (De Stefani et al, 1992, 1993; Launoy et al, 2000). Since hand-made cigarettes are also filled with blond tobacco, there is uncertaintly concerning about the chemical composition of the blond tobacco used for fill hand-rolled cigarettes. More precisely, hand-made blond tobacco could contain higher amounts of carcinogenic chemicals compared with the flue-cured tobacco used for manufactured cigarettes. Further studies are needed in order to clarify this issue.

At difference with the mechanisms of action of tobacco, alcohol drinking has been the subject of considerable debate (IARC, 1988; Blot, 1999). Recent reviews suggested that alcohol drinking acts through ethanol or its major metabolite (acetaldehyde) (World Cancer Research Fund, 1997, Blot, 1999). On the other hand, beer, wine and hard liquor could contain carcinogenic substances (Schlecht et al, 2001). Also, it is possible that alcohol could be a solvent for tobacco carcinogens or facilitate the action of these carcinogens inducing injury of the mucosa (Blot, 1999). Since hypopharyngeal mucosa is in direct contact with alcohol, this mechanism could fit with our findings. On the other hand, laryngeal mucosa is mainly related with the inhaled tobacco.

As other case-control studies, our study has a several limitations. Perhaps the most important drawback is the potential for selection bias. This bias is almost impossible to exclude. We tried to minimize selection bias by frequency matching cases and controls on age, residence and urban/rural status. Another important bias is classification bias. Since is widely known that tobacco smoking and alcohol drinking are the main determinants of these malignancies, both patients and interviewers could induce differential reponse of the cases. This could result in results close to the null. Our study has also strengths. The precise validation of the lesion by an expert endoscopist is a strength. Also, the high response rate (both for cases and controls) is another important strength.
In summary, we conducted a case-control study in Uruguay in order to compare OR's for hypopharyngeal and laryngeal carcinomas. Tobacco smoking was associated with higher risks in lesions of the larynx, but

Table 4. Joint effects of tobacco smoking and alcohol drinking in hypopharyngeal and laryngeal cancers (1)

Hypopharynx				
Alcohol drinking				
	0-60	**61-120**	**121+**	**Total**
Cigarettes/day	**OR 95 % CI**	**OR 95 % CI**	**OR 95 % CI**	**OR 95 % CI**
0-14	1.0	5.1 1.1-23.3	4.6 0.8-25.6	1.0
15-24	1.9 0.3-12.8	16.3 4.2-62.9	22.3 5.8-86.3	3.3 1.5-6.9
25+	4.3 0.8-23.5	21.3 5.3-85.0	43.9 11.5-116.8	5.2 2.4-11.0
Total	1.0	5.6 2.4-13.1	9.4 4.1-21.6	
Larynx				
Alcohol drinking				
	0-60	**61-120**	**121+**	**Total**
Cigarettes/day	**OR 95 % CI**	**OR 95 % CI**	**OR 95 % CI**	**OR 95 % CI**
0-14	1.0	5.1 1.1-23.3	2.5 0.7-9.0	1.0
15-24	4.3 1.7-11.0	15.0 6.8-33.0	13.7 5.8-32.3	5.9 3.4-10.3
25+	12.8 5.4-30.2	20.7 9.1-47.3	42.2 18.9-94.6	13.0 7.4-22.6
Total	1.0	2.2 1.4-3.5	3.0 1.9-4.8	

1-Adjusted for age, residence, urban/rural status, education, body mass index and for each other.

the differences with hypopharyngeal squamous cell carcinomas of the hypopharynx did not reach statistical significance. Most of the variables related with alcohol drinking displayed significantly higher OR's among hypopharyngeal carcinomas compared with laryngeal cancers. These results suggest that, concerning smoking and drinking, hypopharyngeal and laryngeal could be distinct epidemiological entities. Therefore, these tumors sites should not be joined as a single disease in future diseases.

Acknowledgements

Supported by a grant from International Agency for Research on Cancer.

References

Austin DF and Reynolds P (**1996**) Laryngeal cancer In D Schottenfeld and JF Fraumeni Jr (eds): Cancer epidemiology and prevention. Second Edition pp 619-636 Oxford University Press New York

Barón AE, Franceschi S, Barra S, Talamini R and La Vecchia C (**1993**) 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** 2, 519-523

Benhamou S, Benhamou E, Tirmarche M and Flamant R (**1985**) Lung cancer and use of cigarettes: a French case-control study. **J Natl Cancer Inst** 74, 1169-1175

Blot WJ (**1999**) Invited commentary: More evidence of increased risks of cancer among alcohol drinkers. **Am J Epidemiol** 150, 1138-1140

Boffetta P (**1993**) Black (air-cured) and blond (flue-cured) tobacco and cancer risk III: Oral cavity. **Eur J Cancer** 29A, 284-287

Breslow NE and Day NE (**1980**) Statistical methods of cancer research. Volume 1-The analysis of case-control studies. IARC Scientific Publications Nº 32. Lyon, IARC

Brugere J, Guenel P, Leclerc A and Rodriguez J (**1986**) Differential effects of tobacco and alcohol in cancer of the larynx pharynx and mouth. **Cancer** 57 391-395

Cattaruzza MS, Maisonneuve P and Boyle P (**1996**) Epidemiology of laryngeal cancer. **Oral Oncol** 32B, 293-305

Comisión Honoraria de Lucha contra el Cáncer (**1993**) Conocimientos, creencias, actitud y prácticas sobre cáncer. Encuesta de población. Cooperación técnica OPP/BID/PNUD. Comisión Honoraria de Lucha contra el Cáncer, (In Spanish)

De Stefani De Stefani E, Barrios E and Fierro L (**1993**) Black (air-cured) and blond (flue-cured) tobacco and cancer risk III: Oesophageal cancer. **Eur J Cancer** 29A, 763-766

De Stefani E, Correa P, Oreggia F et al (1987) Risk factors for laryngeal cancer. **Cancer** 60, 3087-3091

De Stefani E, Correa P, Oreggia F, Deneo-Pellegrini H, Fernández G, Zavala D, Carzoglio J Leiva J, Fontham E and Rivero S (**1988**) Black tobacco wine and mate in oropharyngeal cancer. A case-control study from Uruguay. Rev Epidém et Santé Publ 36, 389-394

De Stefani E, Fierro L, Barrios E and Ronco A (**1994**) Cancer mortality trends in Uruguay 1953-1991. **Int J Cancer** 56, 634-639

De Stefani E, Oreggia F, Rivero S and Fierro L (**1992**) Hand-rolled cigarette smoking and risk of cancer of the mouth pharynx and larynx. **Cancer**, 70 679-682

Estève J, Riboli E, Péquignot G, Terracini B, Merletti F, Crosignani P, Ascunce N, Zubiri L, Blanchet F, Raymond L, Repetto F and Tuyns AJ (**1996**) Diet and cancers of the larynx and hypopharynx: the IARC multi-center study in southeastern. **Europe Cancer Causes Control** 7, 240-252

Hecht SS (**2002**) Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. **Lancet Oncol** 3, 461-469

Hosmer DW Jr and Lemeshow S (**1989**) Applied logistic regression New York: John Wiley & Sons,

IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Tobacco smoking Volume 38 IARC Lyon France **1986**

IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Alcohol drinking. Volume 44, IARC, Lyon, France, **1988**

Launoy G, Milan C, Faivre J, Pienkowski P and Gignoux M (**2000**) Tobacco type and risk of squamous cell cancer of the oesophagus in males: a French multicentre case-control study. **Int J Epidemiol** 29, 36-42

Parkin DM, Whelan SL, Ferlay J, Raymond L and Young J (eds) (**1997**) Cancer Incidence in Five Continents Vol VII IARC Scientific Publications nº 148 Lyon IARC

Riboli E, Kaaks R and Estève J (**1996**) Nutrition and laryngeal cancer. **Cancer Causes Control** 7, 147-156

Rothman KJ and Greenland S (**1998**) Modern Epidemiology. Second Edition, Lippincott-Raven Publishers

Sancho-Garnier H and Theobald S (**1993**) Black (air-cured) and blond (flue-cured) tobacco and cancer riskII: Pharynx and larynx cancer. **Eur J Cancer** 29A, 273-276

Schlecht NF, Pintos J, Kowalski LP and Franco EL (**2001**) Effect of type of alcoholic beverage on the risks of upper aerodigestive tract cancers in Brazil. **Cancer Causes Control** 12, 579-587

Stata Reference Manual. Release 6. Stata Press. College Station, Texas **1999**.

Tuyns AJ, Estève JRaymond L et al (**1988**) 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** 41, 483-491

World Cancer Research Fund (**1997**) Food nutrition and the prevention of cancer: a global perspective. American Institute for Cancer Research, Washington DC

World Health Organization International Classification of Diseases for Oncology. (ICD-O), **1976**

Wynder EL, Covey LS, Mabuchi K and Mushinski M (**1976**) Environmental factors in cancer of the larynx A second look. **Cancer** 38, 1591-1601