ORIGINAL REPORT

Looking Beyond Tobacco and Alcohol: The Role of Lifestyle and Other Environmental Risk Factors for Laryngeal Cancer

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ABSTRACT

Laryngeal cancer incidence in São Paulo, Brazil, is one of the highest in the world. OBJECTIVE: This hospital-based case-control study was designed to investigate exposure-disease relationship between larynx cancer and smoking and drinking history, diet, occupational exposures and other characteristics. MATERIAL AND METHODS: The study was conducted in 3 metropolitan areas in Brazil: São Paulo (South-east), Curitiba (South) and Goiânia (Central-west). We have analyzed information on demographics, occupational history, environmental exposures, tobacco smoking and alcohol drinking habits obtained from interviews with 194 cases and 804 controls (non-cancer inpatients) matched on 5-year age group, gender, hospital catchments area, and trimester of admission. RESULTS: Tobacco and alcohol consumption were the most important factors for prediction of laryngeal cancer. Other important risk factors were indoor exposure to wood stove fumes (RR= 2.6), woodworking (RR=1.9), family history of cancer (RR=2.1), and high consumption of coffee and "chimarrão"(a kind of maté tea). There was a protective effect for the consumption of citric fruits and for carotene-rich vegetables. CONCLUSION: regionally specific lifestyle ("chimarrão", high consumption of coffee, and indoor use of wood stove for cooking), behavioral characteristics (smoking and drinking), woodworking, and family history of cancer may be responsible for a substantial proportion of incident laryngeal cancer cases.

Key words: Laryngeal neoplasms. Risk factors. Epidemiology. Case-control studies.

INTRODUCTION

Laryngeal cancer incidence varies widely throughout the world. It is the second most common respiratory cancer preceded only by lung cancer, with highest risk areas occurring

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in Southern and Eastern Europe, Western Asia and South America.[1] The high rates in southern Brazil markedly increased incidence in tropical South America. Men highest rates in Brazil are found in São Paulo, while the lowest in the world are among Japanese living in Los Angeles, USA.[2] The age-standardized rates (for the 60's world population) for the cancer of larynx (ICD-10 C32) among São Paulo city male and females inhabitants are 17.8 and 1.3 per 100.000 in 1978 and 16.2 and 1.9 in 1997-1999, respectively.[3,4] Laryngeal cancer incidence rates have considerably increased in the United States. Its risk has practically doubled for males and has tripled for females from 1947 to 1984.[5] American Cancer Society estimates that approximately 10,000 cases of laryngeal cancer occurred in the United States in 2001, with 4,000 deaths.[6]

Tobacco and alcohol consumption have long been identified as the two most important risk factors for laryngeal carcinoma.[7-12] Socio economic status and carotene rich diet and green vegetables may be protective.[7,13-16] In contrast, the role of occupational exposure to asbestos has not unequivocally been demonstrated as a risk factor for laryngeal carcinoma.[7,17-20]

The high incidence of laryngeal cancer in Brazil may provide an excellent opportunity to quantify the effect of several potential risk factors. A multi-institutional hospital-based case-control study was designed to investigate exposure-disease relationships for certain environmental and lifestyle characteristics prevalent in Central and Southern Brazil.

MATERIAL AND METHODS
CASES

Subjects with histologically confirmed squamous cell carcinomas for the larynx neoplasms and with no prior treatment for cancer were eligible to participation. A total of 194 consecutive patients with newly diagnosed carcinomas of the larynx (ICD-10 C32) admitted at one of the head-and-neck surgery service located in São Paulo (Heliópolis Hospital), Curitiba (Erasto Gaertner Hospital) or Goiânia (Araújo Jorge Hospital) during the period of January 1987 through January 1989 were identified and selected for the study. All diagnoses were confirmed histopathologically, and, prior to start of the treatment, a direct

laryngoscope has ascertained the anatomic site. Two cases were withdrawn from the study, one for physical conditions and the other for lack of suitable controls.

CONTROLS

Eight hundred and four control subjects were selected among inpatients from the same hospitals to which cases had been admitted or from neighboring general hospitals. Two to five control patients were matched to each case on the basis of gender, age group, and trimester of admission. Patients with a diagnosis of neoplastic disease (ICD-10 C00-D48) or of mental disorder (ICD-10 F01-F99) were not eligible as controls. There were no refusals to participate among control subjects. The primary cause of hospitalization among control patients could be grouped in 14 diagnostic categories of the ICD-10. Digestive system diseases (ICD-10 K00-K92) represented the most common cause (209 controls, 26.0%) followed by cardiovascular diseases (ICD-10 I00-I99, 199 cases, 24.8%). Ninety-five (11.8%) patients were assigned as ill-defined (ICD-10 R00-R99) (Table 1).

Each case and control patient was submitted for 40 to 60 minutes to structured, questionnaire-based, standard interview by specially trained interviewers. They were totally blind to all etiologic hypotheses being tested. Interviews were carried out prior to any major medical procedure and in privacy, assuring the patient complete information confidentiality.

Table 1 - Distribution of primary causes of hospitalization among the 804 control patients

Diagnostic categories	Controls	%
Gastrointestinal diseases	209	26.0
Cardiovascular diseases	199	24.7
Trauma	80	10.0
Genitourinary diseases	61	7.6
Respiratory diseases	40	5.0
Infectious diseases	33	4.1
Orthopedic diseases	22	2.7
Endocrine diseases	21	2.6
Bone diseases	19	2.4
Dermatologic diseases	16	2.0
Ill-defined diseases	95	11.8
Other	9	1.1

Interviews were immediately interrupted if the patient had any communication difficulty due to pain, speech or breathing problems and they were not included in this study. Interviews brought out detailed information on demographics, socio economic status, personal and family medical histories, environmental and occupational exposures, tobacco smoking, alcoholic beverage consumption, dietary habits, and oral hygiene habits.

STATISTICAL ANALYSIS

The odds ratio was the measure of association used to estimate the relative risk (RR) of disease due to each study factor. Point and interval estimates for the RR were obtained by multiple logistic regression using conditional maximum likelihood estimation based on the matching factors (age, gender, hospital and trimester of admission).[21,22] The covariate

Table 2 - Cases and controls distribution according to selected demographic and socio economic characteristics

Variable	Categories	Cases	(%)	Controls	(%)
Geographical region lived the last >=5 years	North/North-east	19	9.8	148	18.4
	South-east	57	29.4	248	30.8
	South	80	41.2	300	37.3
	Central- West	32	16.5	82	10.2
	Other	6	3.1	26	3.2
Residence in rural area > 5 years	No	43	22.2	134	16.7
	Yes	151	77.8	670	83.3
Ethnic background	White	163	84	640	79.5
	Mulatto	17	8.8	109	13.6
	Black	13	6.7	44	5.5
	Other	0		5	0.6
Marital status	Never married	9	4.6	54	6.7
	Currently married	148	76.3	621	77.2
	Formerly married	37	19.1	129	16.1
Religion	Catholic	177	91.2	665	82.7
	Protestant	12	6.2	99	12.3
	Other	5	2.6	40	5.0
Schooling level	Illiterate	62	32.0	221	27.5
	Grade school	119	61.3	495	61.6
	High school	9	4.6	64	7.9
	College	4	2.1	23	2.9
Household income (US$/month)	<=30	45	23.2	150	18.7
	31-60	40	20.6	169	21.0
	61-110	37	19.1	148	18.4
	111-200	30	15.5	163	20.3
	>=201				

Percent values may not add up to 100 because of subject exclusion with missing information.

adjustments in the analysis were based on the histories of tobacco and alcohol consumption.

The consumption of tobacco and alcohol was transformed into continuous variables expressed by pack-years and grams of alcohol, respectively. A pack-year was defined as the cumulative exposure to a pack-a-day commercial brand cigarette smoking during one year. Equivalents in doses were calculated as follows:

Table 3 - Relative risks of laryngeal cancer according to lifetime tobacco and alcohol consumption

Lifetime consumption	Categories	Cases	(%)	Controls	(%)	RR crude	95% CI*	RR adjusted**	95% CI*
Tobacco	<1	4	2.1	158	19.7	1.0	(ref.@)	1.0	ref
(pack-years)	2-15	19	9.8	111	13.8	9.5	2.7-33.2	8.6	2.4-30.0
	16-35	47	24.2	152	18.9	20.5	6.1-69.1	16.9	5.0-57.2
	36-75	57	29.4	198	24.6	20.7	3.2-69.4	15.2	4.5-51.2
	>75	66	34.0	181	22.5	28.9	8.6-97.7	18.9	5.5-64.6
Alcoholic	<1	21	10.8	136	16.9	1.0	ref	1.0	ref
beverages	1-100	19	9.8	183	22.8	1.1	0.5-2.3	0.9	0.4-2.1
(Kg of alcohol)	101-400	31	16.0	115	14.3	3.5	1.7-7.4	2.3	1.0-5.1
	401-1000	41	21.1	147	18.3	3.8	1.8-7.8	2.4	1.1-5.1
	1001-2000	61	31.4	177	22.0	5.1	2.5-10.4	3.0	1.4-6.6
	>2000	21	10.8	42	5.2	7.6	3.2-17.9	4.5	1.8-11.1

* 95% Confidence interval; @ Reference category; ** Mutually adjusted for tobacco and alcohol consumption

20 manufactured cigarettes = 4 cigars = 5 pipefuls with regular pipe = 4 hand-rolled, black tobacco cigarettes = 1 pack; ethanol concentration in beer = 5%, wine = 10%, hard liquor and "cachaça"= 50%. The cut-off values for categorization of tobacco and alcohol consumption were selected to obtain the highest possible likelihood ratio statistics in the models studied.

RESULTS

Case distribution by location was as follow: 44 (22.7%) in São Paulo, 97 (50.0%) in Curitiba, and 53 (27.3%) in Goiânia. There were 168 (86.6%) male and 26 (13.4%) female patients. Age distribution by year range was as follow: under 40, 5 (2.6%); 40-49, 24 (12.4%); 50-59, 68 (35.1%); 60-69, 67 (34.4%); equal or over 70, 30 (15.5%).

Table 2 shows the distribution of cases and controls according to selected demographic and socio-economic variables. The proportion of white patients among cases (84.0%) was slightly higher than controls (79.5%). There were no significant differences in the distributions of cases and controls according to marital status. The proportion of catholic patients was higher in cases (91.2%) than in controls (82.7%). Family monthly income categories were based on the quintiles of the distribution in cases with known answers for this variable.

Table 3 shows the distribution of cases and controls according to lifetime tobacco and alcohol consumption. It is noteworthy that of the 194 cases with laryngeal cancer only 4 patients were non-smokers or had minimal cumulative exposure to tobacco products (< 1 pack-year equivalent). The various categories of smoking and drinking behavior were the major factors for prediction of laryngeal cancer risk, with strong associations and significant dose-response trends in risk (P for trend <0.0001 for tobacco and 0.0005 for alcohol).

Laryngeal cancer RR estimates for selected occupational and environmental factors are shown in Table 4. Except for a moderate risk increase associated with woodworking (RR 1.9), cases and controls had comparable frequency distributions. Pesticide exposure related to farming and household asbestos exposure were not associated with risk. Living in a wood house was associated with increased RR of laryngeal cancer (RR 2.2). Household exposure to fumes

Table 4 - Relative risks of laryngeal cancer according to employment in selected occupational settings and some environmental exposures. Crude

Exposure	Cases Never/ever	Controls Never/ever	Crude analysis RR	95%CI*	Adjusted analysis** RR	95%CI
(a) Employment in specific occupational settings:						
Textile	182/10	769/34	1.2	0.6-2.6	1.6	0.7-3.5
Wood	155/38	704/99	1.9	1.2-2.9	2.0	1.2-3.1
Paper	189/04	791/11	1.4	0.5-4.5	1.6	0.5-5.4
Leather	186/07	785/18	1.6	0.7-3.8	2.3	0.9-6.1
Metal	177/16	725/78	0.9	0.5-1.7	0.9	0.5-1.8
Sugar/alcohol	187/06	789/14	2.1	0.8-5.6	1.5	0.5-4.6
Rubber/plastic	191/02	791/12	0.8	0.2-3.6	0.8	0.2-3.7
(b) Environmental exposures:						
Pesticides	124/70	502/301	1.1	0.6-1.7	0.8	0.6-1.2
Asbestos	181/13	739/65	0.7	0.4-1.4	0.7	0.4-1.4
(c) Home characteristics:						
Type: Brick	71	349	1.0	(ref @)	1.0	(ref.)
Wood	106	351	1.6	1.1-2.4	1.4	1.2-3.0
Wood stove	104/90	286/517	2.6	1.8-3.8	2.4	1.6-3.6
Refrigerator	77/117	261/543	0.8	0.5-1.1	0.9	0.6-1.3

* 95% Confidence interval; @ Reference category; ** adjusted for tobacco and alcohol consumption.

Table 5 - Relative risks of laryngeal cancer according to selected personal and family medical history, oral hygiene and dental health

Variable	Categories	Cases/controls	Crude analysis RR	95%CI*	Adjusted analysis RR	95%CI**
Cancer in family	No	151/680	1.0	(ref.) @	1.0	
	Immediate family	06/39	0.6	0.2-1.5	0.5	0.2-1.4
	Distant family	37/84	2.1	1.4-3.3	2.3	1.4-3.6
Malaria	No	152/596	1.0		1.0	
	Yes	52/208	1.0	0.7-1.4	0.9	0.6-1.3
Blastomicosis	No	191/794	1.0		1.0	
	Yes	2/9	0.8	0.2-3.9	0.6	0.1-2.9
Teeth Brushing	Daily	136/637	1.0		1.0	
	Rarely	55/156	1.8	1.2-2.7	1.6	1.1-2.4
Bad teeth	No	100/481	1.0		1.0	
	Yes	93/317	1.6	1.1-2.2	1.5	1.0-2.1

* 95% Confidence interval; @ Reference category; ** adjusted for tobacco and alcohol consumption.

emitted from wood stoves was associated with more than a doubled risk, even after adjustment for tobacco and alcohol.

A significant association between risk of laryngeal cancer and a history of cancer in non first-degree relatives was observed even after adjustment for tobacco and alcohol (Table 5). No association evidence was seen between a past medical history for malaria or South American blastomicosis with laryngeal cancer. Irregular tooth brushing and poor dentition were more frequently reported by cases than by controls and with significant increase in the associated RRs. Further mutual adjustment using these variables in addition to tobacco and alcohol consumption did not substantially change the risk estimates.

Table 6 shows the association between the risk of laryngeal cancer and certain food items. A protective effect was seen with increased consumption of carotene-rich vegetables, citric fruits, and green vegetables. A significant relationship was observed in the univariate analyses for the consumption of smoked meat. However, adjustment for smoking and alcohol reduced the strength of this association. Cases were no more likely than controls to report the consumption of very hot foods (Adjusted RR 1.2, 95% CI 0.8-1.7). Positive significant trends were seen in dose-risk relationships with coffee and "chimarrão" drinking frequency. After adjustment for tobacco and alcohol consumption only levels of consumption more than 10 cups of coffee/day and 60 cups of "chimarrão"/ month remained significant. There were no excess risks associated with tea and chocolate drinking (data not shown). The proportion of cases and controls that reported to intake these beverages warm (RR 0.8, 95% CI 0.5-1.1) or hot (RR 0.8, 95% CI 0.5-1.3) were similar.

DISCUSSION

A wealth of experimental and epidemiological evidence has long incriminated several risk factors of laryngeal cancer such as tobacco smoking and alcohol drinking, occupational and environmental exposures, and dietary habits. Exposure to such risk factors varies widely as a function of economic, cultural, demographic and geographical characteristics in different countries, states and cities. There is no information regarding risk determinants of laryngeal cancer in Brazil. Because of the high endemicity of this neoplasm in many areas of the country and lack of information related to its risk factors, an epidemiological and clinical study was initiated in 1986.[23] This investigation was carried out by the Ludwig Institute for Cancer Research in collaboration with the Head-and Neck Surgery services of Heliópolis Hospital (São Paulo, Southeast of Brazil), Erasto Gaertner Hospital (Curitiba, South), and Araújo Jorge Hospital (Goiânia, Central-west).

The main risk determinants of laryngeal cancer in Brazil were tobacco smoking and alcohol consumption. The dose-dependent effect with pack-years of tobacco consumption was consistent with several other publications.[7-9,24,25] It is unlikely that this hospital-based study has introduced a conservative bias based on the magnitude of the estimate RR for these two variables. In a recent sensitivity analysis we compared the associations obtained with and without the exclusion of controls admitted with tobacco and alcohol consumption related diseases. The results have shown only very small differences of no practical importance, regardless the extent of conservatism used in the exclusion of the controls from the analysis.[26]

A number of potential occupational factors were investigated using information from interview employment histories. Except for woodworking and household exposure to fumes exhaled from wood burning stoves, none of the other occupational factors studied were associated with an increased risk of laryngeal cancer. On the other hand, use of wood stove was associated with more than a doubled risk even after adjustment for the possible confounding effect of tobacco and alcohol consumption. Previous studies from our group found important associations between the use of wood stove for cooking and oral[27] and head-and-neck cancers.[28] Furthermore, a similar association was considered in regard to lung cancer risk among women in China.[29] Hamada et al.[30] have studied the wood stove effects on indoor air quality in Brazilian homes. The magnitude of indoor Polycyclic Aromatic Hydrocarbons (PAHs), compounds with demonstrated evidence for carcinogenicity, depends mainly on the presence of wood burning emissions. Suspended particulate

Table 6 - Relative risks of laryngeal cancer according to the frequency of selected food items and non-alcoholic beverages consumption

Food group	Frequency	Cases/controls	Crude analysis		Adjusted analysis	
			RR	95%CI*	RR	95%CI**
Carotene-rich	<1/mo	63/202	1.0	(ref.) @	1.0	
	1/mo-3wk	97/446	0.6	0.4-0.9	0.6	0.4-1.0
	>=4/wk	33/156	0.5	0.3-0.9	0.5	0.3-0.9
Citric fruits	<1/mo.	69/218	1.0		1.0	
	1/mo.-3wk	67/321	0.6	0.4-0.9	0.7	0.5-1.1
	>= 4/wk	58/264	0.6	0.4-1.0	0.7	0.4-1.1
Green vegetables	<1/mo.	37/117	1.0		1.0	
	1/mo.-3wk	106/493	0.7	0.4-1.0	0.7	0.4-1.0
	>=4/wk	50/193	0.7	0.4-1.3	0.8	0.5-1.3
Manioc (cassava)	<1/mo.	46/195	1.0		1.0	
	1/mo.-3wk	98/419	0.9	0.6-1.4	0.8	0.5-1.2
	>=4/wk	50/185	1.1	0.7-1.7	0.8	0.5-1.4
Smoked meat	<1/mo.	142/633	1.0		1.0	
	1/mo.-3wk	39/133	1.6	1.0-2.5	1.4	0.9-2.2
	>= 4/wk	9/26	1.8	0.8-4.1	1.3	0.5-3.2
Charcoal-grilled meat	<1/mo.	129/560	1.0		1.0	
	1/mo.-3wk	59/218	1.2	0.8-3.2	1.2	0.8-1.8
	>= 4/wk	5/20	1.1	0.4-3.2	1.0	0.2-2.2
Pepper	<1/mo.	78/344	1.0		1.0	
	1/mo.-3wk	47/178	1.2	0.8-1.8	1.0	0.6-1.5
	>=4/wk	67/270	1.1	0.8-1.6	0.8	0.8-1.2
Coffee	<1	09/72	1.0		1.0	
(cups/day)	1-2	59/303	1.6	0.7-3.4	1.5	0.5-2.8
	3-4	50/204	2.0	0.9-4.2	2.0	0.9-4.4
	5-9	35/111	2.5	1.1-5.6	2.1	0.9-4.9
	>9	41/114	2.9	1.3-6.4	2.2	1.0-5.2
"Chimarrão"	<1	136/622	1.0		1.0	
(maté)	1	03/21	0.8	0.2-2.8	0.9	0.3-3.4
(cups/month)	2-24	34/116	1.8	1.1-3.0	1.6	0.9-2.7
	>24	21/45	2.6	1.4-4.7	2.1	1.1-3.9

* 95% Confidence interval; @ Reference category; ** adjusted by tobacco and alcohol consumption

matter was also in higher concentrations in kitchens with wood stove.

Evidences from epidemiological studies for some occupational exposures and job categories as suspected determinants of laryngeal cancer risk are: asbestos, dusts, isopropyl oils, sulfuric acid, insecticides, silica, leather working, metal processing and working, mustard gas manufacturing, nickel refining, textile fiber processing, sewage plant, and vulcanization process.[7,9,17-19,31,32] However, it is still uncertain if the effect of such variables and of social determinants is real or biased by other than occupational factors.[33] Although substantial evidence confirms asbestos as a risk factor for laryngeal cancer.[9,18,31,32] the number of asbestos workers in this study was very small and the effect of this occupational exposure could not be fully appreciated. Household asbestos exposure was not associated with risk of laryngeal cancer. Woodworking is strongly associated with nasal and paranasal sinus cancers.[7,34,35] Although the present study may have been limited in its ability to assess the effect of occupational risk factors, a striking finding was the significant association with woodworking. The vegetable extracts used in wood processing contain tannins, which have been identified in the sawdust of certain woods.[7]

A protective effect was seen with increased consumption of carotene-rich vegetables, citric fruits and green vegetables. The proper investigation of the role of dietary factors in epidemiological studies is overwhelmed with methodological problems that can impair the validity of results. Dietary histories based on frequency and amount of food intake are prone to remarkable recall and classification biases. For this reason, it is frequent to find contradictory results in the literature. Nevertheless, Graham et al.[13] and De Stefani et al.[16] have found an inverse association between fruits and fresh vegetables consumption and risk of larynx cancer. Additional evidence was provided by cohort and case-control studies showing that risk of upper aerodigestive system cancers is lower among individuals with higher serum levels of beta-carotene or higher ingestion of vitamin A precursor-rich foods.[7,15]

The consumption of "chimarrão", a type of tea (an infusion of the herb *Ilex paraguariensi*)

generally drunk hot in Southern Brazilian states, was positively related to the risk of larynx cancer in this study and described in previous studies by our group.[23,36] An increased risk among "chimarrão" drinkers had been previously shown for laryngeal,[8] oral,[27] pharyngeal,[36] and esophageal[37,38] cancers. The positive association with risk of laryngeal cancer was seen with a high daily coffee consumption. However, this association was partially misinterpreted by smoking, as further adjustment by this variable reduced the magnitude of the level-specific RR estimates. Our results point out to an effect other than temperature for the increase in cancer risk observed for "chimarrão" and coffee consumption. Other studies have also failed to detect an increase in risk associated with temperature during consumption of non-alcoholic beverages.[36,39]

Oral hygiene characteristics are strongly related with oral cancer.[27,40,41] Wynder et al.[42] have found an association with edentia in laryngeal but not in oral and pharyngeal cancers. We have detected an increased risk of laryngeal cancer using tooth-brushing frequency and poor dentition as markers for oral hygiene. Our adjustment for tobacco and alcohol consumption has not changed risk estimates, additionally the subjects of this study and association between dental factor and family history are published by Velly et al., 1998[41] and Foulkes et al., 1995[43] respectively.

Family cancer history was one of the variables related to the risk of laryngeal cancer. Adjustment by alcohol drinking and tobacco smoking has not changed risk estimates for this factor. Some epidemiological surveys have shown a strong family aggregation in the occurrence of esophageal cancer in areas with high incidence such as China and Iran.[44,45] Furthermore, Morita et al.[46] have shown the risk of a second cancer in the upper aerodigestive tract associated with significantly increase (8-fold) of esophageal cancer in patients who had close relatives with those cancers, compared with those without a family cancer history. An increased adjusted 2.3-fold risk of developing larynx cancer if a first-degree relative had cancer was obtained by Foulkes et al.[43], and whether a father or sibling had cancer the risk of head-and- neck cancer was around 2-fold. It is

reasonable to assume that the same risk habits such as diet, tobacco smoking and drinking occur within the same family. Another important issue is that cancer patients are probably more likely to recall a family history which may lead to substantial recall bias.

Davidson et al.[47] reviewed the literature on the genetics of tobacco-induced cancers, and concluded that factors that influence carcinogenesis among tobacco-exposed individuals include a combination of environmental exposures and genetic susceptibility.

There are interindividual differences in several enzymatic pathways involved in the metabolism of ingested or inhaled external agents. Such genetic polymorphisms have been found to be associated with increased susceptibility to several cancers.[48]

In conclusion, our study has shown the relative importance of regionally specific lifestyle ("chimarrão" and coffee high consumption, and indoor use of wood stove for cooking), occupational exposures (woodworking) and behavioral characteristics (smoking and drinking), as well as a family cancer history are possible risk factors for laryngeal cancers. Further studies should be designed to elucidate the public health importance of these factors in Latin American populations. Finally, better characterization of cancer susceptibility in members of the same family and the relationship with environmental risk factors are necessary.

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