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Original Article

Risk Factors Related to Human Papillomavirus Infection in Oral Squamous Cell Carcinoma

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Abstract

Background: In addition to tobacco and alcohol consumption, some infectious pathogens such as human papillomavirus (HPV) have been proposed as carcinogenic factors in oral cancer. **Objective:** The objective of the study is to assess the possible influence of HPV detection in oral squamous cell carcinoma (OSCC). **Materials and Methods:** A PubMed search through April 2018, using the following Medical Subject Headings terms, was performed: "mouth neoplasms" and "papillomavirus infections." Studies with findings on HPV detection in OSCCs were assessed. From 77 studies with full-text availability, 59 were excluded for several reasons: no usable/irrelevant data (32), tonsils, base of tongue and non-OSCC cases studies (26), and animal testing studies (1). The data were analyzed using statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (ORs) using Haenszel–Mantel method with 95% confidence intervals. **Results:** Eighteen studies on HPV detection in OSCCs were included in this meta-analysis. The mean percentage of HPV detection in OSCC was 37.1%. Oral cancer patients showed a higher risk of being infected with HPV than controls (OR: 4.85) and they were more likely to be infected with high-risk HPV (OR: 11.46). A larger number of smokers had HPV-infected tumors (OR: 1.45). Younger age, gender, tobacco and/or alcohol consumption, tumor differentiation degree, tumor size (T-status), and lymph node metastasis (N-status) were factors that did not have a significant influence on HPV-infected oral cancers. **Conclusion:** HPV infection, especially of high-risk HPV, is more frequent in patients with OSCC.

Keywords: Mouth neoplasms, papillomavirus infections, risk factors

Introduction

Head-and-neck cancer is the fifth type of cancer and the sixth most common cause of cancer death worldwide with approximately 550,000 new cases annually.[1]

The involvement of human papillomavirus (HPV) in oropharyngeal carcinogenesis has been suggested for its epitheliotropic nature, the oncogenic potential of some high-risk HPV genotypes (mainly types 16 and 18) in the pathogenesis of uterine cervix carcinoma and in the great morphological similarity between the genital and oropharyngeal epithelia.[2]

More than 90% of the carcinomas of the oral cavity are derived from squamous epithelial cells. Oral carcinogenesis is characterized as a multipass and multifactorial process. In addition to tobacco and alcohol consumption, some infectious pathogens such as HPV can act as carcinogenic factors in head-and-neck cancer and particularly, in oropharyngeal cancer.[3]

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In the oropharynx, HPV has a marked predilection for sites that harbor tonsillar tissues and approximately a 47.7% of oropharyngeal carcinomas are HPV positives. In the oral cavity, the prevalence of HPV in oral cancer is lower, range between 23.5% and 38.1%.[4] The aim of this study was to assess the possible influence of HPV infection in oral squamous cell carcinoma (OSCC).

Materials and Methods

A PubMed search of studies on HPV in OSCC was conducted. Search strategies included the combination of the following terms from the Medical Subject Headings (MeSH): "mouth

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neoplasms" and "papillomavirus infections." A total of 779 articles from 1985 to April 2018 were found. The inclusion criteria were as follows: (a) type of studies – clinical trials, clinical studies, comparative studies, multicenter studies, and observational studies (n = 82), all the studies had to have two or more comparable study groups and (b) studies with full-text availability (n = 77). Exclusion criteria were studies with no usable/irrelevant data (n = 32), tonsils, base of tongue, and non-OSCC cases studies (n = 26), and animal testing studies (n = 1). After applying the inclusion and exclusion criteria, 18 studies were included in this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For the dichotomous variables, the odds ratio (OR) was used with the Haenszel–Mantel Chi-square formula with 95% confidence intervals (95% CIs). Heterogeneity was determined according to P values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effects model was applied. The statistical significance level was set at $P < 0.05$.

Results

Table 1 presents the descriptive characteristics of the 18 included studies in the meta-analysis. The prevalence of HPV in OSCC lesions was determined in populations from nine different countries.[5-22] The mean prevalence was 37.1% ranging from a minimum of 5.9% in the United States[18] to a maximum of 73.3% in India[17] according to these different studies.

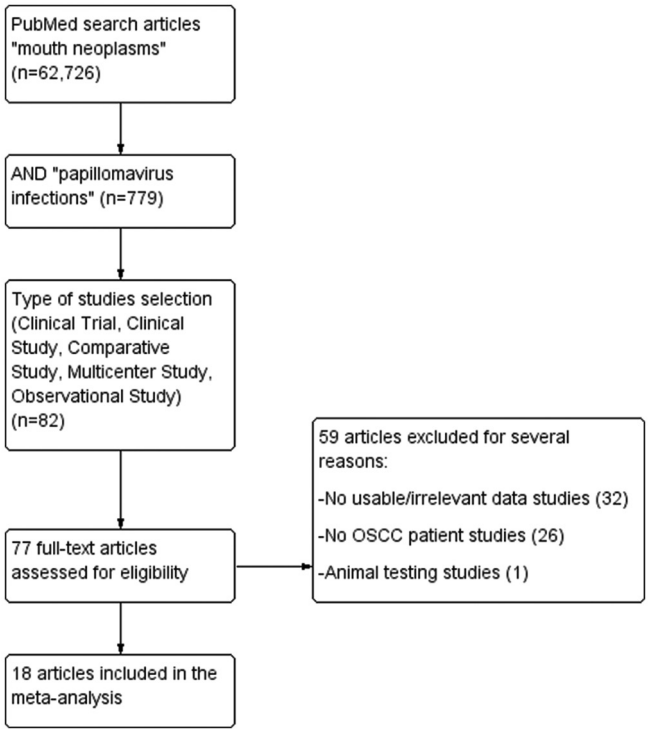

Figure 1: Study flow diagram

The possible influence of other factors related to HPV-infected oral carcinomas is shown in Table 2. Three studies examined HPV detection in patients with OSCC and in controls without cancer lesions.[9,10,12] OSCC patients increased 4.85-fold higher the risk of HPV infection, with highly significant statistical differences (OR: 4.85, 95% CI: 2.79, 8.44, and $P < 0.001$).

Six studies compared the prevalence of low-risk (types 6 and 11) and high-risk (types 16 and 18) HPV types in oral cancer patients.[9,10,12,16,17,21] A high-risk HPV infection were 11.46 times more likely than a low-risk HPV infection in oral cancer patients with a highly significant statistical association (OR: 11.46, 95% CI: 4.66, 28.14, and $P < 0.001$).

Five studies analyzed whether an age above or below 50 years could influence the risk of developing HPV-infected oral carcinomas, noting that HPV-positive oral cancers seemed to be more frequent in younger patients although the results were not statistically significant (OR: 1.66, 95% CI: 0.82, 3.36, and $P = 0.16$).[6,8,14,21,22]

Ten studies assessed the possible influence of the gender on the risk of HPV-infected oral carcinomas.[5,6,8,11,13,14,18,20-22] Although a higher number of males with HPV-infected lesions was observed, no statistically significant differences were found (OR: 0.92, 95% CI: 0.56, 1.49, and $P = 0.73$).

Nine studies considered the possible influence of HPV infection on the location of OSCCs, comparing tongue location, the most frequent intraoral site of oral cancer, versus other oral locations.[5,9,11,14,15,17,18,20,21] HPV-positive oral cancer lesions had not preference for tongue location. After the statistical analysis, no significant relationship was noted (OR: 0.78, 95% CI: 0.61, 1.01, and $P = 0.06$).

Regarding the harmful habits in patients with HPV-infected oral cancers, seven studies[8,10,13,14,20-22] examined tobacco consumption and other five ones,[8,10,13,14,21] the alcohol intake. There were more smokers among patients with HPV-positive OSCCs ($P = 0.01$); nevertheless, alcohol consumption had no significant influence ($P = 0.14$) on risk of HPV infection of OSCC.

In HPV-infected oral cancers, six studies[7,8,11,13,21,22] analyzed the degree of tumor differentiation and other six ones[6,13,14,18,21,22] examined the tumor size (T-status), and finally, five studies[13,14,18,20,21] considered the existence of lymph node metastases (N-status). A poorly differentiated tumor ($P = 0.11$), T3-T4 tumors ($P = 0.46$), and the lymph node involvement ($P = 0.83$) were factors that did not have a significant effect on developing HPV-infected OSCCs.

Discussion

In the present meta-analysis on the role of HPV in OSCC, data from 18 studies have been included.

Considering the different studies analyzed, the mean prevalence of HPV-infection in OSCCs was 37.1%. Other authors[4] reported a prevalence of HPV-positive oral cancers

Table 1: Descriptive characteristics of included studies

Author	Years	Country	HPV detection method	OSCC cases HPV + *n*/*N* (%)	Controls HPV + *n*/*N* (%)	Risk factors assessed
Tsuhako *et al*.[5]	2000	Japan	PCR, ISH	58/101 (57.4)		Gender, location
Ritchie *et al*.[6]*	2003	USA	PCR	10/94 (10.6)		Age, gender, tobacco consumption, alcohol consumption, T-status
Tang *et al*.[7]	2003	Japan	PCR	33/60 (55.0)		Tumor differentiation
Kozomara *et al*.[8]	2005	Serbia	PCR	32/50 (64.0)		Age, gender, tobacco consumption, alcohol consumption, tumor differentiation
Hansson *et al*.[9]*	2005	Sweden	PCR	17/85 (20.0)	14/320 (4.4)	HPV type
Anaya-Saavedra *et al*.[10]	2008	Mexico	PCR	27/62 (43.5)	43/248 (17.3)	HPV type, tobacco consumption, alcohol consumption
Bhawal *et al*.[11]	2008	Japan	PCR	11/29 (37.9)		Gender, location, tumor differentiation
Pintos *et al*.[12]	2008	Canada	Exfoliated cells, ELISA	14/58 (24.1)	6/123 (4.9)	HPV type
Xue *et al*.[13]	2009	China	ISH	7/21 (33.3)		Gender, tumor differentiation, T-status, N-status
Chaudhary *et al*.[14]	2010	India	PCR	72/222 (32.4)		Age, gender, location, tobacco consumption, Alcohol consumption, T-status, N-status
Jalouli *et al*.[15]	2010	Sweden	PCR	15/72 (20.8)		Location
Kulkarni *et al*.[16]	2011	India	PCR	24/34 (70.6)		HPV type
Mathew *et al*.[17]	2011	India	PCR	33/45 (73.3)		Location, HPV type
Lingen *et al*.[18]	2013	USA	PCR	24/409 (5.9)		Gender, location, T-status, N-status
Walline *et al*.[19]*	2013	USA	ISH, PCR	5/19 (26.3)		
Kane *et al*.[20]	2015	India	p16IHC	16/124 (12.9)		Gender, location, tobacco consumption, N-status
Lee *et al*.[21]	2015	China	PCR	194/1002 (19.4)		Age, gender, location, HPV type, tobacco consumption, alcohol consumption, tumor differentiation, T-status, N-status
Lai *et al*.[22]*	2017	Australia	p16IHC	58/95 (61.1)		Age, gender, location, tobacco consumption, T-status

*Excluded other cases different to OSCC. OSCC: Oral squamous cell carcinoma, HPV: Human papillomavirus, PCR: Polymerase chain reaction, ISH: *In situ* hybridization, ELISA: Enzyme-linked immunosorbent assay, p16IHC: p16 immunohistochemistry, *n*: HPV-positive cases, *N*: Total number of cases, T-status: Tumor status, N-status: Lymph node metastases status

Table 2: Risk factors studied for human papillomavirus-infected oral cancer cases

Risk factor	*n*	Reference value	OR	95% CI	I^2 (%)	*P*
HPV						
HPV detection	4	OSCC patients	4.85	2.79–8.44	67	<0.001*
HPV types	6	High-risk HPV	11.46	4.66–28.14	66	<0.001*
Age	5	<50 years-old	1.66	0.82–3.36	81	0.16
Gender	10	Males	0.92	0.56–1.49	53	0.73
Location	9	Tongue	0.78	0.61–1.01	0	0.06
Tobacco consumption	7	Yes	1.45	1.09–1.93	71	0.01*
Alcohol consumption	5	Yes	1.56	0.50–4.83	91	0.44
Tumor differentiation	6	PD	0.71	0.47–1.08	0	0.11
T-status	6	T3–T4	1.10	0.86–1.40	24	0.46
N-status	5	N positive	1.04	0.71–1.53	21	0.83

*Statistically significant. OSCC patients: Oral squamous cell carcinoma patients, PD: Poorly differentiated, T-status: Tumor status, N-status: Lymph node metastases status, *n*: Number of studies, OR: Odds ratio, 95% CI: 95% confidence interval, I^2: Higgins statistic for heterogeneity, HPV: Human papillomavirus

ranged between 23.5% and 38.1%, a percentage similar to the present study. Nevertheless, the great variability observed in the prevalence rates of HPV infection in patients with oral cancer could be justified in the different diagnostic methods used, the particular characteristics of the populations studied, and the little standardization that exists in the anatomical location of cancer since not all articles indicated the exact location of the primary tumor.[23] In addition, it has been proven that the oropharynx, specifically the tonsils, lymphoid aggregates that are part of Waldeyer's ring, are a favorite site

for the development of oropharyngeal carcinoma associated with HPV. This is also explained by the great similarity of this epithelium with that of the uterine cervix which is also especially susceptible to HPV infection. However, the results found on the high prevalence of HPV in other oral locations such as soft palate, floor of the mouth, tongue, gingiva, buccal mucosa, and lip could presume that HPV is a relevant etiological factor for the development of OSCC.[24] In the present study, only OSCCs were considered, excluding malignant tumors located in the tonsils, base of tongue, oropharynx, larynx, or other head-and-neck neoplasms.

When comparing the presence of HPV in patients with OSCC and in controls without the disease, oral cancer lesions were 4.85 times more likely to be HPV infected. All the studies indicated a higher HPV prevalence in patients with oral cancer compared to controls.[10,12] Chaitanya *et al*.[23] found 2.82 times more probability of HPV infection in patients with OSCC, and Syrjänen *et al*.[24] reported an OR of 3.98, lower values than those observed in this study. These differences are explained in the different types of HPV considered although some studies did not differentiate between low-risk and high-risk HPV. There were studies that did not analyze other possible risk factors of confusion of HPV infection such as age, tobacco consumption, sexual habits, or other potential risk factors.[23] The mere detection of HPV in biopsies of patients with OSCC did not imply direct causality because the virus could be coinfecting the tumor although it was not directly involved in the carcinogenesis.[3]

In the present study, the probability of finding high-risk HPV (types 16 and 18) increased 11.46-fold higher compared to low-risk HPV (types 6 and 11) in oral cancer patients with highly significant statistical differences ($P < 0.001$). Most of the studies agreed, observing a higher prevalence of high-risk HPV in OSCC patients.[10,12,16,17,21] In fact, many studies focused only on the detection of high-risk HPV, specifically type 16,[15,16] not considering cases of cancer patients infected with low-risk HPV. Similarly, there was little data on the detection of this high-risk HPV in patients with benign lesions or in healthy controls.[21]

The possible influence of epidemiological parameters such as age and sex on HPV-infected oral cancers was also analyzed. Although a higher prevalence of HPV-infected oral cancers in males below the age of 50 was observed, no statistically significant association was found related to age or sex. However, two studies observed a greater significant prevalence in patients older than 50 years, although their study samples had a high average age, a fact that could have conditioned these results.[6,23] Regarding sex, one study[18] found a significant predilection for the male sex and another one,[13] for the female sex. Probably, the possible bias in the selection of populations and their distribution by gender influenced these apparently opposite results. However, it should be noted that oral cancer is a more frequent disease in men and its incidence increases with age.

In this meta-analysis, tobacco ($P = 0.01$) but not alcohol consumption ($P = 0.14$) showed a statistically significant relationship with HPV-infected malignant oral neoplasms. In the case of tobacco consumption, the results seem to be opposite, with one study[10] with a significant number of smokers and another one,[19] with a greater number of nonsmokers patients with HPV-infected tumors.

In the case of alcohol consumption, a similar trend was also observed. There was one study,[10] in which alcohol was a significant risk factor and another one,[14] in which a greater number of nondrinkers patients with HPV-infected oral carcinomas was observed.

Most of the articles did not present an adjusted analysis on the tobacco and alcohol use, without isolating them as confusing variables. The intrinsic characteristics and the provenance of the study samples might be factors of great influence in their harmful habits. Studies with larger and stratified population samples are required to determine the real role of harmful habits in the oral carcinogenesis process, independently or not of the existence of HPV infection.[19]

The possible influence of HPV infection on the biological behavior of OSCCs was also tried to determine. The degree of tumor differentiation, tumor size (T-status), or the existence of lymph node metastases (N-status) were assessed. However, no statistically significant association ($P > 0.05$) was found between these parameters and the HPV-infected tumors. It seemed that HPV infection of the OSCCs did not worsen the biological behavior of these malignant lesions.

HPV-infected oral tumors have differentiating characteristics compared to HPV noninfected oral cancers. For example, HPV-positive cancers tend to be localized in the tonsils and oropharynx and not in the tongue that is the main location of oral cancers not infected by HPV.[23]

HPV-infected tumors usually have a less aggressive biological behavior than that observed in patients with HPV-negative cancers. These differences could be explained by the influence of factors other than those conventionally established, mainly tobacco and/or alcohol consumption, such as sexual habits that increase the likelihood of HPV infection and in part, justify the increased incidence of oral cancer in younger patients observed in the last decades.[24]

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of the studies included and the presence of different bias. The differences among studies could be conditioned by the study design, the methods used to collect data, the type of analysis used, and the particular features of the study populations.

About 20% of OSCCs and approximately 80% of oropharyngeal carcinomas might be related to HPV infection with a distinctive biological behavior compared to HPV-negative tumors. Finally, in OSCC, HPV infection is probably not an independent causative factor but acts as a modifying cofactor

along with other well-established carcinogenic factors such as tobacco consumption and/or alcohol intake. On the contrary, in oropharyngeal carcinomas, HPV infection plays a more relevant and independent role in the carcinogenesis process.

Conclusion

In this meta-analysis, the mean percentage of HPV detection in patients with OSCC was 37.1%. Oral cancer patients had a higher risk of being infected with HPV than controls (OR: 4.85). They were also more likely to be infected with high-risk HPV than with low-risk HPV (OR: 11.46). A larger number of smokers had HPV-infected tumors (OR: 1.45). In contrast, younger age, gender, tumor location, alcohol consumption, tumor differentiation degree, T-status, and N-status were factors that did not have a significant influence on HPV-infected OSCCs.

In summary, although HPV detection rates in OSCC are lower than in oropharyngeal cancer, HPV infection seems to play an important role in OSCC, improving the biological behavior of these lesions compared to HPV-negative oral tumors. New studies to establish separately the real impact of HPV infection in oral, oropharyngeal, and head-and-neck tumors are needed.

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Conflicts of interest

There are no conflicts of interest.

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