Brazilian Journal of Otorhinolaryngology 2021;87(3):346–352

Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

REVIEW ARTICLE

Human papillomavirus infection and oral squamous cell carcinoma - a systematic review

Bernardo Augusto de Carvalho Melo[a], **Luisa Gallo Vilar**[a], **Natália Rodrigues de Oliveira**[a], **Priscila Oliveira de Lima**[b], **Melina de Barros Pinheiro**[a], **Caroline Pereira Domingueti**[a], **Michele Conceição Pereira**[a,*]

[a] *Universidade Federal de São João Del Rei, Divinópolis, MG, Brazil*
[b] *The University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Australia*

Received 22 September 2020; accepted 19 October 2020
Available online 29 November 2020

KEYWORDS
Mouth neoplasms;
Papillomaviridae;
Systematic review

Abstract
Introduction: The association between uterine cervix and anogenital carcinomas and human papillomavirus, HPV, is well established, however the involvement of this virus in the development of oral squamous cell carcinomas remains controversial.
Objectives: To evaluate the relationship between HPV infection and oral squamous cell carcinomas, and to estimate the incidence of this infection in these patients.
Methods: Four electronic databases were searched to find studies that met the following inclusion criteria: i) performed in humans; ii) were cohort, case-control or cross-sectional; iii) assessed the HPV oncogenic activity by the E6 and E7 mRNA; iv) included primary oral squamous cell carcinomas which; v) diagnosis had been confirmed by biopsy. Information about the country; study period; sample obtainment; sites of oral squamous cell carcinomas; number, gender and age range of the population; the prevalence of HPV infection and subtypes detected; use of tobacco or alcohol and oral sex practice were extracted. The methodological quality of included articles was assessed using 14 criteria.
Results: The search strategy retrieved 2129 articles. Assessment of the full text was done for 626 articles, but five were included. The total of participants included was 383, most of them male with mean age between 51.0 and 63.5 years old. Seventeen patients were HPV/mRNA-positive, being the subtypes 16 and 18 detected more frequently. Nine of the HPV/mRNA-positive oral squamous cell carcinomas occurred on the tongue. The quality score average of included articles was five points.

* Corresponding author.
E-mail: michelepereira@ufsj.edu.br (M.C. Pereira).
Peer Review under the responsibility of Associação Brasileira de Otorrinolaringologia e Cirurgia Cérvico-Facial.

https://doi.org/10.1016/j.bjorl.2020.10.017

Conclusions: Among the 383 oral squamous cell carcinoma patients included, 17 (4.4%) were HPV/mRNA-positive, nevertheless it was not possible to assess if HPV infection was associated with oral squamous cell carcinomas because none of the studies included was longitudinal and cross-sectional investigations do not have control group.

Introduction

It is estimated that the oral cavity ranges from the sixth to the ninth most frequent anatomical location affected by cancer, depending especially on the country and gender of the investigated patients. Annually, about 275,000 new cases of oral cancer are recorded worldwide[1] with squamous cell carcinoma (SCC) accounting for approximately 80%–90% of all malignancies.[2]

Oral SCC (OSCC) can originate in any location of the mucosa, but the sites most frequently affected are the tongue and floor of the mouth.[3,4] Clinically, it presents as an ulcerated lesion, with a central necrotic area, surrounded by raised borders.[2] It predominantly affects men between the fifth and sixth decades of life, being rare in patients under 40 years of age.[4,5] However, its incidence in younger patients has increased in recent decades.[6]

Tobacco and alcohol consumption are well established risk factors for OSCC,[3,5] but 15%–20% of patients still develop OSCC in the absence of exposure to such risk factors.[3,7] In addition, in younger patients, the role of these risk factors is not fully understood due to the shorter exposure time.[5] Therefore, it is suggested that other factors could influence the genesis of OSCC,[8] such as genetic predisposition, diet and viral agents.[7]

Sexual behavior and exposure to human papillomavirus (HPV) are consistent risk factors for anogenital cancers and oropharyngeal SCC,[9] but the role of HPV in OSCC pathogenesis remains controversial.[10] HPV viruses have circular double-stranded DNA genomes of approximately 8000 base pairs,[4,9] and exhibit specific tropism for the squamous epithelium.[9] To date, 202 different virus subtypes have been identified.[9] HPVs are divided into high (hr) and low risk (lr). A benign proliferation is associated with the lr HPV type and malignancy is associated with the hr HPV. Subtypes 16 and 18, and 6 and 11 were considered hr and lr HPV, respectively.[9,11]

The oncogenic potential of hr HPVs is attributed to their ability to insert specific fragments of their DNA, the E6 and E7 genes, into the genome of infected cells. This insertion leads to the abolition of some functions of major tumor suppressor genes, resulting in alterations in the regulation of cell proliferation, apoptosis and genetic stability.[9,12,13] Syrjanen et al.[14] proposed the possible contribution of HPVs to oral carcinogenesis for the first time. This hypothesis was based on their epithelial tropism, the oncogenic potential of hr HPVs in the pathogenesis of anogenital neoplasia, especially cervical SCCs, and morphological similarities between the oropharyngeal and genital epithelia.

Studies conducted worldwide have shown the presence of HPV DNA in OSCCs,[10,15] however these works showed a great variability in viral prevalence which could be justified by several factors. For instance, sample collection and preservation methods; sensitivity of the virus detection technique, absence of consensus regarding the anatomical division of the oral cavity, clustering of head and neck tumors as a single entity, risk of carryover contamination with previously amplified *material*, and lack of proof of the actual HPV oncogenic activity, since the presence of HPV DNA alone is an insufficient evidence for a causal association from a molecular perspective.[1,3,13] The expression of E6 and E7 oncogenes has been considered the gold standard test to assess the involvement of HPV in those tumors,[10] but previous reviews have not used this criterion.

Clarifying the relationship between HPV infection and OSCC could have a very positive impact on the diagnosis and treatment of this specific group of patients, as well as contribute to the implementation of more effective health policies and programs. In this context, the present study aimed to perform a systematic review of the literature to evaluate the relationship between HPV infection and OSCC, and to estimate the proportion of this viral infection in OSCC patients.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[16] A review protocol was created a priori and registered on PROSPERO international prospective register of systematic reviews (2016: CRD42016042670).

Search strategy

We conducted a search on Medline, Embase, Web of Science and Lilacs databases from the earliest record to February 2018. Optimized search strategies were performed using the key terms ''oral cancer'' or ''oral squamous cell carcinoma'' or ''oral SCC'' or ''oral tumor'' or ''oral neoplasm'' or ''mouth neoplasms'' or ''gingival neoplasms'' or ''palatal neoplasms'' or ''tongue neoplasms'' AND ''papillomaviridae'' or ''expalphapapillomavirus'' or ''human papillomavirus'' or ''papillomavirus infections'' or ''papillomavirus infection'' or ''HPV''. No restriction was applied on the year of publication. Studies included in the review were restricted to English, Spanish and Portuguese

Table 1 Eligibility criteria for cross-sectional, cohort or case-control studies inclusion in the systematic review.

Criterion	Description	
	Cross-sectional study	Cohort or case-control study
Population	OSCC patients	OSCC patients
Exposure	HPV infection	HPV infection
Comparison	OSCC patients without HPV infection	Not applicable
Outcome	OSCC	OSCC

OSCC, Oral Squamous Cell Carcinoma; HPV, Human Papillomavirus.

languages. Citation tracking was performed by manually screening reference lists.

Eligibility criteria

Eligible studies included those that were i) performed in humans; ii) were cohort, case-control or cross-sectional; iii) assessed the HPV oncogenic activity by the E6 and E7 mRNA; iv) included primary OSCCs which; v) diagnosis had been confirmed by biopsy.

The Population, Exposition, Comparators, Outcomes, Study design (PECOS) and PEOS statements are summarized in Table 1.

Exclusion criteria

We excluded studies that were not original, included SCCs of lip or other OSCC variants, duplicated information from previously published papers, did not mention the number of OSCCs analyzed, and did not report the prevalence of HPV infection.

Study selection and data extraction

The first evaluation of potentially eligible articles involved the screening of titles and abstracts by two independent reviewers. Relevant records selected from this stage were examined by analysis of the full text. Disagreements were resolved by a third reviewer. The following data were extracted from each included study: continent, country, period of study, sample obtainment, OSCC sites, number, gender, and age, besides the prevalence of HPV infection. For the HPV/mRNA-positive patients, mean age, tumor location, detected HPV subtypes, number and percentage of smokers, drinkers and oral sex practitioners were collected.

Quality assessment

The methodological quality of included articles was assessed using a checklist based on previously employed tools.[17] Fourteen quality criteria were applied: i) whether sample size was at least 50 patients, ii) whether the cases were recruited randomly or consecutively, or were incident cases, iii) the recruitment period was stated, whether there was description of; iv) inclusion criteria; e v) exclusion criteria, whether the paper contained specific information for HPV/mRNA-positive patients about vi) gender; vii) age, viii) tobacco use, ix) alcohol consumption,; whether the confounding factors x) drinking, xi) smoking, xii) oral sex practice or xiii) other confounding factors were considered and xiv) contamination control was mentioned on the papers.

Each item was scored as yes (1) or no (0). A total score was also calculated as the sum of the results for each individual item. Two independent reviewers assessed the quality of the articles with a third reviewer resolving any disagreements.

Statistical analysis

Pooling of studies was not possible because of their heterogeneity in terms of study design, age, gender, smoking, drinking and oral sex practice, for HPV/mRNA-positive patients. Therefore, results are presented descriptively including quantitative results for each study.

Results

Searches performed through the databases retrieved 3146 articles, which added to the 72 identified from a systematic review by Ndiaye et al.,[17] resulted in 3218 studies (Fig. 1). After excluding the duplicates, 2129 articles had their titles and abstracts screened. The full text was assessed in 626 of them, but only five were included. The main reason for paper exclusion was the lack of E6/E7 mRNA expression analysis to characterize the HPV oncogenic activity. The selection process of studies can be visualized in Fig. 1.

All included papers were published between 2013 and 2016 and reported data from North and South America, Asia, and Europe. Most of them (60%) did not describe the study period (Table 2). In regard to sample obtainment, 40% were not specified, 40% came from surgical specimens and biopsies and 20% only biopsies.

The five articles included a total of 383 patients, most of them male (Table 2). Participants included in the studies had an age of 19–92 years. The highest mean age of patients with OSCC, identified by Chor et al.,[18] was 63.5. Also, two studies analyzed the HPV prevalence in anatomic sites of OSCC patients and described the tongue as the affected site in 131 cases.

Among the 383 OSCC patients included, 17 cases (4.4%) were HPV/mRNA-positive. Two studies reported that the mean age of patients was 51.2 and 60.4 years old.[6,19] Poling et al.[19] identified a single HPV/mRNA-positive patient, who was 62 years old. Chor et al.[18] did not identify any HPV/mRNA-positive patients.

Nine HPV/mRNA-positive OSCC cases were located on the tongue, one was on the alveolar ridge and seven had no specified site. The most prevalent subtype was the HPV-16, described in 14 cases, followed by the HPV-18.

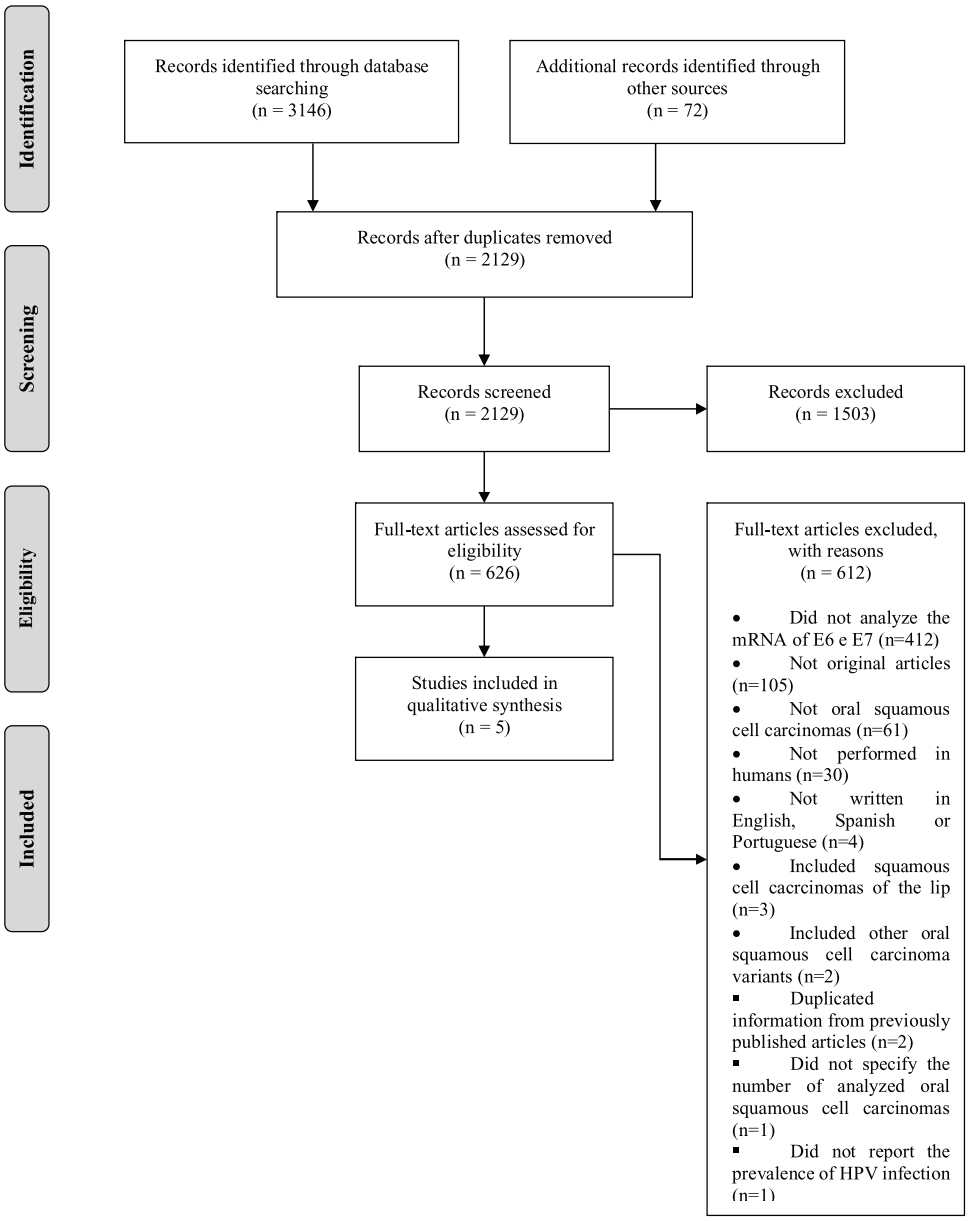

Figure 1 Flowchart of the phases of the systematic review.

Only two papers presented information on the number of tobacco smokers and alcohol consumers.[6,19] Poling et al.[19] reported one patient positive for HPV/mRNA who was a smoker and also a heavy drinker. According to Tsimplaki et al.,[6] in a group of five HPV/mRNA-positive patients, only one was a smoker and a drinker. No study divulged any data related to oral sex practice. A summary of results from included articles that analyzed HPV/mRNA-positive OSCCs is shown in Table 3.

The quality score average of included articles was five points; none of them reached the maximum score. The highest score (nine points) was attributed to the study performed by Poling et al.,[19] In terms of paper quality, the main limitations were: lack of information about the patients' recruitment, exclusion criteria adopted in the selection of study population and the consideration of confounding factors during the statistical analysis.

Discussion

It was not possible to evaluate if HPV infection was associated with OSCC because none of the included studies was longitudinal and cross-sectional do not have a control group.

Seventeen cases (4.4%) were HPV/mRNA-positive. 14 cases were positive for HPV-16 and two for HPV-18. Admittedly, the subtypes 16 and 18 play an important role in the development of certain tumors, including in OSCC.[7] The subtype 16 is identified in 90%–95% of HPV-positive oropharyngeal SCC. For OSCCs, there is greater variability in the prevalence of the infecting subtype.[20] Interestingly, a systematic review[20] evaluated worldwide studies and estimated a higher prevalence of HPV/mRNA-positive OSCCs (7%–16%) compared to the one described in this review (4.4%).

Table 2 Summary of data from included articles.

Study	Country	Study design	Study period	Sample obtention	OSCC patients (n)	OSCC site	OSCC patients' gender		Mean age
							Male n (%)	Female n (%)	
Lleras et al. (2013)	United States of America	Cross sectional	Not mentioned	Surgical specimen and biopsies	35	Not mentioned	24 (70%)	11 (30%)	61
Poling et al. (2014)	United States of America	Cross sectional	Not mentioned	Not mentioned	78	Tongue	36 (46%)	42 (54%)	55
Tsimplaki et al. (2014)	Greece	Cross sectional	Not mentioned	Biopsies	53	Tongue	39 (73.6%)	14 (26.4%)	51
Reyes et al. (2015)	Chile	Cross sectional	2000–2014	Not mentioned	80	Not mentioned	44 (55%)	36 (45%)	Not mentioned
Chor et al. (2016)	China	Cross sectional	January 2012 to December 2014	Surgical Specimen and Biopsies	137	Not mentioned	1.2/1[a]	1/1.2[b]	63.5

OSCC, Oral Squamous Cell Carcinoma.
[a] Ratio between men and women, according to information collected from the study.
[b] Ratio between women and men, according to information collected from the study.

Table 3 Summary of data regarding HPV/mRNA-positive patients from included studies.

Study	Mean age	Tumor site (n)	HPV subtypes		Tobacco use n (%)	Alcohol consumption n (%)	Oral sex practice
			HPV 16 n (%)	HPV 18 n (%)			
Lleras et al. (2013)	Not mentioned	Not specified	6 (17%)	–	Not specified	Not specified	Not specified
Poling et al. (2014)	62[a]	Tongue (1)	Not specified		1 (100%)	1 (100%)	Not specified
Tsimplaki et al. (2014)	51.2	Tongue (5)	4 (7.5%)	1 (1.9%)	1 (20%)	1 (20%)	Not specified
Reyes et al. (2015)	60.4	Tongue (3), alveolar ridge (1), and not specified (1)	4 (80%)	1 (20%)	Not specified	Not specified	Not specified
Chor et al. (2016)	–	–	–	–	–	–	–

HPV, Human Papillomavirus; (–) No patient was HPV/mRNA-positive.
[a] The only HPV/mRNA-positive patient was 62 years old.

Few studies met the inclusion criteria established in this systematic review, which means that a limited number of articles employed the gold standard test to assess the involvement of HPV in OSCC. Additionally, most of the papers selected did not report data stratified by age, gender, smoking, alcohol consumption and oral sex practice for HPV/mRNA-positive patients.

Since the 1960s, many studies have shown an increasing incidence of head and neck SCC (HNSCC) worldwide, particularly in the tongue and oropharynx of young adults.[21] However, this has been simultaneously associated with a decrease in the prevalence of smoking habits in the general population.[22] It has been suggested that genetic factors, viral infections and behavioral risk factors could be involved in the etiology of these cancers.[23] Most studies have attributed such epidemiological change to HPV.[24]

Although the articles included in this systematic review reported data from the United States, Greece, Chile and China, none of them specified the patient's country or continent of origin. Due to this fact, the possible association between ethnicity and prevalence of HPV infection could not be evaluated. The ethno-geographical origin of the individ-

uals represents a well-known variability factor in relation to the HPV prevalence in HNSCC. Based on the high prevalence of HPV in the oral cancers of Asiatic patients, Termine et al.[13] suggested that this viral infection is an important etiological factor, capable of causing additional mutations in the carcinogenic process along with eating habits and genetic predisposition.[13] Additionally, Boy et al.[25] and VanRensburg et al.[26] described the low prevalence of HPV in South African patients with OSCCs, which ranged from 0% to 11.9%.

Regarding the OSCC sample acquisition, two studies obtained samples from surgical resections and biopsies,[18,27] one only through biopsies[6] and two[19,28] did not supply information about that. According to Termine et al.,[13] the biopsy remains one of the most common procedures to obtain oral cavity samples, allowing the same specimen to be used in morphological analysis and molecular tests for HPV detection. However, surgical specimens provide more representative samples of tumors compared to biopsies.

The maximum and minimum age of OSCC patients was 92 and 19 years old, respectively. OSCCs occur more frequently in elderly or middle-aged individuals, but this neoplasia has been increasingly documented in young adults.[5,21,23] Thus, the results acquired in the present review corroborate the epidemiological data described before.

Also, only two papers[6,19] reported data on the HPV prevalence related to anatomic sites in OSCCs. The tongue was the only site described on these papers. According to the literature, even though any area of the mucosa can be affected by OSCC, the most common sites are the tongue and the floor of the mouth.[29]

Among the 383 OSCC patients identified in the five articles selected for this review, the majority were male. OSCCs are more common in men than women (2:1), but the incidence in females has probably increased due to the greater exposure of this group to carcinogenic agents such as alcohol and tobacco.[30]

Furthermore, some confounding factors were taken into account. Smoking is an important risk factor for oral and oropharyngeal SCC. Although tobacco smoking has been declining or stabilizing in developed countries, its use has been increasing in low- and middle-income countries. Gandini et al.[31] showed that active smokers have a relative risk of 6.76 for developing oropharyngeal SCC and 3.43 for OSCC when compared to nonsmokers.

The abusive consumption of ethanol (> 60 g per day) is associated with an increased risk of oral and oropharyngeal SCC. Recent meta-analyzes have estimated that, for 10 g of alcohol per day, the relative risk is 1.3 for HNSCC. This risk increases to 13.0 when 125 g of ethanol is consumed per day.[20]

The present study sought to obtain data on the number of HPV/mRNA-positive patients, smokers and/or consumers of alcohol. However, few studies provided that information. Poling et al.[19] reported that the only HPV/mRNA-positive patient was both heavy drinker and smoker, whereas Tsimplaki et al.[6] observed that in a group of 5 HPV/mRNA-positive patients, only one used tobacco and ingested alcohol.

No study discussed any correlation between oral sex practices and HPV infection in HNSCCs. According to Heck et al.,[32] there is growing evidence that sexual behaviors, such as oral sex, are associated with an increased risk of HPV infection and the development of HNSCC. However, the same authors found little evidence of the association between sexual behaviors and OSCC.

Conclusions

In our systematic review, seventeen cases (4.4%) were HPV/mRNA-positive. It was not possible to assess if HPV infection was associated with OSCC because none of the five studies included was longitudinal and cross-sectional do not have a control group. This fact emphasizes the need and importance of conducting studies that assess this issue.

Conflict of interest

The authors declare no conflicts of interest

Acknowledgments

To the Universidade Federal de São João Del Rei (UFSJ) for the scientific initiation scholarships granted to the students who participate in this work team.

To Marina de Barros Pinheiro and Gustavo de Carvalho Machado, both from The University of Sydney, for the technical support.

References

1. Mirghani H, Amen F, Moreau F, Lacau St Guily J. Do high-risk human papillomaviruses cause oral cavity squamous cell carcinoma? Oral Oncol. 2015;51:229–36.
2. Pires FR, Ramos AB, Oliveira JB, Tavares AS, Luz PS, Santos TC. Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. J Appl Oral Sci. 2013;21:460–7.
3. Duray A, Descamps G, Decaestecker C, Remmelink M, Sirtaine N, Lechien J, et al. Human papillomavirus DNA strongly correlates with a poorer prognosis in oral cavity carcinoma. Laryngoscope. 2012;122:1558–65.
4. Kouketsu A, Sato I, Abe S, Oikawa M, Shimizu Y, Takahashi T, et al. Detection of human papillomavirus infection in oral squamous cell carcinoma: a cohort study of Japanese patients. J Oral Pathol Med. 2016;45:565–72.
5. Kaminagakura E, Villa LL, Andreoli MA, Sobrinho JS, Vartanian JG, Soares FA, et al. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. Int J Cancer. 2012;130:1726–32.
6. Tsimplaki E, Argyri E, Xesfyngi D, Daskalopoulou D, Stravopodis DJ, Panotopoulou E. Prevalence and expression of human papillomavirus in 53 patients with oral tongue squamous cell carcinoma. Anticancer Res. 2014;34:1021–5.
7. Bouda M, Gorgoulis VG, Kastrinakis NG, Giannoudis A, Tsoli E, Danassi-Afentaki D, et al. High risk HPV types are frequently detected in potentially malignant and malignant oral lesions, but not in normal oral mucosa. Mod Pathol. 2000;13:644–53.
8. Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982-1997. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91:622–35.
9. Hubbers CU, Akgul B. HPV and cancer of the oral cavity. Virulence. 2015;6:244–8.
10. Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillo-

mavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49:1–8.
11. Hauck F, Oliveira-Silva M, Dreyer JH, Perrusi VJ, Arcuri RA, Hassan R, et al. Prevalence of HPV infection in head and neck carcinomas shows geographical variability: a comparative study from Brazil and Germany. Virchows Arch. 2015;466:685–93.
12. Shaikh MH, McMillan NA, Johnson NW. HPV-associated head and neck cancers in the Asia Pacific: a critical literature review & meta-analysis. Cancer Epidemiol. 2015;39:923–38.
13. Termine N, Panzarella V, Falaschini S, Russo A, Matranga D, Lo Muzio L, et al. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). Ann Oncol. 2008;19:1681–90.
14. Syrjanen K, Syrjanen S, Lamberg M, Pyrhonen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. Int J Oral Surg. 1983;12:418–24.
15. Termine N, Giovannelli L, Rodolico V, Matranga D, Pannone G, Campisi G. Biopsy vs. brushing: comparison of two sampling methods for the detection of HPV-DNA in squamous cell carcinoma of the oral cavity. Oral Oncol. 2012;48:870–5.
16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
17. Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsague X, Laporte L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol. 2014;15:1319–31.
18. Chor JS, Vlantis AC, Chow TL, Fung SC, Ng FY, Lau CH, et al. The role of human papillomavirus in head and neck squamous cell carcinoma: A case control study on a southern Chinese population. J Med Virol. 2016;88:877–87.
19. Poling JS, Ma XJ, Bui S, Luo Y, Li R, Koch WM, et al. Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue. Oral Oncol. 2014;50:306–10.
20. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma–an update. CA Cancer J Clin. 2015;65:401–21.
21. Lee YC, Marron M, Benhamou S, Bouchardy C, Ahrens W, Pohlabeln H, et al. Active and involuntary tobacco smoking and upper aerodigestive tract cancer risks in a multicenter case-control study. Cancer Epidemiol Biomarkers Prev. 2009;18:3353–61.
22. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110:1429–35.
23. Majchrzak E, Szybiak B, Wegner A, Pienkowski P, Pazdrowski J, Luczewski L, et al. Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature. Radiol Oncol. 2014;48:1–10.
24. Hemminki K, Dong C, Frisch M. Tonsillar and other upper aerodigestive tract cancers among cervical cancer patients and their husbands. Eur J Cancer Prev. 2000;9:433–7.
25. Boy S, Van Rensburg EJ, Engelbrecht S, Dreyer L, van Heerden M, van Heerden W. HPV detection in primary intra-oral squamous cell carcinomas–commensal, aetiological agent or contamination? J Oral Pathol Med. 2006;35:86–90.
26. van Rensburg EJ, Engelbrecht S, Van Heerden WF, Raubennheimer EJ, Schoub BD. Human papillomavirus DNA in oral squamous cell carcinomas from an African population sample. Anticancer Res. 1996;16:969–73.
27. Lleras RA, Smith RV, Adrien LR, Schlecht NF, Burk RD, Harris TM, et al. Unique DNA methylation loci distinguish anatomic site and HPV status in head and neck squamous cell carcinoma. Clin Cancer Res. 2013;19:5444–55.
28. Reyes M, Rojas-Alcayaga G, Pennacchiotti G, Carrillo D, Munoz JP, Pena N, et al. Human papillomavirus infection in oral squamous cell carcinomas from Chilean patients. Exp Mol Pathol. 2015;99:95–9.
29. Feller LL, Khammissa RR, Kramer BB, Lemmer JJ. Oral squamous cell carcinoma in relation to field precancerisation: pathobiology. Cancer Cell Int. 2013;13:31.
30. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002;52:195–215.
31. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 2008;122:155–64.
32. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010;39:166–81.