International Dental & Medical Journal of Advanced Research (2019), 5, 1–9

ORIGINAL ARTICLE

Differential characteristics of human papillomavirus-positive and human papillomavirus-negative oral carcinomas

Alberto Rodriguez-Archilla, Victoria E. Ortiz-Mosquera

Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, 18071 Granada, Spain

Keywords:
Epidemiology, mouth neoplasms, oral manifestations, papillomavirus infections, signs and symptoms

Correspondence:
Alberto Rodriguez-Archilla, Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, 18071 Granada, Spain. Phone: +34 958 244 085.
E-mail: alberodr@ugr.es

Received 16 April 2019;
Accepted 01 June 2019

doi: 10.15713/ins.idmjar.102

Abstract

Background: In addition to, tobacco consumption and/or alcohol intake, human papillomavirus (HPV) infection plays an increasingly important role as an etiologic factor for oral cancer, especially for oropharyngeal cancer.

Aim: The aim of the study was to describe the differential characteristics of HPV-positive and HPV-negative mouth neoplasms.

Methodology: A PubMed search through December 2018, considering Medical Subject Headings terms such as "mouth neoplasms" and "papillomavirus infections" were achieved. Studies with results of HPV detection in oral carcinomas were assessed. From 202 studies with full-text availability, 173 were excluded for several reasons: Studies that did not compare HPV positive and HPV negative oral tumors (161), and studies with no usable/irrelevant data (12). Statistical analysis was performed using the statistical software IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). Descriptive statistics included means, standard deviations, and percentages. For continuous variables, the Student's *t*-test was used. For categorical variables, the Pearson Chi-square test with Fisher's exact test when required was also used.

Results: Twenty-nine studies on HPV infection and oral cancer were considered. 37.4% of oral cancers were infected by HPV. Positive HPV oral tumors appeared in younger patients ($P = 0.02$), with male gender ($P < 0.001$), with smaller tumor sizes (T1, T2, $P < 0.01$), a greater lymph node involvement (N+, $P < 0.001$), a higher tumor stage ($P < 0.001$), and a lower tobacco consumption ($P = 0.01$) although higher alcohol intake ($P = 0.01$) and an overexpression of the p16 protein ($P < 0.001$).

Conclusions: HPV-infected oral cancers have both different characteristics and biological behavior than those of uninfected tumors.

Clinical Significance: The increased incidence of oral HPV-positive tumors highlights the current primordial role of HPV infection in oral carcinogenesis along with other well-known factors such as tobacco and/or alcohol consumption.

Introduction

Oropharyngeal cancer was responsible for 529,500 new cases (3.8% of all cancers) and 292,300 deaths (3.6% of all cancer deaths) worldwide in 2012.[1]

In recent decades, there has been an increase in the incidence of oral cancer in young individuals where the classic etiological factors of oral cancer, such as tobacco and/or alcohol consumption, seems to have a lesser influence, highlighting the involvement of human papillomavirus (HPV) infection as a relevant causative agent in oral and oropharyngeal cancer. In fact, by the year 2020, it is estimated that the cases of oral cancers related to HPV will exceed the cases of invasive cervix cancer closely associated with HPV infection.[2]

Mouth cancers infected with HPV-positive and uninfected HPV-negative have both different clinical characteristics and biological behaviors. Oral HPV-positive cancers often affect the base of the tongue or the tonsils, they are usually well-differentiated neoplasms, with less depth of invasion and stromal infiltration and better survival rate at 5 years (71%) compared with oral HPV-negative tumors (49%).[3] However, some studies suggest that HPV infection is related to an increased risk of distant metastases and lower survival in oral cancers.[4] The

aim of this study was to assess the differential characteristics of oral HPV-positive and HPV-negative oral carcinomas.

Methodology

A PubMed database search of studies on HPV infection in mouth neoplasms was performed. Search strategies included the following terms from the medical subject headings: "Mouth neoplasms" and "papillomavirus infections." A total of 822 articles from 1969 to 2018 were found. The inclusion criteria were: (a) Type of studies: Clinical studies, comparative studies, evaluation studies, multicenter studies, observational studies, clinical trials, meta-analysis, reviews, and systematic reviews (n = 249) and (b) studies conducted in humans (n = 237). The exclusion criteria were: (a) Studies without full-text availability (n = 35), (b) studies that did not compare HPV-positive and HPV-negative oral tumors (n = 161), and (c) studies with no usable/irrelevant data (n = 12). After considering these inclusion and exclusion criteria, 29 studies were analyzed in this review.

Statistical analysis

The data were processed with the statistical software IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). The descriptive statistic included means, standard deviations, and percentages. To analyze continuous variables, the Student's t-test was used. Categorical variables were assessed using the Pearson Chi-square test with Fisher's exact test when required. The statistical significance level was set at $P < 0.05$.

Results

Table 1 shows the distribution of studies on oral cancer associated or not with HPV, according to age and gender of the patients. The 29 studies analyzed[5-33] comprised a total of 51,041 patients with oral cancer, 19,087 (37.4%) with HPV-infected tumors infected and 31,954 (62.6%) with non-infected cancers. Oral cancer patients had a mean age of 59.6 ± 3.9 years; by gender, 34,004 (66.6%) were male and 17,037 (33.4%), female.

Table 2 presents the distribution of oral cancer studies associated or not with HPV based on the location of the tumors.[6,8,10,11,15-17,19,20,22-24,27-33] If the three main locations (oral cavity, oropharynx, and larynx) are considered, there are a total of 3497 cases. Of these, 2476 (70.8%) affected the oral cavity, 757 (21.7%) to the oropharynx, and 264 cases (7.5%) were located in the larynx. Regarding the tumors that were located exclusively in the oral cavity, of the 2476 cases, 809 (32.7%) were localized in the tongue and 1667 (67.3%) had other different locations in the oral cavity.

The distribution of oral cancer studies associated or not with HPV according to tumor size (T-parameter) and the existence of lymph node metastases (N-parameter) are shown in Table 3. Fifteen studies[5,7,9,11,14,15,18,22-26,28,32,33] analyzed these parameters. Considering the tumor size, 625 tumors (24.7%) were T1 tumors, 870 (34.4%) were T2, 399 (15.8%) were T3 and, finally, 633 (25.1%) were T4 tumors. Regarding lymph node metastases, 1716 tumors (48.3%) did not have lymph node metastases (N0) and 1836 tumors (51.7%) had lymph node metastases (N+).

Twenty-one studies[5,6,8-11,13-15,17,18,20-22,24,26,27,29,31-33] distributed the oral cancers associated or not with HPV considering the degree of tumor differentiation and the harmful habits-tobacco and/or alcohol consumption [Table 4].

With respect to the tumor differentiation, 1088 tumors (43.7%) were well-differentiated tumors, 1122 (45.1%) were moderately differentiated ones, and the remaining 279 (11.2%) were poorly differentiated (PD) neoplasms. Regarding tobacco consumption, 1894 patients (65.4%) were smokers, while 1001 patients (34.6%) were not smokers. Concerning the alcohol intake, in 1655 patients (59.1%) there was regular alcohol intake and in 1143 (40.9%), patients were not habitual drinkers.

Table 5 details the comparison of different parameters of the study of HPV-infected (HPV positive) and HPV-non-infected (HPV negative) oral tumors. Patients with HPV positive tumors had a lower mean age than patients with HPV negative tumors (58.0 ± 4.1 years vs. 61.2 ± 2.8 years) with statistically significant differences (P = 0.02). Regarding gender, higher percentages of men with HPV positive tumors and women with HPV negative tumors were observed, with a statistically significant relationship ($P < 0.001$).

In the tumor location, the majority of HPV negative tumors (76%) were located in the oral cavity. After statistical analysis, a highly significant association was found ($P < 0.001$). With regard to tumor size, HPV positive tumors tended to have a lower tumor size than HPV negative tumors, with statistically significant differences ($P < 0.01$).

Concerning lymph node metastases, 66.7% of HPV positive tumors showed lymph node metastases compared to 46.2% of HPV negative tumors with statistically significant differences ($P < 0.001$).

Taking into account tumor differentiation, the percentage of PD tumors is higher in HPV-positive tumors (15.2%) than in HPV-negative tumors (9.9%), with a statistically significant association ($P < 0.001$). According to the tumor stage, 81.0% of HPV-positive tumors and 42.7% of HPV-negative ones were Stage IV tumors, with a statistically significant relationship ($P < 0.001$).

With regard to harmful habits, a higher percentage of smokers (66.7%) with HPV-negative tumors and a higher percentage of drinkers (63.5%) with HPV-positive tumors were observed. This association was statistically significant (P = 0.01).

Finally, a high percentage of HPV positive tumors (68.4%) showed a p16 protein overexpression; whereas, the vast majority of HPV negative tumors (89.2%) did not express the p16 protein. Highly statistically significant differences were observed ($P < 0.001$).

Discussion

In this review on the differential characteristics of HPV-positive and HPV-negative oral cancers, data from 29 studies have been considered.

Table 1: Distribution of oral cancer studies related to HPV according to age and gender

First author, year	Country	Age						Gender			
		Mean age		<60 years		>60 years		Male		Female	
		HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−
Anderson *et al*., 1994[5]	Canada	58	61								
Tsuhako *et al*., 2000[6]	Japan	64	63					40	36	18	8
Schwartz *et al*., 2001[7]	USA	50	55					26	137	14	77
Ritchie *et al*., 2003[8]	USA	52	63					21	68	8	42
Campisi *et al*., 2006[9]	Italy			10	14	14	25	10	18	14	21
Gallegos-Hernández *et al*., 2007[10]	Mexico			15	31	35	37	35	42	15	26
Sugiyama *et al*., 2007[11]	Japan			7	12	17	30	13	30	11	12
Chaturvedi *et al*., 2008[12]	USA	61	64					12749	17416	4831	10728
Simonato *et al*., 2008[13]	Brazil			3	20	2	4	5	22	0	2
Attner *et al*., 2010[14]	Sweden	63	62					49	16	22	8
Machado *et al*., 2010[15]	Canada			11	39	8	34	15	49	4	24
Rades *et al*., 2011[16]	Germany			25	86	15	44	32	104	8	26
Ibieta-Zarco *et al*., 2012[17]	Mexico	63	62					10	17	6	10
González-Ramírez *et al*., 2013[18]	Mexico			4	9	0	67	1	33	3	43
Quintero *et al*., 2013[19]	Colombia	60	65					25	86	8	56
Krupar *et al*., 2014[20]	Germany	54	59					4	73	2	6
Ramshankar *et al*., 2014[21]	India			72	60	9	15	56	52	25	23
Lee *et al*., 2015[22]	China			53	265	48	165	182	756	12	52
Näsman *et al*., 2015[23]	Sweden	60	65					140	41	46	26
Singh *et al*., 2015[24]	India			14	149	9	78	14	186	9	41
Götz *et al*., 2016[25]	Germany	57	58					4	141	3	54
Fakhry *et al*., 2017[26]	USA	58	58					110	438	54	257
Lai *et al*., 2017[27]	Australia	59	62					35	25	23	12
Petito *et al*., 2017[28]	Brazil	53	60					18	46	3	15
Phusingha *et al*., 2017[29]	Thailand			30	27	52	37	29	24	53	40
Taberna *et al*., 2017[30]	USA			87	63	55	57	125	88	17	32
Tsimplaki *et al*., 2017[31]	Greece			12	71	10	79	12	102	10	48
Ali *et al*., 2018[32]	Pakistan							62	20	33	25
Kim *et al*., 2018[33]	South Korea			10	84	3	90	10	106	3	68
Total		58.0±4.1	61.2±2.8	353	930	277	762	13832	20172	5255	11782

HPV: Human papillomavirus, HPV+: Human papillomavirus-infected tumors, HPV−: Human papillomavirus-non-infected tumors

HPV genomic DNA of HPV-positive cancers does not show same mutations attributed to traditional oral cancer risk factors such as tobacco and alcohol. The HPV oncoproteins E6 and E7 degrade p53 and inactivate pRb, two tumor suppressor genes. The degradation of p53 protein mediated by E6 leads to the deregulation of the cell cycle, inducing the loss of both p21 protein function and p53-mediated apoptosis. In turn, E7 regulated by Ras protein, inactivates pRb favoring malignant transformation. E7 also regulates the Myc gene, increasing cell proliferation. However, HPV-infected oral cancers show the presence of the activator protein 1 (AP-1) in combination with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the absence of the signal transducer and activator of transcription 3 (STAT3) and of the Survivin, an inhibitor of apoptosis. All this cause a limitation in the ability of invasion of the neoplastic cells. HPV-positive tumors have a different molecular profile from HPV-negative ones with upregulation of several cellular proteins (Ras, Myc, p16, NF-κB, and AP-1), functional loss of pro-apoptotic proteins (p53, pRb and Bak) and the deregulation of STAT3 and Survivin. Thus, HPV-positive oral cancers have a better prognosis and increased survival.[3]

Table 2: Distribution of oral cancer studies related to HPV depending on the location of the tumor

First author, year	Country	Tongue		Other oral locations		Oral cavity		Oropharynx		Larynx	
		HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−
Tsuhako *et al*., 2000[6]	Japan	16	20	31	16	47	36	9	8	2	0
Ritchie *et al*., 2003[8]	USA					10	84	19	26		
Gallegos-Hernández *et al*., 2007[10]	Mexico	7	21	17	23	24	44	12	9	16	16
Sugiyama *et al*., 2007[11]	Japan	6	12	10	17	16	29				
Machado *et al*., 2010[15]	Canada	1	28	1	7	2	35	16	6	1	16
Rades *et al*., 2011[16]	Germany					5	19	31	95	4	16
Ibieta-Zarco *et al*., 2012[17]	Mexico							11	7	1	6
Quintero *et al*., 2013[19]	Colombia					16	51	6	39	11	52
Krupar *et al*., 2014[20]	Germany					0	2	4	11	0	49
Lee *et al*., 2015[22]	China	57	265	124	501	181	766	13	42		
Näsman *et al*., 2015[23]	Sweden	58	33	0	0	58	33	128	34		
Singh *et al*., 2015[24]	India	6	57	16	165	22	222	1	5		
Lai *et al*., 2017[27]	Australia	36	26	22	11	58	37				
Petito *et al*., 2017[28]	Brazil					10	29	11	32		
Phusingha *et al*., 2017[29]	Thailand	17	3	65	62	82	65				
Taberna *et al*., 2017[30]	USA					1	89	134	26		
Tsimplaki *et al*., 2017[31]	Greece					8	68	4	18	10	64
Ali *et al*., 2018[32]	Pakistan	61	25	34	20	95	45				
Kim *et al*., 2018[33]	South Korea	6	48	7	126	13	174				
Total		271	538	327	948	648	1828	399	358	45	219

HPV: Human papillomavirus, HPV+: Human papillomavirus-infected tumors, HPV−: Human papillomavirus-non-infected tumors

Table 3: Distribution of oral cancer studies related to HPV according to tumor size (T parameter) and lymph node metastasis (N parameter)

First author, year	Country	Tumor size								Lymph node metastasis			
		T1		T2		T3		T4		No		Yes	
		HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−
Anderson *et al*., 1994[5]	Canada	1	4	2	10	0	3	5	10				
Schwartz *et al*., 2001[7]	USA									12	28	132	82
Campisi *et al*., 2006[9]	Italy	8	25	10	4	5	4	1	6				
Sugiyama *et al*., 2007[11]	Japan	6	11	10	18	5	4	3	9	18	38	6	4
Attner *et al*., 2010[14]	Sweden	19	6	23	2	5	7	24	8	15	13	56	10
Machado *et al*., 2010[15]	Canada									1	45	15	28
González-Ramírez, 2013[18]	Mexico									1	47	3	29
Lee *et al*., 2015[22]	China	40	143	74	334	24	115	56	216	119	521	75	287
Näsman *et al*., 2015[23]	Sweden	58	13	71	18	31	19	26	17	24	24	158	42
Singh *et al*., 2015[24]	India									8	95	15	132
Götz *et al*., 2016[25]	Germany	2	72	1	73	2	21	2	29	3	100	4	95
Fakhry *et al*., 2017[26]	USA	53	164	59	161	19	135	28	193	23	308	141	387
Petito *et al*., 2017[28]	Brazil									14	26	7	35
Ali *et al*., 2018[32]	Pakistan									71	31	23	14
Kim *et al*., 2018[33]	South Korea									10	121	3	53
Total		187	438	250	620	91	308	145	488	319	1397	638	1198

HPV: Human papillomavirus, HPV+: Human papillomavirus-infected tumors, HPV−: Human papillomavirus-non-infected tumors, cm: Centimeters, T1: Tumor size ≤2 cm, T2: Tumor size 2–4 cm, T3: Tumor size >4 cm, T4: Tumor invades adjacent tissues

Table 4: Distribution of oral cancer studies related to HPV depending on the degree of tumor differentiation and tobacco and/or alcohol consumption

First author, year	Tumor differentiation						Tobacco				Alcohol			
	WD		MD		PD		Yes		No		Yes		No	
	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−	HPV+	HPV−
Anderson *et al*., 1994[5]	3	6	3	12	0	3								
Tsuhako *et al*., 2000[6]	34	19	19	14	5	11								
Ritchie *et al*., 2003[8]							26	88	3	22	24	82	5	28
Campisi *et al*., 2006[9]	14	22	7	11	3	6	11	21	13	18	6	11	18	28
Gallegos-Hernández *et al*., 2007[10]							38	46	12	22	39	52	11	16
Sugiyama *et al*., 2007[11]	15	23	5	18	4	1	9	14	15	28	7	17	17	25
Simonato *et al*., 2008[13]	1	6	4	17	0	1	3	23	2	1	2	16	3	8
Attner *et al*., 2010[14]	4	2	18	9	47	11								
Machado *et al*., 2010[15]	0	1	12	68	5	18	11	47	6	26	9	43	2	17
Ibieta-Zarco *et al*., 2012[17]	5	11	10	12	1	4	7	14	9	13	1	1	15	26
González-Ramírez, 2013[18]	0	23	3	47	1	6	0	38	4	38	0	33	4	43
Krupar *et al*., 2014[20]	0	11	3	45	2	19								
Ramshankar *et al*., 2014[21]	54	63	17	4	5	2								
Lee *et al*., 2015[22]	54	268	108	419	22	71	164	680	30	128	151	605	43	203
Singh *et al*., 2015[24]	14	129	8	92	1	6	19	171	4	56	7	66	16	161
Fakhry *et al*., 2017[26]							35	209	99	306	65	246	64	259
Lai *et al*., 2017[27]							38	28	12	8				
Phusingha *et al*., 2017[29]	58	39	18	20	2	3								
Tsimplaki *et al*., 2017[31]							10	93	12	57	6	58	16	92
Ali *et al*., 2018[32]	36	19	54	25	5	1	38	13	38	19	76	32	12	11
Kim *et al*., 2018[33]	9	145	1	19	3	10								
Total	301	787	290	832	106	173	409	1485	259	742	393	1262	226	917

HPV: Human papillomavirus, HPV+: Human papillomavirus-infected tumors, HPV−: Human papillomavirus-non-infected tumors, WD: Well-differentiated, MD: Moderately differentiated, PD: Poorly differentiated

With respect to age, HPV-infected tumors were more frequent in the younger population compared to tumors without HPV infection. This finding agreed with several studies,[12,19,20,23] which pointed out that patients with oral HPV positive carcinomas were diagnosed at younger ages than patients with HPV-negative tumors. However, some researchers did not find this possible relationship with a younger age if other factors were considered.[8,14,25] For example, patients who performed oro-genital sex practices had an average age 18 years lesser than patients without these practices.[8]

In this study, HPV-positive tumors were much more frequent in men than in women with a highly statistically significant relationship ($P < 0.001$). In fact, most studies[6,8,10-12,19,24] agreed with this finding, reporting a higher prevalence of oral HPV-positive cancers in males. However, in some studies,[18,29] the number of women with oral HPV positive cancers was greater, although these differences are probably not due to gender but to other factors that influenced these study populations that conditioned the HPV infection.

Considering the tumor locations (oral cavity, oropharynx, or larynx), HPV-positive tumors had a predilection for affecting the oropharynx (52.7% of the cases) followed by the oral cavity (26.2%) and the larynx (17.0%). This finding was in consonance with published in literature, being the oropharynx, especially the base of the tongue and the tonsils, the main sites of the HPV-positive tumors.[8,10,15,16] Indeed, the HPV detection rates in the tonsils of patients with oropharyngeal cancer reach 80%.[10] The histological peculiarities of the oropharyngeal mucosa with

Table 5: Comparison of the different variables between HPV-positive and HPV-negative oral cancer patients

Variable	Study references	HPV+ *n* (%)	HPV− *n* (%)	*P*-value
Age				
$\bar{X}$ ±SD years	[5-8,12,14,17,19,20,23,25-28]	58.0±4.1	61.2±2.8	0.02*
<60 years	[9-11,13,15,16,18,21,22, 24, 29-31,33]	353 (56.0)	930 (55.0)	0.68
>60 years		277 (44.0)	762 (45.0)	
Gender				
Male	[6-33]	13832 (72.5)	20172 (63.1)	<0.001*
Female		5255 (27.5)	11782 (36.9)	
Location				
Tongue	[6,10,11,15,22-24,27,29,32,33]	271 (45.3)	538 (36.2)	<0.001*
Other oral locations		327 (54.7)	950 (63.8)	
Oral cavity	[6,8,10,11,15-17, 19,20,22-24,27-33]	648 (27.2)	1828 (72.8)	<0.001*
Oropharynx		399 (52.7)	358 (47.3)	
Larynx		45 (17.0)	219 (83.0)	
Tumor size				
T1	[5,9,11,14,22,23,25,26]	187 (27.8)	438 (23.6)	<0.01*
T2		250 (37.2)	620 (33.4)	
T3		91 (13.5)	308 (16.6)	
T4		145 (21.5)	488 (26.4)	
Lymph node metastasis				
No	[7,11,14,15,18,22-26,28,32,33]	319 (33.3)	1397 (53.8)	<0.001*
Yes		638 (66.7)	1198 (46.2)	
Tumor differentiation				
WD	[5,6,9,11,13-15,17,18,20-22,24,29,32,33]	301 (43.2)	787 (43.9)	<0.001*
MD		290 (41.6)	832 (46.4)	
PD		106 (15.2)	173 (9.7)	
Tumor stage				
I	[5,6,8,9,14,15,22-25,30,32,33]	94 (4.4)	217 (11.7)	<0.001*
II		126 (5.9)	473 (25.6)	
III		184 (8.6)	369 (20.0)	
IV		1726 (81.1)	788 (42.7)	
Tobacco consumption				
Yes	[8-11,13,15,17,18,22,24,26,27,31,32]	409 (61.2)	1485 (57.9)	0.01*
No		259 (38.8)	742 (42.1)	
Alcohol intake				
Yes	[8-11,13,15,17,18,22,24,26,31,32]	393 (63.5)	1262 (57.9)	0.01*
No		226 (36.5)	917 (42.1)	
p16 protein overexpression				
Yes	[21,23,24,25]	203 (68.4)	39 (10.8)	<0.001*
No		94 (31.6)	321 (89.2)	

HPV+: HPV-infected tumors, HPV−: HPV-non-infected tumors; $\bar{X}$±SD: Mean±standard deviation, T1: Tumor size ≤2 cm, T2: Tumor size 2–4 cm, T3: Tumor size >4 cm, T4: Tumor invades adjacent tissues; WD: Tumor well differentiated, MD: Moderately differentiated, PD: Poorly differentiated, *statistically significant

respect to the oral mucosa could explain the affinity of HPV for this location. The oropharyngeal mucosa is an invaginated mucosa formed by "crypts" lined by a reticulated epithelium with a discontinuous basal layer and an underlying lymphoid stroma

known as "lymphoepithelial tissue."[8] This tissue facilitates the colonization by HPV, also acts as a reservoir for this virus and contributes to chronic HPV infection with oncogenic potential.[16]

Unlike what happens with HPV negative tumors that had a predilection for locate on the lateral edges of the tongue, HPV-positive tumors tended to occur in other locations different to the tongue. This fact could explain the differences in tumor behavior according to the presence or absence of HPV infection.[3]

In the present study, the HPV positive tumors had smaller tumor sizes (T1-T2) than the HPV negative tumors (T3-T4). Although most studies did not find a significant influence of HPV infection on tumor size,[5,9,11,22,25,26] some ones[14,23] found that patients with HPV-positive tumors had small tumors more frequently. This smaller size could be justified in the tumor growth pattern, which is usually an exophytic or mixed pattern. Probably HPV infection influence on the lymph node affectation (N parameter) more than on tumor size (T parameter).[23]

Similarly to what has been observed in other studies[14,15,18,23] that assessed the lymph node metastasis, in this study, 66.7% of HPV-positive tumors and 46.2% of HPV-negative ones presented lymph node metastasis with statistically significant differences ($P < 0.001$). The HPV-positive tumors, mainly the oropharyngeal tumors, showed a great tendency to spread to cervical lymph nodes.[26]

Regarding the degree of tumor differentiation, 15.2% of HPV-positive tumors and 9.9% of HPV-negative ones were PD tumors, suggesting a possible association between the HPV infection and worse tumor differentiation. However, the findings are controversial because there are studies in favor of this worse tumor differentiation,[9,20] and on the contrary, other ones[6,18] that found a greater number of well-differentiated HPV-positive tumors. Some researchers[14,15] did not observe a significant influence of HPV infection on tumor differentiation. These apparent discrepancies could be due to the particular characteristics of the tumors considered in the different studies and to the subjectivity of the pathologist when evaluating the degree of tumor differentiation.

In this study, 69.7% of HPV positive tumors were Stage IV tumors compared to 79% of HPV-negative tumors that were Stage II tumors with statistically significant differences ($P < 0.001$). Numerous studies coincided with this finding, observing higher tumor stages in HPV-infected tumors.[14,23,30] Recently, a modification of the primary tumor size (T), lymph node involvement (N), and distant metastasis (M), TNM staging for oropharyngeal carcinoma has been proposed. Stage IV has been subdivided into Stages IVA, IVB, and IVC to consider more the lymph node dissemination of the tumor than its size.[23] However, other studies[15,24] have not found differences between positive and negative HPV oral tumors according to tumor stage.

Harmful habits (tobacco and/or alcohol consumption) had a relevant influence on the HPV infection in oral tumors. Thus, 20.6% of patients with HPV positive tumors and 79.4% of those with HPV negative tumors were smokers with statistically significant differences ($P = 0.01$). It seems that smoking has an alleged protective effect on HPV infection in the oral cavity and the oropharynx by increasing the keratinization of normal surfaces of the parakeratinized epithelium. The increase in keratinization could make the mucosa more resistant to trauma, avoiding the loss of mucosal integrity, one of the events necessary for the infection of basal epithelial cells by HPV.[8]

Concerning alcohol intake, the results are different from those found in the case of tobacco consumption. Alcohol intake was higher in patients with HPV-positive tumors, revealing the influence of alcohol on HPV-positive tumors ($P = 0.01$). However, in other studies,[11,13,15,17] the presence of HPV was not significantly associated with smoking or alcohol consumption.

When the overexpression of the p16 protein was compared with HPV infection, a very high percentage (84.9%) of HPV-positive tumors showed p16 protein overexpression; meanwhile, this percentage fell to 15.1% in the case of negative HPV tumors with highly statistically significant differences ($P < 0.001$). Several studies that assessed this parameter pointed out an overexpression of the p16 protein in HPV-positive tumors.[21,23-25] However, in some of them,[24,25] the results were not statistically significant, indicating that the expression of p16 could not be used as a reliable marker of the existence of HPV infection in the population. Furthermore, in these studies, all cases with p16 overexpression had tobacco consumption as an associated factor, implying that the possible oncogenic pathway related to tobacco coexisted with HPV-related events. Tobacco consumption induces changes in the oral mucosa with possible local lesions after the rupture of mucosal integrity, facilitating the colonization and infection by HPV.[24]

The results of this study should be interpreted, taking into account its limitations. The current review only considered studies primarily in English language identified in the PubMed database. This criterion may have introduced the possibility of language and publication bias. Moreover, the methods of both tissue sample preservation and HPV detection could not be considered. In the case of tobacco consumption and/or alcohol intake, the amount of them consumed could not be quantified. Furthermore, the differences in the patient population, collection methodology, detection technique, or diagnostic criteria could have caused variability in the results.

Conclusions

In this study, 37.4% of neoplasms were HPV-infected oral cancers. HPV-positive oral tumors appeared in younger patients ($P = 0.02$), male gender ($P < 0.001$), with smaller tumor sizes (T1, T2, $P < 0.01$), a greater lymph node involvement (N+, $P < 0.001$), a higher tumor stage ($P < 0.001$), and a lower consumption of tobacco ($P = 0.01$) although a higher alcohol consumption ($P = 0.01$) and an overexpression of the p16 protein ($P < 0.001$).

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int

J Cancer 2015;136:E359-86.
2. Huber MA, Tantiwongkosi B. Oral and oropharyngeal cancer. Med Clin North Am 2014;98:1299-321.
3. Yete S, D'Souza W, Saranath D. High-risk human papillomavirus in oral cancer: Clinical implications. Oncology 2018;94:133-41.
4. Lee LA, Huang CG, Liao CT, Lee LY, Hsueh C, Chen TC, *et al.* Human papillomavirus-16 infection in advanced oral cavity cancer patients is related to an increased risk of distant metastases and poor survival. PLoS One 2012;7:e40767.
5. Anderson JA, Irish JC, McLachlin CM, Ngan BY. H-ras oncogene mutation and human papillomavirus infection in oral carcinomas. Arch Otolaryngol Head Neck Surg 1994;120:755-60.
6. Tsuhako K, Nakazato I, Miyagi J, Iwamasa T, Arasaki A, Hiratsuka H, *et al.* Comparative study of oral squamous cell carcinoma in okinawa, southern Japan and Sapporo in Hokkaido, Northern Japan; with special reference to human papillomavirus and epstein-barr virus infection. J Oral Pathol Med 2000;29:70-9.
7. Schwartz SR, Yueh B, McDougall JK, Daling JR, Schwartz SM. Human papillomavirus infection and survival in oral squamous cell cancer: A population-based study. Otolaryngol Head Neck Surg 2001;125:1-9.
8. Ritchie JM, Smith EM, Summersgill KF, Hoffman HT, Wang D, Klussmann JP, *et al.* Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. Int J Cancer 2003;104:336-44.
9. Campisi G, Giovannelli L, Calvino F, Matranga D, Colella G, Di Liberto C, *et al.* HPV infection in relation to OSCC histological grading and TNM stage. Evaluation by traditional statistics and fuzzy logic model. Oral Oncol 2006;42:638-45.
10. Gallegos-Hernández JF, Paredes-Hernández E, Flores-Díaz R, Minauro-Muñoz G, Apresa-García T, Hernández-Hernández DM. Virus del papiloma humano asociado con cáncer de cabeza y cuello. Cir Cir 2007;75:151-5.
11. Sugiyama M, Bhawal UK, Kawamura M, Ishioka Y, Shigeishi H, Higashikawa K, *et al.* Human papillomavirus-16 in oral squamous cell carcinoma: Clinical correlates and 5-year survival. Br J Oral Maxillofac Surg 2007;45:116-22.
12. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and-unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612-9.
13. Simonato LE, Garcia JF, Sundefeld ML, Mattar NJ, Veronese LA, Miyahara GI, *et al.* Detection of HPV in mouth floor squamous cell carcinoma and its correlation with clinicopathologic variables, risk factors and survival. J Oral Pathol Med 2008;37:593-8.
14. Attner P, Du J, Näsman A, Hammarstedt L, Ramqvist T, Lindholm J, *et al.* The role of human papillomavirus in the increased incidence of base of tongue cancer. Int J Cancer 2010;126:2879-84.
15. Machado J, Reis PP, Zhang T, Simpson C, Xu W, Perez-Ordonez B, *et al.* Low prevalence of human papillomavirus in oral cavity carcinomas. Head Neck Oncol 2010;2:6.
16. Rades D, Seibold ND, Gebhard MP, Noack F, Schild SE, Thorns C, *et al.* Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma of the head and neck (SCCHN). Strahlenther Onkol 2011;187:626-32.
17. Ibieta-Zarco BR, Carrillo-García A, Ponce-de-León-Rosales S, Flores-Miranda MM, Mohar A, Lizano M, *et al.* Frequency and genotype distribution of multiple human papillomavirus infections in cancer of the head and neck in a mexican population. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:350-7.
18. González-Ramírez I, Irigoyen-Camacho ME, Ramírez-Amador V, Lizano-Soberón M, Carrillo-García A, García-Carrancá A, *et al.* Association between age and high-risk human papilloma virus in mexican oral cancer patients. Oral Dis 2013;19:796-804.
19. Quintero K, Giraldo GA, Uribe ML, Baena A, Lopez C, Alvarez E, *et al.* Human papillomavirus types in cases of squamous cell carcinoma of head and neck in Colombia. Braz J Otorhinolaryngol 2013;79:375-81.
20. Krupar R, Hartl M, Wirsching K, Dietmaier W, Strutz J, Hofstaedter F, *et al.* Comparison of HPV prevalence in HNSCC patients with regard to regional and socioeconomic factors. Eur Arch Otorhinolaryngol 2014;271:1737-45.
21. Ramshankar V, Soundara VT, Shyamsundar V, Ramani P, Krishnamurthy A. Risk stratification of early stage oral tongue cancers based on HPV status and p16 immunoexpression. Asian Pac J Cancer Prev 2014;15:8351-9.
22. Lee LA, Huang CG, Tsao KC, Liao CT, Kang CJ, Chang KP, *et al.* Human papillomavirus infections are common and predict mortality in a retrospective cohort study of taiwanese patients with oral cavity cancer. Medicine (Baltimore) 2015;94:e2069.
23. Näsman A, Nordfors C, Holzhauser S, Vlastos A, Tertipis N, Hammar U, *et al.* Incidence of human papillomavirus positive tonsillar and base of tongue carcinoma: A stabilisation of an epidemic of viral induced carcinoma? Eur J Cancer 2015;51:55-61.
24. Singh V, Husain N, Akhtar N, Kumar V, Tewari S, Mishra S, *et al.* Do human papilloma viruses play any role in oral squamous cell carcinoma in North Indians? Asian Pac J Cancer Prev 2015;16:7077-84.
25. Götz C, Drecoll E, Straub M, Bissinger O, Wolff KD, Kolk A, *et al.* Impact of HPV infection on oral squamous cell carcinoma. Oncotarget 2016;7:76704-12.
26. Fakhry C, Westra WH, Wang SJ, van Zante A, Zhang Y, Rettig E, *et al.* The prognostic role of sex, race, and human papillomavirus in oropharyngeal and nonoropharyngeal head and neck squamous cell cancer. Cancer 2017;123:1566-75.
27. Lai K, Killingsworth M, Matthews S, Caixeiro N, Evangelista C, Wu X, *et al.* Differences in survival outcome between oropharyngeal and oral cavity squamous cell carcinoma in relation to HPV status. J Oral Pathol Med 2017;46:574-82.
28. Petito G, Carneiro MA, Santos SH, Silva AM, Alencar RC, Gontijo AP, *et al.* Human papillomavirus in oral cavity and oropharynx carcinomas in the central region of Brazil. Braz J Otorhinolaryngol 2017;83:38-44.
29. Phusingha P, Ekalaksananan T, Vatanasapt P, Loyha K, Promthet S, Kongyingyoes B, *et al.* Human papillomavirus (HPV) infection in a case-control study of oral squamous cell carcinoma and its increasing trend in Northeastern Thailand. J Med Virol 2017;89:1096-101.
30. Taberna M, Inglehart RC, Pickard RK, Fakhry C, Agrawal A, Katz ML, *et al.* Significant changes in sexual behavior after a diagnosis of human papillomavirus-positive and human papillomavirus-negative oral cancer. Cancer 2017;123:1156-65.
31. Tsimplaki E, Argyri E, Sakellaridis A, Kyrodimos E, Xesfyngi D, Panotopoulou E, *et al.* Oropharyngeal and laryngeal but not oral cancers are strongly associated with high-risk

human papillomavirus in 172 greek patients. J Med Virol 2017;89:170-6.
32. Ali SM, Awan MS, Atif S, Ali N, Mirza Y. Correlation of human papillomavirus infection and clinical parameters with five-year survival in oral squamous cell carcinoma. J Laryngol Otol 2018;132:628-35.
33. Kim SM, Kwon IJ, Myoung H, Lee JH, Lee SK. Identification of human papillomavirus (HPV) subtype in oral cancer patients through microarray technology. Eur Arch Otorhinolaryngol 2018;275:535-43.

How to cite this article: Rodriguez-Archilla A, Ortiz-Mosquera VE. Differential characteristics of human papillomavirus-positive and human papillomavirus-negative oral carcinomas. Int Dent Med J Adv Res 2019;5:1-9.