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ORIGINAL ARTICLE

Human Papilloma Virus infection in individuals with oral cavity and oropharynx cancer treated at a tertiary hospital in Salvador, state of Bahia, Brazil

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The study was carried out at Hospital Aristides Maltez (HAM), Salvador, state of Bahia, Brasil.

Abstract

Introduction: Oropharyngeal and oral cavity carcinoma (OOCC) ranks as the fifth most common cancer in men, in Brazil. Traditionally, OOCC has been linked with smoking and alcohol consumption in older individuals; however, the emergence of these cancers in younger individuals has been associated with Human Papillomavirus (HPV) infection. Despite this connection, there are currently no available data estimating the prevalence of this infection in our population. **Objective:** Investigate HPV infection in patients diagnosed with OOCC treated at a tertiary cancer-specialized hospital in Salvador, state of Bahia, Brazil. **Methods:** Retrospective, observational, descriptive study on patients diagnosed with OOCC at Hospital Aristides Maltez (HAM) from 2017 to 2020. Clinical and epidemiological data were collected from medical records and analyzed by the SPSS® 22.0 software considering a statistical significance level of 5% (p<0.05) . **Results:** Of the 39 individuals with OOCC, 43.6% were over 60 years old, and 79.5% were male. Ten individuals (25.6%) were HPV-positive due to p16 expression. These patients were older (63.0 ±10) compared with HPV-negative individuals (p=0.03). The older population was associated with more advanced conditions among HPV-negative patients (r=0.397; p=0.04). The prevalence of HPV infection among OOCC patients, based on p16 expression by immunohistochemistry assay, was 25.6%. The group with HPV-positive OOCC had a higher mean age. **Conclusion:** Most cases of OOCC in the studied population do not seem to be associated with HPV infection. The prevalence of HPV infection in our population indicates that public policies should focus on preventing alcohol and tobacco use, fostering immunization, and providing comprehensive sex education.

Keywords: neoplasms; mouth neoplasms; papillomavirus infections; retrospective studies

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Introduction

Cancer is one of the main causes of morbidity and mortality in the world. In 2018, there were approximately 18 million new cases and 9.6 million deaths resulting from cancer, making it the second leading cause of death globally, surpassed only by cardiovascular diseases[1,2]. Among all types of cancer, oral cavity and oropharyngeal cancer (OOCC) represents about 4% of all cases and forms one of the largest groups of cancers in the head and neck region. In Brazil, OOCC ranks fifth in prevalence among men[1,3,4].

In 2019, the National Cancer Institute (INCA) estimated the incidence rate for neoplasms of the oral cavity in the state of Bahia to be 7.85/100,000 inhabitants for men and 2.1/100,000 inhabitants for women[5]. For the city of Salvador, the same study predicted approximately 150 and 40 new cases per year for males and females, respectively, during the triennium 2020-2022[5]. In Brazil as a whole, the estimated number of new cases of oral and oropharyngeal cancer per year was 15,190, with 11,180 cases in men and 4,010 cases in women[5]. OOCC is strongly related to classic risk factors such as smoking and alcohol consumption, often in association[6], especially among older individuals[1]. However, in the early 1990s, the emergence of neoplasms of the oral cavity and oropharynx was noticed in younger patients without a marked history of smoking and alcohol consumption[7]. wherein this group, the main factor involved in the carcinogenesis was found to be the Human Papilloma Virus (HPV) infection[7].

Currently, approximately 120 HPV subtypes are categorized as capable of causing infection in humans[8]. However, the progression to cancer is associated with about 20 high-risk types, with HPV 16 and HPV 18 being the most prominent among them[9].

The incidence of HPV-related oropharyngeal carcinoma, especially HPV-16, is on the rise among middle-aged, medium-to-high class white men who engage in oral sex[10-12]. As a result, since 2007, the World Health Organization (WHO) has recognized HPV as an important factor associated with OOCC[12]. Individuals who have had many sexual partners are at a higher risk of HPV infection, and there is a higher prevalence of oropharyngeal cancer in those who have had or currently have genital HPV infection[13]. Within the head and neck region, the anatomical site most strongly associated with HPV infection is the oropharynx, particularly the tonsils and the base of the tongue[14].

In the last decades, several changes have occurred in the sexual behaviors of the population, including the initiation of sexual activity at an early age, an increase in the number of sexual partners, and the widespread practice of orogenital sex[15]. Moreover, approximately 6 million people are infected by HPV each year, and it is estimated that 13.0% of the world's population is infected with the virus[12]. Therefore, the risk of developing cancers related to HPV has become a significant public health problem.

The determination of HPV infection in OOCC is essential for establishing the appropriate therapeutic strategy and prognosis for affected individuals[16]. Currently, the immunohistochemistry (IHC) assay for detecting the p16 protein is recommended by the American College of Pathologists (CAP) as a marker of HPV infection. This serves as a valuable tool for differential diagnosis, offering excellent cost-effectiveness, reproducibility, and sensitivity ranging from 80 to 98%[17].

Thus, there is an increasing demand for information on the prevalence of HPV infection in OOCC in individuals treated at the tertiary hospital in the city of Salvador, state of Bahia, Brazil. The objective is to characterize the features of this population, including their sociodemographic characteristics, and to identify factors associated factors with the development of this pathology.

Considering the lack of information on the population affected by OOCC in the state of Bahia, we studied the individuals who were attended, diagnosed, and treated at the Hospital Aristides Maltez, located in the city of Salvador. It is a non-profit philanthropic institution specialized in cancer treatment and the main public cancer care unit for the population in the state. Our objective was to characterize the diagnosed population and identify the prevalence of HPV associated with the development of this pathology.

Method

This is a retrospective, observational, descriptive study conducted on individuals residing in the state of Bahia, aged ≥18 years, who were referred for diagnosis, staging, and/or treatment of oropharyngeal or oral cavity carcinoma (OOCC) (ICD C10.0-9 / C04.0-9) at Hospital Aristides Maltez (HAM) from 2017 to 2020. HAM is a tertiary hospital specialized in cancer treatment and is located in Salvador. Individuals with other concomitant neoplasms and those whose clinical findings did not agree with the initial diagnostic suspicion were excluded from the study. The study protocol was approved by the Institutional Review and Ethics Committee of the Pharmacy School at the Federal University of Bahia (CAAE 16933819.3.0000.8035). The requirement for written informed consent was waived because the data were collected from the electronic systems of the HAM.

The data were collected through the analysis of medical and surgical records of the HAM Head and Neck Surgery Service. Sociodemographic and clinical information was obtained, including sex, age, skin color, occupation, address, alcohol consumption and smoking history, type of carcinoma diagnosis, staging, tumor size, and the results of the immunohistochemical examination regarding the presence of HPV through the expression of the p16 protein.

The Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to assess the normality of the data. For the distribution of variables, mean, standard deviation, median, and percentiles were calculated when applicable. Student-*t* tests were used for numerical variables following a normal distribution, and Mann-Whitney tests were used for non-parametric data. The chi-square test (or Fisher's exact test) was used to assess the association of proportions between qualitative/categorical variables. The Pearson's test was utilized for correlation analysis of numerical variables with a normal distribution, and the Spearman's test was employed for non-parametric data. Multivariate analysis was performed to independently assess the association of HPV with risk factors such as smoking, alcohol consumption, age, and diagnosis. All statistical analyses were performed using the SSPS 20.0 software adopting a significance level of 5% ($p< 0.05$).

Results

From 2017 to 2021, a total of 44 patients underwent immunohistochemical tests to detect the p16 protein and were diagnosed with OOCC. Data were available from 39 patients, among whom 43.6% (17) were over 60 years of age, 79.5% (31) were male, and 97.5% (38) were of black or mixed-race ethnicity. Regarding occupation, most individuals were farmers, accounting for 41.7% (n=15) of the study participants (Table 1).

Regarding clinical data and exposure factors related to oropharyngeal carcinoma, it was observed that most patients were either current smokers or had a history of smoking (27, 69.2%), and a significant proportion were alcoholics (29, 74.4%). It is worth noting that three individuals were classified as TX, indicating that it was not possible to estimate the size of the primary tumor, which accounts for the discrepancy in these data in relation to the total number of the individuals in the disease staging classification. Most of the patients were also diagnosed with oropharyngeal carcinoma (24; 61.5%), at stage III, IVa or IVb (28; 77.8%), with tumor sizes classified as T3 and T4 (18; 52.9%).

Table 1. Sociodemographic variables of patients with oral cavity and oropharynx carcinoma (OOCC) treated at Hospital Aristides Maltez from 2017 to 2021 according to the presence of HPV verified through the expression of the p16 protein.

VARIABLE	TOTAL N (%)	HPV+ N (%)	HPV– N (%)	*P*-VALUE
GENDER				
FEMALE	8 (20.5)	2 (20.0)	6 (20.7)	0.67
MALE	31 (79.5)	8 (80.0)	23 (79.3)	
AGE (YEARS)				
<60	22 (56.4)	3 (30.0)	19 (65.5)	0.05
≥60	17 (43.6)	7 (70.0)	10 (34.5)	
SKIN COLOR				
WHITE	1 (2.6)	1 (10.0)	-	-
BROWN	34 (87.2)	7 (70.0)	27 (93.1)	
BLACK	4 (10.3)	2 (20.0)	2 (6.9)	
RESIDENCY				
SALVADOR	13 (34.2)	3 (30.0)	10 (34.5)	0.53
INTERIOR	25 (65.8)	7 (70.0)	18 (62.1)	
OCCUPATION				
TECHNICIAN	4 (11.1)	1 (10.0)	3 (11.1)	0.87
SALES PERSON	12 (33.3)	4 (40.0)	8 (29.6)	
FARMER	15 (41.7)	3(30.0)	12 (44.4)	
HOUSEWIFE / HOUSEHUSBAND	5 (13.9)	1 (10.0)	4 (14.8)	
TOTAL	39	10	29	

Additionally, the majority tested negative for p16 expression, indicating a negative result for HPV by this diagnostic screening (29; 74.4%). There was no significant difference between groups when categorized in relation to the presence or absence of HPV based on p16 expression (Table 2).

The mean age of the individuals included in the study was 57.3 ±11 years. Patients diagnosed with OOCC and HPV (p16 positive) were older (63.0 ±10) compared with HPV-negative patients (55.4 ±11) (p=0.03; Mann-Whitney) (Figure 1).

Table 2. Clinical variables of OOCC patients treated at Hospital Aristides Maltez from 2017 to 2021 according to the presence of HPV from p16 expression.

Variables	TOTAL N (%)	HPV+ N (%)	HPV– N (%)	*P*-value
Smoking				
Yes/Former	27(69.2)	8 (80.0)	19 (65.5)	0.33
No	12(30.8)	2 (20.0)	10 (34.5)	
Alcohol consumption				
Yes/Former	29(74.4)	9 (90.0)	20 (69.0)	0.18
No	10(25.6)	1 (10.0)	9 (31.0)	
Diagnosis**				
Oral cavity	7(17.9)	1 (10.0)	6 (20.6)	0.82*
Oropharynx	25(64.2)	7 (70.0)	18 (60.2)	
Other	7(17.9)	2 (20.0)	5 (17.2)	
Tumor Staging***				
Stages 0 - I – II	8 (22.2)	2 (22.2)	6 (22.2)	0.66*
Stage III – IVa-IVb	28 (77.8)	7 (77.8)	21 (77.8)	
Size ****				
T0-T2	16 (47.1)	4 (44.4)	12 (48.0)	0.58*
T3-T4	18 (52.9)	5 (55.6)	13 (52.0)	
HPV (p16)				
Yes	10(25.6)	10 (100)	-	-
No	29(74.4)	-	29 (100)	

*Fisher's test; p<0.05. *** Missing tumor staging (n=3): no information available on medical record. **** Size T (n=4) – primary site tumor size not available for measurement.

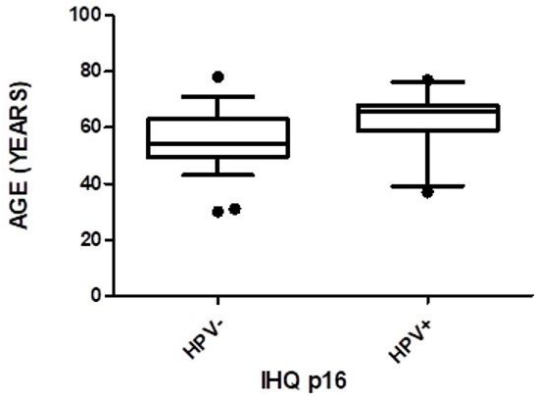

Figure 1. Age distribution of OOCC patients according to the presence of HPV (p=0.03; Mann-Whitney).

The co-occurrence of smoking and alcohol consumption was identified in 90.5% of patients with more advanced tumor staging (p=0.03; Mann-Whitney) (Table 3).

A correlation between increasing age and tumor staging was observed among HPV-negative patients (r=0.397; p=0.04; Spearman) (Figure 2). However, the same correlation was not found in the group of HPV-positive patients (r=-0.229; p=0.32; Spearman).

Multivariate analysis was performed to assess whether HPV infection was independently associated with smoking, alcohol consumption, age, and diagnosis. The results showed that there was no significant association between HPV infection and the variables considered in the evaluated individuals (Table 4).

Table 3. Association of smoking and alcohol consumption with clinical stage of OOCC in patients treated at Hospital Aristides Maltez from 2017 to 2021.

Variable	Smoking OR Alcohol consumption	Smoking AND Alcohol consumption	*P*-value
Tumor Staging**			
Stages 0 – I – II	6 (40.0)	2 (9.5)	**0.03***
Stage III – IVa-IVb	9 (60.0)	19 (90.5)	
Size***			
T0-T2	9 (64.3)	7 (35.0)	0.58*
T3-T4	5 (35.7)	13 (65.0)	

*Fisher's test; p<0,05. ** - Missing tumor staging (n=3): no information available on medical record. *** Size TX (n=3) – Primary site tumor size not available for measurement.

Table 4. Association between factors of interest and HPV infection among OOCC patients treated at Hospital Aristides Maltez from 2017 to 2021.

		B	SE	WALD TEST	DF	*P*-VALUE	OR
TUMOR STAGING	T0-T2	0.300	0.977	0.94	1	0.8525	1.35
	T3-T4	0	.	.	0	.	.
SMOKING	No	-0.32	1.025	0.001	1	0.975	0.968
	Yes	0	.	.	0	.	.
ALCOHOL CONSUMPTION	No	1.35	1.228	1.253	1	0.263	3.953
	Yes	0	.	.	0	.	.
AGE (YEARS)	<60	1.266	.885	2.025	1	0.155	3.545
	>60	0	.	.	0	.	.
TUMOR SITE	Oral cavity	0.298	1.093	0.75	1	0.785	1.348
	Oropharynx	0.594	1.584	0.140	1	0.708	1.810

Caption: SE = Standard Error; OR = Odds ratio; DF = degrees of freedom; p<0.05. β Coefficient

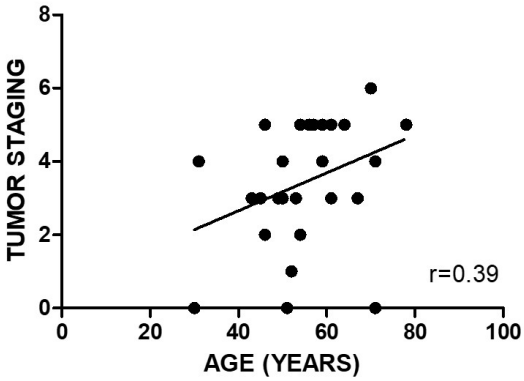

Figure 2. Correlation between tumor staging and age for HPV-negative OOCC patients treated at Hospital Aristides Maltez from 2017 to 2021 and its relationship with tumor staging.

Discussion

The prevalence of HPV infection among individuals with oral cavity and oropharynx cancer was 25.6%, based on p16 expression by IHC assay. This number corresponds to more than a quarter of the population evaluated and is similar to that found in other parts of Brazil (23.2%) in the study by Tristão et al.[16].

However, the frequency found in this study is much lower than that reported in developed countries, as observed by Mehanna et al.[17], who found a prevalence of 72.2% in North America and Europe, and by Mirghani et al.[18], who identified a prevalence of 43.1% of HPV-positive oropharyngeal and oral cavity cancer (OOCC) patients detected by hyperexpression of the p16 protein in France.

In addition, a study carried out with a Danish sample over 18 years identified 2,169 patients with OOCC, with 55% testing positive for HPV infection[19]. Also, a study conducted in Barcelona, Spain between December 2000 and December 2011 identified 155 patients with OOCC; of these patients, 26 (12.6%) were found to have HPV infection based on the expression of the p16 protein[20].

Moreover, in 2017, Anantharama et al.[21] conducted a multicenter study involving centers in the USA, Italy, the United Kingdom, and Brazil to assess the presence of HPV in individuals with head and neck cancer. They detected divergent prevalence values among the different regions. Specifically, the American patients showed a 59.3% HPV detection rate, European patients had 31.1%, while Brazilian patients had the lowest rate, totaling only 4.1%. This divergence can be explained, in part, by the heterogeneity of the tumor site. According to Combes and Francheschi[22], the probability of a cancer of the oral cavity, larynx or hypopharynx being related to HPV can be up to five times lower than that of oropharyngeal cancer. This difference can be verified in our study, where 70% of the cancers identified in HPV-positive patients were located in the oropharynx, while 10% of the cases were located in the oral cavity, and 20% were found in other sites.

In this study, it was observed that 20.5% of the patients were women while 79.5% were men, regardless of whether they were HPV positive or negative, maintaining the same proportion in both groups. This distribution between men and women aligns with findings in the literature and corroborates the data from INCA (2020), which indicates that OOCC occurs more frequently in men than in women. According to Gillison et al.[23], men have a higher prevalence of HPV infection than women (approximately 11% *vs*. 3%) and high-risk HPV infection (approximately 7% vs 1.5%). Other available studies also show similar proportions in the division by sex[24].

In this study, the group with HPV-positive OOCC had a higher mean age, corroborating the findings in the study conducted by Girardi[25] in southern Brazil. This finding differs from what is commonly reported in the literature worldwide, where tumors related to HPV infection are more prevalent in individuals under the age of 60 years[24].

The variables skin color and locality did not show any statistical difference between the groups of HPV positive or negative patients with OOCC. However, concerning the variable occupation, it was noted that most of the individuals in the study work as farmers or activities linked to rural life. Interestingly, data from the National Health Survey (PNS) in 2019 revealed a slightly higher proportion of tobacco smokers over 18 years of age in rural areas (13.7%) compared with those in urban areas (12, 4%). Smoking is one of the main risk factors for OOCC[1].

In this study, most OOCC patients were HPV-negative (74.35%), while HPV-positive tumors accounted for 25.65%. Gillison et al.[23] found a proportion of 20.9% of HPV-positive oropharyngeal cancers in the American population when analyzing samples prior to 1990. However, there was a significant change in this proportion to 65.4% positivity for HPV when samples of oropharyngeal cancer obtained after the year 2000 were considered[24]. This finding indicates a clear epidemiological transition in relation to risk factors associated with the carcinogenesis of these tumors during this period.

A similar transition was observed through an increase in the number of HPV-positive oropharyngeal cancers in eight centers in Australia, described from 1995 to 2010. The proportion of HPV-positive cases rose from 20.2 to 63.5%[26]. Also, Habbous et al.[27] estimated that the prevalence of HPV-positive oropharyngeal cancer at six Canadian centers increased from approximately 47% in 2000 to around 74% in 2012.

The findings above suggest that the proportion of HPV infection in OOCC in the population studied is similar to that of developed countries before the 2000s. These cancers still seem to be associated with classic risk factors such as smoking and alcohol consumption. This is supported by the observation that the smoking habit was present in both the HPV-positive and the HPV-negative groups, accounting for 80 and 65.5%, respectively, in the present study.

The present study also revealed significant data when analyzing smoking and alcohol consumption concomitantly, showing an association with more advanced tumor grades. McDermott and Bowles[28] reported that smoking, whether from cigarettes, cigars, or pipes, increases the risk of squamous cell carcinoma of the head and neck by 5 to 25 times, with a clear dose relationship between duration and amount of cigarette use and cancer incidence.

Furthermore, alcohol consumption independently doubles the risk of developing head and neck cancer, and when used in combination with tobacco, is the risk is considered to be synergistic. In the US, the risk of head and neck cancer related to concomitant alcohol consumption and smoking is even higher in African Americans and those of lower socioeconomic status[29].

It has been observed that most patients who consumed alcohol and smoked had a more advanced tumor stage, reaching at least stage III (defined as tumor >4 cm in greatest dimensions or >10 mm in depth of invasion or with compromised regional lymph nodes). This finding indicates a worse prognosis in these individuals, as reported by Moro et al.[29] In their study, the death rate of patients with advanced OOCC was 49% over a 10-year period, with a mean survival time of 4 years (95% confidence interval − 95% CI 4.44-5.90)[30].

The frequency of HPV infection in patients with OOCC in our population resembles rates observed in developed countries about 20 years ago. This similarity presents an opportunity to develop strategies to prevent HPV infection, including immunization. The advantage lies in the fact that we can now focus on prevention in primary healthcare systems. Experimental data, mainly from preclinical studies, support HPV vaccination in head and neck cancer. Studies involving HPV-vaccinated mice demonstrated immunity to oral HPV pseudovirus development. Additionally, research on HPV vaccine-treated individuals showed high levels of antibodies to neutralizing HPV in their saliva. A study conducted with women in Costa Rica further demonstrated that vaccination against HPV 16/18 was associated with a 93% reduction in the prevalence of oral HPV 16/18[29].

Although this is an observational, retrospective study based on medical records, we firmly believe that the results reported here reflect the real picture of HPV infection in our population. This confidence arises from the fact that our hospital is a referral center in the state of Bahia, serving almost all patients with this diagnosis. The use of IHC assay for the diagnosis of HPV infection is widely validated in the literature and is recommended by the American College of Pathologists.

Conclusion

Most cases of oral cavity and oropharynx cancer (OOCC) in our population are not associated with HPV infection, but rather with classic factors, such as smoking and alcohol consumption, which, synergistically, contribute to the development of advanced tumors. Individuals diagnosed with HPV-positive OOCC were statistically significantly older than those HPV-negative cancer. The findings related to HPV infection and OOCC found in this study agree with those reported in the literature worldwide. However, the prevalence of HPV infection resembles rates observed in developed countries about 20 years ago, indicating that public policies should focus on preventing alcohol and tobacco use, as well as HPV infection, by fostering immunization and providing comprehensive sex education.

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