OCCUPATION AND ORAL CAVITY AND PHARYNGEAL SQUAMOUS CELL CARCINOMA: A CASE-CONTROL STUDY

OCUPAÇÃO E CARCINOMA DE CÉLULAS ESCAMOSAS DE CAVIDADE ORAL E FARÍNGEA: UM ESTUDO DE CASO-CONTROLE

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ABSTRACT

Purpose: The aim of the present case-control study was to investigate whether there was any association between occupation and oral squamous cell carcinoma (OSCC) in a Brazilian population. Methods: This population-based study investigated an occupation that was classified according to the International Standard Classification of Occupations. The sample consisted of 665 individuals, of whom 133 were cases of OSCC, selected from reference hospitals for cancer in Paraíba; and 532 were part of a control group, paired by age, gender, place and smoking habit, who participated in the study. Results: There was statistically significant association between OSCC and occupation ($p<0.001$), alcohol consumption ($p<0.001$) and marital status ($p=0.003$). The variables marital status, occupation, alcoholism and smoking were shown to be statistically associated with the development of cancer of the oropharynx with Odds Ratio (OR) ranging from 1.8 to 11.2 Conclusion: Occupational exposure to chemical and physical carcinogenic substances, as well as the condition of living with a partner may be raised as possible risk factors for the development of cancer of the mouth and oropharynx.

KEYWORDS: Carcinoma; Case-Control Studies; Employment.

INTRODUCTION

Among the 6.4 million malignant neoplasms diagnosed in the world, approximately 10% affect the mouth, this type being ranked the sixth most prevalent cancer in various countries in the world[1].

Studies have analyzed the relationship between occupational exposure and risk for cancer of the oral cavity[2-10]. However, the majority of associations were not shown to be statistically significant, and cohort studies did not control the confounding variables smoking and alcohol.

Positive association between exposure to perchloroethylene (organic solvent used in dry cleaning) and cancer of the tongue has been observed in industrial workers and truck drivers[4,6]. Industrial manual workers and farmers were at an approximately 2-fold increased risk compared with clerical workers of either gender[7]. The overall contribution to the risk of cancer of the oral cavity or pharynx associated with occupational exposure in Puerto Rico appeared to be low, however, elevated risks were seen among sugarcane farmers and subjects with high cumulative exposure to solvents[8].

A body of scientific evidence has suggested that occupations such as dentists; hairdressers; waiters; cooks; shop and beverage salespersons; boiler/furnace operators and petroleum industry workers are at high risk for cancer of the tongue[2,9].

Workers with low professional qualification are at greater risk for developing squamous cell carcinoma (SCC) of the oropharynx (OSCC)[11] Workers in mechanical and industrial workshops, such as metal works and petrochemical plants, as well as painters, butchers and motorized vehicle drivers are in a situation of risk for this type of tumor, irrespective of age, alcohol and tobacco consumption. This finding was probably due to continual exposure to diverse products such as vapors, acids and solvents inherent to the type of work[12].

Frequent exposure to sunlight has also been reported a risk factor for the increase in OSCC, particularly for SCC of the bottom lip[13]; and this type of cancer mainly affect persons who work out of doors, such as stevedores, port workers, sailors, farmers, workers in the fishing and civil construction industries[11].

Radoï and Luce[14] (2013) emphasized the importance of knowledge about the distribution of the incidence and mortality rates of malignant tumors, including OSCC, for establishing public policy guidelines and planning preventive actions for the control of cancer.

By virtue of the high rate of incidence and mortality due to cancer, as well as the participation of occupational factors in the

etiopathogenesis of the lesion, the authors of this study sought to examine the associations between occupation and incidence of oral cavity and pharyngeal squamous cell carcinoma.

METHODOLOGY

The Study was approved by the Research Ethics Committee of the State University of Paraiba, Northeastern Brazil, Report No. 0337.0.133.000-11. A written term of free and informed consent was obtained from both cases and controls for participation in the study.

Location of Study

This hospital-based case-control study was conducted in two reference centers in the state of Paraíba: the Hospital Napoleão Laureano, localized in the municipality of João Pessoa (coastal region of the state), and the Hospital FAP (Fundação Assistencial da Paraíba), localized in the municipality of Campina Grande (interior of the state). Paraíba, one of the 27 Federal units of Brazil, is located in the northeastern region of Brazil; has a total population of 3,766,528 inhabitants, disposed throughout an area of 56,469,778 km^2 and the capital is the municipality of João Pessoa. The State has 223 municipalities, distributed among 4 large mesoregions: The "Agreste paraibano", composed of 8 microregions; "Borborema", with 4; "Mata paraibana", with 4; and "Sertão paraibano", with 7 microregions[15].

Study population

The study population consisted of individuals suffering from OSCC and non-sufferers, adults and elderly, aged between 29 and 92, resident in the state of Paraíba, selected between August 2011 and March 2012.

The case group was selected from qualifying patients (those who had not begun adjuvant treatment) from two hospitals, with the cancer diagnosis classified under codes C00 to C06 (oral cavity) and C09 to C14 (oropharynx) in accordance with the International Classification of Diseases/ ICD-10[16]. For each individual identified as a case (with histopathological confirmation of OSCC) the referral was requested of four neighbors of similar age (to within five years, either way), same sex, socioeconomic situation, similar profile, to make up the control group.

The control group was composed of clinically healthy individuals who were paired with individuals who made up the case group in terms of smoking habits; and they had to have no history or suspicion of squamous-cell carcinoma or any other type of malign neoplasm in the oral cavity or pharynx.

Excluded from the research study were individuals in the case group who had one or more of the following characteristics: patients with recurring OSCC; who were in adjuvant therapy prior to surgery; with a prior history of oral or pharyngeal cancer or other types of cancer; cases of cancer classified as C00.0-C00.2 (external lip), C07-C08 (salivary glands), C11 (nasopharynx) and C45-C49 (malign neoplasms of mesenchymal origin). The exclusion of these cases was based on the literature that maintained that cancers in these sites did not share the same risk factors as those in the other regions of the oral cavity and pharynx[17].

For sample calculation, the estimated sample size for paired case-control studies was used[18]. The odds ratio (2.3) and proportion of exposures between the cases in a previous study were obtained[10]. The test performed with a 95% level of significance and 90% test power determined a sample of 106 cases and 424 controls (ratio of 1:4). To prevent losses, 20% was added to the value found previously. Thus, the minimum numbers to be investigated were 128 cases and 509 controls. The sample was composed of 133 cases (mean of 63 years of age, range 32 – 91 years, 85 men) and 532 controls (mean of 62 years of age, 29 – 92 years, 340 men).

The majority of case patients were interviewed during the clinical investigation procedures for diagnostic confirmation. The interviews were held by a team of interviewers specifically trained to apply the questionnaire developed for the study.

To obtain the number of controls (532) proposed for the research, it was necessary to visit 67 municipalities, comprising a physical area that was pointed out previously.

Data Collection

The dependent variable (event-response) was represented by OSCC. This variable was dichotomized into individuals who did not present the disease (controls) and individuals who presented the disease (cases).

The independent variables were: Sex, color, educational level, religion, income, occupation, type of dwelling, and smoking habit.

The confounding variables (necessary for controlling the outcome): period as smoker, type of smoking, frequency of the habit, whether the individual was a passive smoker, habit of drinking, time of alcoholism, type of drink, alcohol consumption and frequency of drinking.

The smoking habit was divided into two categories: nonsmokers and smokers. Ex-smokers for at least one year before the research were included in the group of nonsmokers[19]. The variable drinking was also divided into two categories: drinker and nondrinker.

The occupational history of the individuals during one year was categorized by trained and calibrated researchers. Information was obtained about the individual's age when practice of the occupation began and ended (for those who were unemployed); the job the individual held; and the name of the company, address, city and branch of activity or productive sector of the company or employer.

Categorization of occupations

For classification of the occupation, the International Standard Classification of Occupations – (ISCO) of the International Labor Organization (http://www.ilo.org/public/english/bureau/stat/isco/index.htm, accessed on 08/Oct/2013) was used, which is the basis of the Brazilian Classification of Occupations ("Classificação Brasileira de Ocupações") (http://www.mte.gov.br/empregador/caged/estatistica/nocupacional/default.asp, accessed on 08/Oct/2013).

Characterization of the tasks performed allowed the occupation to be included in the most representative code among the specific categories in each professional grouping.

Jobs outside of the formal market were also evaluated for the purpose of inclusion in the occupational profile, or not, and later analyzed relative to exposure to risk factors. For codification of the periods characterized as non-occupational, such as

retirement, unemployment, domestic work, illness and imprisonment, and occupations that could not be identified, special codes were created.

Statistical Analysis

The data collected were analyzed by using the software program Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM, Chicago, USA). In addition to descriptive statistical analysis, univariate analysis was performed, associating the dependent variable (OSCC) with the independent variables, by using the Chi-square (χ^2), McNemar, and the Chi-square with linear tendency tests. The analysis was adjusted for smoking, alcoholism and age.

With the aim of verifying which of the variables significantly explained the outcome cancer of the oropharynx, logistic regression analysis was performed. In the univariate analyses, the independent variables that attained the following criteria were included: a) those that obtained a p-value lower than 0.20 in the association test; b) those that did not present multicollinearity. Univariate linear regression analyses were performed and the variables that presented p-value <0.05 were selected for the multivariate model. Residue analysis was performed; residues were shown to have normal and random distribution.

RESULTS

The ratio between cases and controls was 1:4. Of the 133 patients in the case group, 85 were men and 48 women. The mean age of cases was 63 years and that of controls 62. The majority of cases and controls were composed of individuals of dark color (41.4%) The sociodemographic characteristics of the 133 cases and 532 controls are described in Table 1.

In the group of individuals with OSCC, the oropharynx was the most frequent site, with 45 cases recorded (34%); followed by the tongue, with 24 (18%); floor of the mouth, with 20 (15%); hard palate, with 18 (14%); mouth (more than 1 anatomic site), with 4 (3%); alveolar ridge and retromolar region, with 7 (5%); soft palate, with 6 (4%); and the jugal mucosa and upper lip, with 1 (1%).

When analyzing the results concerning occupation (Table 2), a high concentration of individuals was evident for both cases and controls, employed in the following sectors: agricultural (44.4% and 36.3%), commerce (9.0% and 17.1%), domestic work (12.0% and 14.7%) and transport (5.3% and 13.7%), respectively.

The results associated with SCC and sociodemographic variables may be seen in Table 3.

Consumption of some type of alcoholic beverage presented positive statistical significance (p<0.001).

Regarding marital status, the condition of living with a partner presented higher frequency when compared with individuals without partners, both in the Control (73.90%) and Case Group (60.90%), showing statistical significance (p<0.003) in the Chi-square test.

With reference to skin color, there was no statistically significant difference (p=0.258) between cases and controls.

Table 4 shows the results of the association between SCC and occupation.

The variables marital status, occupation, alcoholism and smoking were shown to be statistically associated with the development of cancer of the oropharynx with OR ranging from

Table 1 - Distribution of cases and controls according to sociodemogrphic variables

	Cases		Controls		p*
	n	%	n	%	
Gender					
Male	85	63.90	340	63.90	0.999
Female	48	36.10	192	36.10	
Marital Status					
Married/Cohabiting	81	61.00	393	73.90	0.003
Widow/widower/Divorced	36	27.00	103	19.40	
Single	16	12.00	36	6.70	
Schooling					
Illiterate	58	43.60	98	18.40	<0.001
Until 8 years of schooling	73	54.70	430	80.80	
University.education (incomplete/completed)	2	1.50	4	0.80	
Family Income (U$ 160)					
< 3 minimum wages	123	92.50	501	26.10	0.468
> 3 minimum wages	10	7.50	31	73.90	
Smoker					
Yes	71	53.40	261	49.10	0.372
No	62	46.60	271	50.90	
Use Alcoholic beverages					
Yes	27	20.30	260	48.90	<0.001
No	106	79.70	272	51.10	

* Chi-square test

Table 2 - Frequency of occupations

	Cases		Controls		p*
	n	%	n	%	
Agriculture	59	44.4	179	33.6	<0.001
Civil Construction	11	8.3	25	4.7	
Transport	7	5.3	73	13.7	
Commerce	12	9.0	91	17.1	
Public Service	9	6.8	40	7.5	
Domestic worker	16	12.0	78	14.7	
Independent worker	6	4.5	34	6.4	
Others	13	9.8	12	2.3	

* Chi-square Test

Table 3 - Association between CA and demographic characteristics

	Clinical case	Control	p*
	n (%)	n (%)	
Gender			
Female	48 (36.10)	192 (36.10)	0.999
Male	85 (63.90)	340 (63.90)	
Smoker			
Yes	71 (53.40)	261 (49.10)	0.372
No	62 (46.60)	271 (50.90)	
Alcohol consumer			
Yes	27 (20.30)	260 (48.90)	<0.001
No	106 (79.70)	272 (51.10)	
Marital Status			
Without partner	52 (39.10)	139 (26.10)	0.003
With partner	81 (60.90)	393 (73.90)	
Family Income			
Up to 3 minimum wages	123 (92.50)	501 (94.20)	0.468
Over 3 minimum wages	10 (7.50)	31 (5.80)	

* Chi-square Test

1.8 to 11.2 in the single regression model. In the multiple regression models, the variables occupation and alcoholism showed a chance of developing cancer of the oropharynx ranging from 3.0 to 11.7, irrespective of marital status or smoking (Table 5).

DISCUSSION

In the oral cavity, excluding the lips, a high incidence of OSCC has normally been found involving the tongue and floor or the mouth, respectively[1,20-22]. This research presented a different profile in terms of predominance of anatomic localization, because the oropharynx was the most frequent site, in 34% of cases, followed by the tongue (18%) and floor of the mouth (15%); the three most prevalent (and statistically significant) sites. According to the National Institute of Cancer ("Instituto Nacional do Câncer")[23] the rates of incidence of oral cancer localized in the tonsils, at the base of the tongue and oropharynx, in young adults, have increased in both sexes.

The approach used to evaluate the effect of occupational factors did not allow inferences about specific exposures, because it was prepared without the construction of a *priori* hypotheses about the occupational physical and chemical agents possibly associated with tumors of the oral cavity and oropharynx.

The result of single logistic regression showed smoking as a risk factor for cancer of the oropharynx, corroborating findings in the literature that reported smoking as a well-established risk factor in the pathogenesis of cancer of the mouth and pharynx[24]. Although the result of multiple regressions demonstrated no association of smoking with cancer of the oropharynx, this result must be analyzed with care, because this may have occurred due to the small difference in proportion between smokers and non-smokers in the case and control groups, and may have generated a false negative result.

There was statistical association in marital status and OSCC (p = 0.003). The condition of living with a relative may increase the risk of developing cancer of the mouth and oropharynx (OR = 1,815), since this civilian condition increases a chance of a previous diagnosis of a possible lesion. The partner can visually perceive the normality pattern, especially in the vermilion of the lower lip, besides stimulating the search for a correct diagnosis and appropriate health treatment, when it is necessary, not delaying the conduct that requires urgent care.

In this study, workers in the agricultural area were shown to be at risk for the development of cancer. This may be justified by the extensive exposure to the sun to which these individuals are submitted. Solar radiation is a great occupational risk in agriculture, particularly in relation to its ultraviolet component (UV). Generally, the maximum times of exposure to UV rays were exceeded, or incorrect measures were used for protecting the skin against UV rays[25]. In any of the previously mentioned situations or combination of them, there were increased occupational risks for various acute and chronic effects, especially for the skin and eyes, which were related to the incidence of SCC of the skin and cutaneous malignant melanoma (CMM)[26-28].

Table 4 - Association between CA and occupation

	Clinical case	Control	*p**
	n (%)	n (%)	
Occupation			
Agriculture	59 (44.40)	179 (33.60)	
Civil Construction	11 (8.30)	25 (4.70)	
Transport	7 (5.30)	73 (13.70)	
Commerce	12 (9.00)	91 (17.10)	<0.001
Public Service	9 (6.80)	40 (7.50)	
Domestic worker	16 (12.00)	7.8 (14.70)	
Independent worker	6 (4.50)	34 (6.40)	
Others	13 (9.80)	12 (2.30)	

* Chi-square Test

Table 5 - Logistic Regression (ENTER method) considering presence of cancer of the oropharynx (case) as outcome.

	Univariate				Multivariate (R^2 = 0.165)			
		IC (95%)				IC (95%)		
	OR	Mandibular	Maxillary	*p*	OR	Mandibular	Maxillary	*p*
Marital Status								
Without partner	1				1			
With partner	1.815	1.219	2.703	0.003	1.501	0.980	2.298	0.062
Occupation								
Others	1				1			
Agriculture	3.287	1.422	7.598	0.005	5.243	2.100	13.092	<0.001
Civil Construction	2.462	0.855	7.090	0.095	3.076	0.992	9.541	0.052
Transport	11.298	3.749	34.048	<0.001	11.701	3.679	37.220	<0.001
Commerce	8.215	3.056	22.085	<0.001	10.778	3.757	30.922	<0.001
Public Service	4.815	1.656	13.995	0.004	7.276	2.335	22.672	0.001
Domestic worker	5.281	2.040	13.673	0.001	10.289	3.661	28.915	<0.001
Independent worker	6.139	1.905	19.779	0.002	6.939	2.021	23.819	0.002
Alcoholism								
No	1				1			
Yes	3.753	2.380	5.917	<0.001	3.945	2.402	6.481	<0.001
Smoker								
No	1				-			
Yes	0.841	0.575	1.231	0.373	-			

Therefore, it is essential to conduct studies with the aim of evaluating occupational risk related to exposure to UV radiation and adequate preventive measures for agricultural workers.

UV radiation may also contribute to the appearance of cancer in the civil construction sectors, affecting workers such as bricklayers, painters and job foremen since these workers are active in outdoor areas, and are consequently exposed to sunlight. Moreover, these professionals are exposed to carcinogenic chemical agents, such as asbestos and glass fibers, benzene, toluene, acetylene and other petroleum derivatives that may lead to the mutation and disorderly growth of cells[29].

Construction workers may be exposed to known or suspected airborne carcinogenic agents, including silica, asbestos, cement powder, solvents and diesel particles, with potential exposure of the upper aerodigestive tract. Some reports in various studies have shown that civil construction industry workers may present high rates of cancer of the head and neck[30-32], although this was not found in all the investigations[2-33].

Salespersons, shop counter attendants, watchmakers, bakers and traders fit into the economic activity of commerce. The work done in this sector presented increased risk, with statistical significance, a result similar to that obtained by Merletti *et al*.[34] (1991), but differs from results published by Huebner *et al*.[2] (1992) and Pukkala *et al*.[35] (1994). According to Huebner *et al*.[2] (1992), these workers may be exposed to formaldehyde and/or have easy access to alcohol.

The economic activity denominated civil service included the following occupations: general and military service, street cleaning and maintenance staff, filing clerks and teachers. Pukkala *et al*.[35] (1994), found increased risk in the economic activity related to the area of education, and particularly pointed out the occupation of women teachers with elevated risk for oral cancer. The present study corroborated the findings of the literature, because the occupation of civil service was shown to have a 7 times higher chance of developing cancer of the mouth, compared with other occupations.

The domestic field included the following occupations: charwomen, daily house cleaners, housewives, janitors and cooks. The risk in this branch of activity may be due to the exposure to polycyclic aromatic hydrocarbons (PAHs), resulting from combustion during the process of cooking foods, exposure to nitrosamines, antioxidants and plastic fumes formed during thermo-decomposition of packaging of food products[36]. Furthermore, exposure to chemical and corrosive solvents, and cleaning materials in general, that exude odors and vapors into the environment, and may be toxic and harmful to health[12].

Mechanics, electricians, general services, cooks, waiters, cabinet makers/carpenters, fishermen, watchmen and security guards fitted into the branch of activity denominated autonomous, constituting one of the economic activities of greatest risk for OSCC, as demonstrated in the present study (OR: 6.93; p: 0.002). Vehicle mechanics are habitually exposed to vapors derived from the combustion of engines driven by gasoline, diesel, or anhydrous ethanol; solvents: mists of mineral oil lubricants and strong acids; particles of insulation materials such as asbestos and glass fibers; metal and abrasive dusts; aldehydes, fumes from welding and soot; among others[37]. The results found were not in agreement with those of other studies conducted in other countries, and perhaps expressed singular aspects of the Brazilian socioeconomic structure. Differently from other developed countries where similar studies were conducted, the older fleet of automobiles in Brazil demanded continuous repairs. This has generated multiplication of the number of mechanical workshops, particularly in the peripheral regions of the large Brazilian cities. These workshops, generally of small size, habitually presented precarious occupational hygiene conditions. The results pointed out indicated the need for specific actions of vigilance in the area of workers' health, to control exposure to carcinogenic substances in these environments.

In the manufacture of articles made of wood, some authors have observed the risk for tumors of the mouth for those with a long time of exposure, but without statistical significance[34,38]. The carcinogenic substances recognized in this sector were: dust from wood and its preservatives, formaldehyde and solvents present in glues, varnishes, lacquers, sealants and resins.

The branches of economic activities in Industry included: weavers, machine operator; health and social services, that include nurses, health agents, prosthetists, funeral agents and radio broadcasters; and the unemployed, those without occupation; were treated as one and the same branch of activity, due to the small number of persons in their respective economic activities, who were not shown to be at risk in this study.

Some authors, such as Merletti *et al*.[34] (1991), identified risk for the workers in the social services sector, but not for the health services, even those with long periods of exposure. Pukkala *et al*.[35] (1994) recorded risks for the services in general, including the health and social services. In the health services, the risk may be linked to the exposure to formaldehyde and glutaraldehyde (aldehydes), ionizing radiation, chemotherapies, ethylene oxide and some biological agents.

In spite of being well conducted, the present study may present some limitations. The potential for misclassification of exposure was considerable, since job title and industry classification systems have limited ability to distinguish between subjects with and without actual exposure. The authors suggest that longitudinal studies should be conducted, either to confirm, or not confirm the relative risk of each risk factor, and establish better relations between occupation and cancer of the mouth. Public policies must be elaborated to raise the population's awareness about the prevention of cancer of the oropharynx according to the occupation in which persons are engaged.

CONCLUSION

In spite of alcoholism and smoking being well established risk factors for oral cancer, in the literature, there are other environmental and behavioral conditions that are directly associated with cancer of the mouth and oropharynx.

Occupational exposure to chemical and physical carcinogenic substances, as well as marital status may be raised as possible risk factors for the development of cancer of the mouth and oropharynx.

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RESUMO

Objetivo: O presente estudo de caso-controle teve como objetivo investigar se existe associação entre ocupação e carcinoma de células escamosas orais (OSCC) em uma população brasileira. Métodos: Este estudo populacional investigou a ocupação que foi classificada de acordo com a Norma Internacional de Classificação de Ocupações. Foram incluídos 665 indivíduos, sendo 133 casos de OSCC, selecionados de hospitais de referência para câncer na Paraíba e 532 participantes do grupo controle, pareados por idade, sexo, local e tabagismo. Resultados: Houve associação estatisticamente significativa entre ocupação (p<0,001), consumo de álcool (p<0,001) e estado civil (p=0,003). As variáveis estado civil, ocupação, alcoolismo e tabagismo mostraram-se estatisticamente associadas ao desenvolvimento de câncer da orofaringe com Odds Ratio (OR) entre 1,8 e 11,2. Conclusão: A exposição ocupacional às substâncias químicas e físicas cancerígenas, bem como a condição de viver com um parceiro podem aumentar a possibilidade de fatores de risco para o desenvolvimento de câncer de boca e orofaringe.

PALAVRAS-CHAVE: Carcinoma; Estudos de casos e controles; Emprego.

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