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Factors associated with lip and oral cavity cancer

Fatores associados ao câncer de lábio e cavidade oral

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ABSTRACT: *Purpose:* This study aimed to identify factors associated with the occurrence of primary cancer of the lip and oral cavity regions compared to other types of head and neck cancers according to demographic, socioeconomic data and lifestyle, in Brazil, from 2000 to 2011. *Methods:* A study was conducted using Hospital Cancer Records (*Instituto Nacional do Câncer*), from 2000 to 2011, totaling 23,153 cases. Data were analyzed by binary logistic regression (response category: primary cancers located in the lip and oral cavity; comparison category; other types of primary cancer in the head and neck, which does not affect the lip and oral cavity) at a significance level $\alpha = 5\%$. *Results:* The study showed factors associated with higher incidence of cancer in the lip and oral cavity: being of advanced age (OR = 1.16), not having a family history of cancer (OR = 2.38), alcohol consumption (OR = 1.17); former tobacco use (OR = 1.51) or current tobacco use (OR = 1.65); having a previous diagnosis of cancer without treatment (OR =1.66). Being female (OR = 0.92), having completed basic (OR = 0.71) and higher (OR = 0.46) education and having previous diagnosis of cancer with treatment (OR = 0.74) constituted factors associated with lower prevalence of cancer of the lip and oral cavity. *Conclusion:* Age, absence of family history of cancer, smoking habits and alcohol consumption, and previous diagnosis of cancer without treatment were associated with a higher incidence of cancer of the lip and oral cavity.

Keywords: Oncology. Oncology Hospital Service. Oral Neoplasms. Mouth. Public Health. Neoplasms.

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RESUMO: *Objetivos:* Objetivou-se identificar fatores associados à ocorrência de câncer primário nas regiões de lábio e cavidade oral frente aos demais tipos de cânceres de cabeça e pescoço segundo dados demográficos, socioeconômicos e de estilo de vida, no Brasil, no período de 2000 a 2011. *Métodos:* Realizou-se um estudo a partir dos Registros Hospitalares de Câncer (Instituto Nacional do Câncer), no período 2000-2011, totalizando 23.153 casos. Os dados foram analisados pela regressão logística binária (categoria resposta: cânceres de localização primária em lábio e cavidade oral; categoria de comparação: demais tipos de câncer primário em cabeça e pescoço, que não acometem lábio e cavidade oral) ao nível de significância α = 5%. *Resultados:* Revelaram-se como fatores associados à maior ocorrência de câncer em lábio e cavidade oral: possuir idade mais elevada (OR = 1,16); não ter histórico familiar de câncer (OR = 2,38); ser etilista (OR = 1,17); ser ex-tabagista (OR = 1,51) ou tabagista (OR = 1,65); possuir diagnóstico anterior de câncer sem tratamento (OR = 1,66). Ser do sexo feminino (OR = 0,92); possuir ensino fundamental (OR = 0,71) e superior (OR = 0,46) completos e apresentar diagnóstico anterior de câncer com tratamento (OR = 0,74) constituíram-se fatores associados à menor prevalência de câncer em lábio e cavidade oral. *Conclusão:* A idade, ausência de histórico familiar de câncer, hábitos de tabagismo e etilismo e diagnóstico anterior de câncer sem tratamento estiveram associados a uma maior ocorrência de câncer em lábio e cavidade oral.

Palavras-chave: Oncologia. Serviço Hospitalar de Oncologia. Neoplasias Bucais. Boca. Saúde Pública. Neoplasias.

INTRODUCTION

Regarding the areas of the lip and oral cavity, oral cancer has stood out among head and neck tumors due to its expressive incidence and mortality rate, in addition to generally being associated with a late diagnosis[1-3], constituting a relevant public health issue, particularly in developing countries, which is Brazil's case[4].

Within the 6.4 million malignant neoplasms diagnosed around the world, approximately 10% are located in the mouth[5], making it the sixth most common type of cancer[6]. In Brasil, in 2012, it was estimated that 14,170 new cases of mouth cancer would occur, 9,990 affecting men and 4,180 women. The death rate in 2010 was estimated to be 4,891, of these 3,882 being men and 1,009 women[4].

It is known that smoking, alcohol consumption, sun exposure, viral infections, previous occurrences of cancer in the head or neck area and socioeconomic conditions can be related to the occurrence of cancer in the lip or oral cavity regions[3]. However, despite the advances in knowledge concerning oral cancer, it was not yet possible to obtain any sort of control over the risk factors from the perspective of prevention, making it necessary to have studies which contemplate higher populational volumes stricken with such a pathology, as well as jointly evaluate the behavior of potential risk and protective factors[1,3].

With this information in mind, the aim of the study became to identify factors associated with the occurrence of primary cancer of the lip and oral cavity regions in comparison to other types of neck and head cancers according to demographic and socioeconomic data and data related to lifestyle in Brazil, between 2000 and 2011.

METHODS

The study is a time series analysis, in which all the primary head and neck cancer diagnoses were selected (codes C00-C13; C30.0; C31.0; C31.1; C32.0-C32.2; C73) according to the International Classification of Diseases (ICD 10-2011)[7], from 2000 to 2011. This data included Hospital Cancer Registry (RHCs), through the RHC integrator, which combines the information from 260 hospitals into 25 locations all over Brazil, with free acess to the site of the National Cancer Institute (INCA)[8].

Seventy thousand and eleven cases of cancer were collected all over the country in the studied period (2000-2011). Of these, to compose the sample, the only ones taken into consideration were those that had complete information available regarding gender, age, race, level of education, family history of cancer, alcohol consumption, tobacco use and previous cancer diagnosis, considered as independent variables, totaling 23.153 occurrences.

The selection of independent variables is justified by their presence in the spreadsheets from the national databases, through the HCRs, in addition to the studies in the field of head and neck oncology, which have shown that social, economic and demographic characteristics, habits and social behaviors, as well as genetic factors directly influence the increasing incidence of malignant tumors in the oral cavity[3,5,7].

Thus, the outcome was divided into two categories: answers (cancers with a primary location on lip and oral cavity, codes C00-C06); and comparison (other types of primary cancer in the head and neck; codes for cancer in the head and neck which don't include the cancers located on lip and oral cavity remained). The purpose of this dichotomization comes from the interest of the current study in observing if the variables are associated with the appearance of cancer in areas that hold a deeper connection to Dentistry and are under the direct responsibility of dental surgeons (lip, tongue, gum, floor of the mouth, oral mucosa, hard palate and salivary glands) in relation to the other areas of the head and neck.

Descriptive analyses were used for all variables, and the association between these and the outcome was tested, through the univariate analysis, using the χ^2 test . For this initial selection of the possible factors associated with this type of cancer, the significance level was set to $\alpha = 10\%$, and, later on, this pre-selection was submitted to an analysis using the Multiple Logistic Regression at $\alpha = 5\%$, to determine the associated factors, utilizing the *stepwise* method. The variables that didn't prove to be important to the outcome were excluded at the end of the multiple analysis. The software Estatístico R, version 2.15.3, was used for the inferential analysis of the data[9].

RESULTS

Twenty-three thousand one hundred fifty-three cases of Head and Neck Cancer all over Brazil were evaluated, showing a higher number of affected individuals residing in the Southeast, for Lip and Oral Cavity (outcome 1) as well as other areas of the head and neck, which don't affect lip and oral cavity (outcome 2/comparison) (Table 1). In addition, 16,202 (70.0%) were primarily diagnosed in the other areas of the head and neck, and 6,951 (30.0%) in the lips and the oral cavity.

The average age for the occurrence of all head and neck cancers was 58 (± 13) for males and 54 (± 17) for females. According to the dichotomization of the outcome, for the areas including Lip and Oral Cavity, the average age was 58 (± 12), with a minimum of 0 and a maximum of 102 years of age for males and 64 (± 16), with a minimum of 0 and a maximum of 103 for females. For the other regions of the head and neck, for males the average age was 58 (± 13), with a minimum of 0 and a maximum of 98 years of age, and for females the average was 51 (± 17), with a minimum of 0 and a maximum of 98. This information is described in Table 2.

Table 3 contains the variables of interest and their categories, described according to the distribution of data in the HCR integrator, where it is noted that the male gender (73.2%) and the white race (49.9%) are the most affected by cancer of the Lip and Oral Cavity, as well as cancer in other areas of the head and neck (63.8 e 51.6%, respectively). It can also be osberved that people with "Incomplete Primary Education" are among the highest numbers affected by cancer of the Lip and Oral Cavity (52.3%), as well as by cancer of other areas in the head and neck (49.7%).

Still in Table 3, it is possible to observe that the highest incidence of cancer in both categories of outcome is among people who do not have a history of cancer in their families (66.5 and 64.3% for the outcome lip and oral cavity and other regions of head and neck, respectively). There was a higher incidence of Lip and Oral Cavity cancer among alcohol consumers (59.0%) and tobacco users (74.2%); yet, for the other areas of the head and neck, the highest incidences were observed among people who have never consumed alcohol (51.5%) and those who use products made out of tobacco (58.7%). For the variable "Previous diagnosis" of cancer, for the occurrence of Lip and Oral Cavity, a higher percentage was found for cases with people who had "diagnosis without treatment" (47.4%), while for the remaining areas of the head and neck, the highest occurrence was found for individuals "without previous diagnosis" of cancer (50.4%).

In Table 4, the results for the univaried analysis of the independent variables can be observed. These variables were selected as potential factors associated with the occurrence of lip and oral cavity cancer from 2000 to 2011 in Brazil. From all of the variables included in the univaried analysis, only the categories "yellow" and "indigenous" from the variable "Race" were not considered significantly associated to the outcome, thus being excluded from the multiple analysis.

Table 1. Occurrence of head and neck cancers, according to the region of the country, in Brazil, in the period 2000 – 2011.

Region of the country	Lip and Oral Cavity		Other areas of head and neck		Total	
	n	%	n	%	n	%
North	196	2.8	465	2.9	661	2.9
Northeast	2,060	29,6	4,859	30	6,919	29,9
Central-West	73	1.1	134	0.8	207	0.9
Southeast	3.598	51.8	7.706	47.6	11.304	48.8
South	1.024	14.7	3.038	18.7	4.062	17.5
Total	6.951	100.0	16.202	100.0	23.153	100.0

Table 2. Ages for cases of head and neck cancer, according to sex and outcome.

	Gender			
	Male		Female	
	Lip and Oral Cavity	Other areas of head and neck	Lip and Oral Cavity	Other areas of head and neck
Age				
Mean	58	58	64	51
Standard Deviation	12	13	16	17
Minimum	0	0	0	0
Maximum	102	98	103	98

Table 5 shows the results for the analysis by Multiple Logistic Regression, with results for the variables which, at the end of the analysis, presented a connection to the outcome, where it was possible to observe that: being female (Odds Ratio – OR = 0.924), having been previously diagnosed with cancer and having had treatment (OR = 0.740), and having a higher level of education were associated with the lowest occurrence of lip and oral cavity cancer, compared to the other areas of the head and neck. Additionally, the factors associated with a higher occurrence are: age (OR = 1.161); not having a family history of cancer (OR = 1.089); current (OR = 1.657) or former use (OR = 1.515) of products derived from tobacco and having previously had a diagnosis of cancer and not have had treatment (OR = 1.661).

Table 3. Frequency values and percentages for the variables of interest for cases of primary cancer in the head and neck, in Brazil, in the period 2000 – 2011.

Variables	Lip and Oral Cavity		Other areas of head and neck		Total	
	n	%	n	%	n	%
Gender						
Male*	5,090	73.2	10,332	63.8	15,422	66.6
Female	1,861	26.8	5,870	36.2	7,731	33.4
Race						
White*	3,472	49.9	8,358	51.6	11,830	51.1
Black	643	9.3	1,379	8.5	2,022	8.7
Yellow	33	0.5	72	0.4	105	0.5
Mixed	2,799	40.3	6,382	39.4	9,181	39.7
Indigenous	4	0.1	11	0.1	15	0.1
Level of Education						
No Education*	1,434	20.6	2,250	13.9	3,684	15.9
Incomplete Primary	3,635	52.3	8,047	49.7	11,682	50.5
Complete Primary	985	14.2	2,514	15.5	3,499	15.1
Secondary Education	707	10.2	2,449	15.1	3,156	13.6
Incomplete Terciary	2	0.0	12	0.1	14	0.1
Complete Terciary	188	2.7	930	5.7	1,118	4.8
Family History						
Yes*	2,326	33.5	5,786	35.7	8,112	35.0
No	4,625	66.5	10,416	64.3	15,041	65.0
Alcohol Consumption						
Never*	2,793	40.2	8,345	51.5	11,138	48.1
Former Consumption	58	0.8	132	0.8	190	0.8
Current Consumption	4,100	59.0	7,725	47.7	11,825	51.1
Tobacco Use						
Never*	1,740	25.0	6,573	40.6	8,313	35.9
Former Smoker	52	0.7	119	0.7	171	0.7
Smoker	5,159	74.2	9,510	58.7	14,669	63.4
Previous Diagnosis						
Without Diagnosis*	3,130	45.0	8,158	50.4	11,288	48.8
With Diagnosis, Without Treatment	3,295	47,4	5,552	34.3	8,847	38.2
With Diagnosis, With Treatment	526	7.6	2,492	15.4	3,018	13.0

*Reference categories for Univariate and Multiple Logistic Regression analysis.

Table 4. Results for univariate analysis of potential predictors for cancer of the lip and oral cavity, compared to other types of head and neck cancer in Brazil, in the period 2000 – 2011.

Variables	B	SP	Sig.	OR	95%CI Exp (B)	
					Inferior	Superior
Gender						
Female	-0.440	0.031	0.000*	0.644	0.583	0.704
Age	0.021	0.001	0.000*	1.021	1.019	1.023
Level of Education						
Incomplete Primary	-0.344	0.039	0.000*	0.708	0.708	0.785
Complete Primary	-0.486	0.050	0.000*	0.615	0.517	0.713
Seconday Education	-0.791	0.054	0.000*	0.453	0.347	0.559
Incomplete Terciary	-1.341	0.764	0.079*	0.261	-1.235	1.759
Complete Terciary	-1.148	0.086	0.000*	0.317	0.148	0.485
Race						
Black	0.115	0.051	0.025*	1.121	1.021	1.221
Yellow	0.098	0.211	0.641	1.102	0.689	1.516
Mixed	0.054	0.030	0.073*	1.055	0.996	1.114
Indigenous	-0.133	0.584	0.819	0.875	-0.269	2.020
Family History						
No	0.099	0.030	0.001*	1.104	1.045	1.162
Alcohol consumption						
Former Consumption	0.272	0.159	0.087*	1.312	1.000	1.624
Current Consumption	0.461	0.029	0.000*	1.585	1.528	1.642
Tobacco use						
Former Smoker	0.501	0.168	0.002*	1.650	1.321	1.979
Smoker	0.717	0.032	0.000*	2.048	1.985	2.110
Previous Diagnosis						
With Diagnosis, Without Treatment	0.436	0.030	0.000*	1.546	1.487	1.605
With Diagnosis, With Treatment	-0.597	0.052	0.000*	0.550	0.448	0.652

B: Logistic Regression Estimator; SP: Standard Deviation; Sig.: Significance; CI: Confidence Interval; OR: Odds Ratio; *p-value ≤ 0.10.

Table 5. Binary Logistic Regression Analysis Multiple identifying predictors of risk / protective for cancer of the lip and oral cavity, in Brazil, in the period 2000 – 2011.

Variables	B	SP	Sig.	OR	95%CI Exp (B)	
					Inferior	Superior
Gender						
Female	-0.078	0.036	0.036	0.924	0.862	0.993
Age	0.015	0.001	0.000	1.161	1.159	1.162
Level of Education						
Incomplete Primary	-0.253	0.041	0.000	0.776	0.716	0.841
Complete Primary	-0.339	0.053	0.000	0.712	0.642	0.790
Seconday Education	-0.435	0.058	0.000	0.647	0.578	0.725
Complete Terciary	-0.756	0.090	0.000	0.469	0.393	0.560
Family History						
No	0.086	0.031	0.006	1.089	1.025	1.157
Alcohol Consumption						
Alcohol Consumption	0.160	0.037	0.000	1.173	1.090	1.261
Tobacco Use						
Former-Smoker	0.416	0.172	0.015	1.515	1.081	2.123
Smoker	0.505	0.040	0.000	1.657	1.531	1.791
Previous Diagnosis						
With Diagnosis, Without Treatment	0.508	0.031	0.000	1.661	1.563	1.764
With Diagnosis, With Treatment	-0.300	0.054	0.000	0.740	0.666	0.823

B: Logistic Regression Estimator; SP: Standard Deviation; Sig.: Significance; CI: Confidence Interval; OR: Odds Ratio; *p-value ≤ 0.05.

DISCUSSION

The concern with the regions of the lip and oral cavity is owed to a higher incidence of malignant lesions in these areas than in others from the head and the neck[10]; besides having a worse clinical presentation, with higher levels of morbidity and mortality being associated with cases diagnosed as Carcinomas of Squamous Cells (90%), a histological type that occurs in 40% of cases in lip and oral cavity areas, 25% in the larynx and 15% in the pharynx, with a lower incidence in the extraoral regions[11-13].

The information produced from the HCRs can, occasionally, present some weakness due to the lack of data[14,15]. This fact was also observed in the current study, resulting in the exclusion of 67% of records from the database. This loss of information is considered to be a limiting factor of research with secondary data. However, the exclusion of records with incomplete information was defined in the planning of the current study, making the complete characterization of each individual included in the regression analysis necessary, so as not to harm the evaluation of the factors associated with the outcome of this analysis.

Although there was a higher number of records of diagnosis of head and neck cancer in the Southeast and Northeast regions and a lower number of records in the Central-West region (Table 1), this data does not reliably reflect the reality of incidence of this type of cancer in the different regions of the country, due to fact that the Hospital Cancer Registry system in still in the implementation/consolidation phase[8], which makes it difficult to know the epidemiologic data of cancer incidence in the country[10]. This was the reason for not having included the region of the country in the assessment of the factors associated with lip and oral cavity cancer.

Under the model of logistic regression, the male gender presented itself as a factor associated to the biggest occurrence of neoplasia in lip and oral cavity, when compared to the other areas of the head and neck, in relation to the female gender. Casati et al.[10] and Silveira et al.[16] also found a higher frequency of occurrences of cancer of the oral cavity in the male gender compared to the female, which, according to Vladimirov and Schiodt[17] is due to the habits and lifestyle of men, especially in relation to tobacco use and alcohol consumption.

The average age for the occurrence of lesions on lip and oral cavity has been the age range from 50 to 70[10,18], which corroborates our findings. In addition, the results obtained for the Multiple Logistic Regression model (Table 5) shows the increase of age as a factor associated to the occurrence of cancer with primary location in lip and oral cavity compared to the other areas of head and neck.

The findings of the present study for education level, corroborate the finding of Melo et al.[18], who also noticed a higher number of cases of oral cancer among individuals who had incomplete primary education (33.9%), followed by those with no education or who were illiterate (25.0%); and of Boing and Antunes[19], who, with systematic review, showed that education level is the most used indicator in epidemiologic studies, containing an association with cancer of the head and neck, with an emphasis on the lip, oral cavity, pharyn and larynx areas.

The family history of cancer has not been considered an important factor associated with the occurrence of oral cancer [20], which is reaffirmed in this study. This result brings attention to other existing results in the literature, where the genetic factor reveals itself as influential in the appearance of cancers[13,21]. The consumption of alcohol has been considered as a potential factor associated to the appearance of malignant lesions in the oral cavity[13], mainly when associated to the use of tobacco[18,22], being that this association is responsible for a twentyfold risk increase in the onset of cancer when compared to

individuals who are not dependent[22]. In the present study, it was noted that alcoholism, when evaluated on its own as well as when evaluated in the multiple model, was considered a factor associated to the occurrence of cancer in lip and oral cavity. Studies have shown that this association is enhanced for men that daily ingest two glasses of alcohol and for women that ingest one[12,23].

Still according to the Multiple Logistic Regression model, the variable of tobacco use was considered as associated to a higher occurrence of lip and oral cavity cancer for former smokers as well as current smokers. Silveira et al.[16] found a higher frequency of cancer of the lip and oral cavity among former smokers than among smokers; however, the time that passed since they had quit the habit was from 0 to 1 year. The vast majority of studies where tobacco use is evaluated shows that it is also directly associated and it is one of the risk factors that most predisposes the occurrence of cancer of the oral cavity[10,13,16,24].

In addition to being an influence on their own, as seen in this study, the combination of alcohol and tobacco is also an imporant risk factor for the development of malignant neoplasms in the oral cavity, mainly in individuals who are male[22,24], where it is noted that the use of tobacco and the consumption of alcohol work synergistically, making it the most potentially carcinogenic of all the factors, responsible for 65 to 90% of oral neoplasias[25] and, in this case,, the risk for the onset of cancer is, mainly, in the areas of the upper larynx, when compared to the inferior laryn[26,27].

Some studies in Oncology have assessed the predisposition of individuals to the onset of cancer[28-30], which can even predispose them to the recurrence of it, with or without treatment. In the literature, cases of genetic predisposition to cancer of the head and neck areas is not well observed, but cases of genetic alteration acquired through the association of behavioral habits, such as tobacco use[29,31], alcohol consumption[29,31], viruses such as HPV[32,33] and even the consumption of red meat[34]. Such findings show that the prevention of this type of cancer becomes more feasible by combating and controlling factors related to habits and associated factors susceptible to intervention.

Although the lip area also accounts for the aggravant of solar radiation as one of the main risk factors[35,36], in the lip area as well as in the different areas that make up the oral cavity, genotypes related to cancer of the head and neck were associated with tobacco use and alcohol consumption, being present in a large portion of tumors with advanced stages and in patients with a lower chance of surviving[29,30].

The awareness of these risk factors enhances the actual prevention of this cancer[5] and, having in mind the comorbidities and the low rate of a five-year survival (30 to 40%), in the last 40 years[13,18,28], in addition to the higher number of deaths by oral cavity cancer which has been noted in males, between the fifth and sixth decade of life with low education level[18,36].

Moreover, the results of this study have the purpose of identifying important components in the decision-making process of the prevention of cancer of the lip and oral cavity, advising that a prevention of the factors understood as associated can contribute to the reduction in the incidence of this type of cancer.

CONCLUSION

It is possible to conclude that the increase in age, not having a family history of cancer, consuming alcohol, using tobacco or being a former smoker, and having previously been diagnosed with cancer without treatment constitute factors associated to a higher occurrence of primary cancer of the lip and oral cavity, compared to cancers located in the other areas of the head and neck. However, being a female, having a higher level of education, and having previously been diagnosed with cancer and having treated it constituted factors associated with a lower occurrence of the same type of cancer, in Brazil, between 2000 and 2011.

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