Association between oral cancer and the presence of HPV- Integrative Review

Associação entre o câncer de boca e a presença do HPV- Revisão integrativa

Asociación entre el cancer oral y la presencia de HPV- Revisión integradora

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REVISA

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RESUMO

Objetivo: realizar uma revisão integrativa sobre a associação entre o câncer de boca e a infecção pelo HPV. **Método:** foi realizada uma busca bibliográfica na base de dados científicos PubMed, utilizando descritores previamente selecionados. Dois revisores independentes avaliaram criticamente os resultados, obedecendo estritamente aos critérios de inclusão e exclusão definidos no protocolo do estudo. Além disso, a qualidade dos artigos foi avaliada considerando o Strengthening the reporting of observational studies in Epidemiology (STROBE). **Resultados:** Após a análise dos artigos, foram selecionados doze artigos, desses, sete mostraram ocorrência de HPV em pacientes com câncer de boca, e apenas dois estudos mostraram o HPV como possível etiologia para o câncer oral. **Conclusão**: não foi possível associar a presença do HPV à etiologia do câncer de boca, necessitando que mais estudos sejam realizados a fim de analisar melhor essa associação.
Descritores: Câncer de boca; HPV; Diagnóstico.

ABSTRACT

Objective: to carry out a integrative review on the association between oral cancer and HPV infection. **Method**: a bibliographic search was performed in the PubMed scientific database, using previously selected descriptors. Two independent reviewers critically evaluated the results, strictly obeying the inclusion and exclusion criteria defined in the study protocol. In addition, the quality of the articles was assessed considering the Strengthening the reporting of observational studies in Epidemiology (STROBE). **Results:** After analyzing the articles, twelve articles were selected, of these, seven showed the occurrence of HPV in patients with oral cancer, and only two studies showed HPV as a possible etiology for oral cancer. **Conclusion:** it was not possible to associate the presence of HPV with the etiology of oral cancer, requiring more studies to be carried out in order to better analyze this association.
Descriptors: Oral cancer; HPV; Diagnosis.

RESUMEN

Objetivo: Objetivo: llevar a cabo una revisión integradora sobre la asociación entre el cáncer oral y la infección por VPH. **Método**: se realizó una búsqueda bibliográfica en la base de datos científica PubMed, utilizando descriptores previamente seleccionados. Dos revisores independientes evaluaron críticamente los resultados, obedeciendo estrictamente los criterios de inclusión y exclusión definidos en el protocolo del estudio. Además, se evaluó la calidad de los artículos considerando el Fortalecimiento de la notificación de estudios observacionales en Epidemiología (STROBE). **Resultados:** Después de analizar los artículos, se seleccionaron doce artículos, de estos, siete mostraron la presencia de HPV en pacientes con cáncer oral, y solo dos estudios mostraron el HPV como una posible etiología para el cáncer oral. La calidad del artículo se evaluó utilizando STROBE. **Conclusión:** no fue posible asociar la presencia de HPV con la etiología del cáncer oral, lo que requirió la realización de más estudios para analizar mejor esta asociación.
Descriptores: Cáncer oral; VPH; Diagnóstico.

REVIEW

Introduction

Mouth cancer is one of the most incident in the world, according to the National Cancer Institute (INCA) it is estimated that in 2020, the estimate of this cancer in Brazil is 11,108 new cases in men and 4,010 in women per 100,000 inhabitants. This lesion affects mainly males, adults over 40 years old and predilection for white and brown skin color.[1]

In hospitals spread across all regions of Brazil, from January 2012 to October 2017, there were 151,573 hospitalizations (8,916 patients / year ± 2,390,011) for oral cavity cancer. The mortality rate for this disease was 11.58% (± 0.5%) and, after the first year of life, it gradually increased, reaching 18.96% in patients over 80 years old.[1-2]

This lesion can affect different locations in the oral cavity, including the hard palate, tongue, lips, gums and oral floor, with the tongue being the most frequent location.[3] In addition to the different locations, the clinical appearance of the lesions varies in shape and size based on their stage of evolution. Usually, these lesions have been ulcerated for more than 15 days, accompanied by persistent pain or local numbness, appearance of nodules, red plaque (erythroplasia) or whitish (leukoplakia).[1-4]

Some factors may be associated with the occurrence of oral cancer, including, smoking, the use of alcoholic beverages, sun exposure, as well as the presence of infectious agents including the Epstein-Barr virus and the Human Papilloma virus (HPV).[5]

HPV is from the papillomaviridae family, with a double-stranded DNA genome. This virus makes up a heterogeneous group with more than 100 viral types and their variants with modification of up to 10% of the original viral genome.[1,6-7]

Studies carried out by the National Cancer Institute of the United States and the São Paulo Research Foundation (FAPESP) in association with the pharmaceutical company Merck Sharp & Dohme evaluated, among other things, the characteristics of HPV infection in anus, mucous membranes genitals and oral mucous membranes in the male audience and how the infection develops and progresses to cancer. The results showed that 24 types of HPV can be associated with malignant oral lesions. Types 6 and 11 are associated with predominantly benign infections with a scaly and warty appearance in the tissue in the internal and external oral epithelium. Types 16 and 18 are more aggressive and have carcinogenic characteristics. When considering the potential for carcinogenesis, types 6 and 11 are low, types 31, 33 and 35 of intermediate risk and types 16 and 18 of high risk. [6-8]

Although some published studies show the association of oral cancer with HPV infection, this association has been questioned, due to the controversy about the opportunistic characteristic of the virus. Thus, it is not possible to specify whether the cancer comes first or after the HPV infection, thus de-characterizing itself as a risk factor, and making it a consequence of the weakening of the normal immune protection functions of the tissue caused by the cancer.[9] Considering the controversies about this association, the objective of the present study was to carry out a systematic review on the association between oral cancer and HPV infection.

Method

A search was carried out at Pubmed from April to May 2020, in order to have access to relevant articles on this topic, published from 2010 to 2020. The descriptors used for the search included: | mouth cancer OR oral cancer | AND | human papilloma virus OR HPV |. The titles and abstracts of the articles found in the researched databases were examined in order to exclude studies without relevance to the study.

We included articles in English, which presented in the title, abstract and keywords mouth cancer and HPV infection and whose focus was to assess HPV as a risk factor for the oral cancer occurrence. In addition, only the articles available in its full version were selected, where the type of study made it possible to assess the determination of a risk factor, including the case control and cohort studies.[10]

Articles written in other languages that did not include oral cancer and HPV infection in the title, abstract and keywords were excluded, and whose focus was not to assess HPV as a risk factor for the occurrence of oral cancer. In addition, those that were not available in their full version on the Internet were excluded.

For the systematization of abstracts, a spreadsheet (Microsoft Excel 2013) was used according to the results obtained in the analyzed studies. After the selection of the relevant abstracts, the articles were read in full version to assess whether they met the inclusion criteria previously defined for this review (Figure 1). The selected articles were organized in a table considering the bibliographic reference, year, country of study, sample size, researched method and main results (Table 1).

The quality of the works was assessed using the Strengthening the reporting of observational studies in Epidemiology (STROBE), which assesses 22 key items that must be present in the title, summary, introduction, methodology, results and discussion of cross-sectional research, case- control and cohort of observational studies. From this analysis, the STROBE results were obtained for each study (Table 1), where articles that included zero to seven items were considered of low quality, between eight and 14 items of intermediate quality and 15 to 22 items of high quality.[11-12]

Results

Initially, 2044 articles were found in the Pubmed database and after analyzing the inclusion and exclusion criteria, 59 articles were selected. Of these, after reading and checking, 13 were discarded for not evaluating the association between HPV and oral cancer, three because the object of investigation was not oral cancer, 28 for not meeting the type of study evaluated and three articles were not available in full form. At the end, twelve articles were selected (Figure 1).

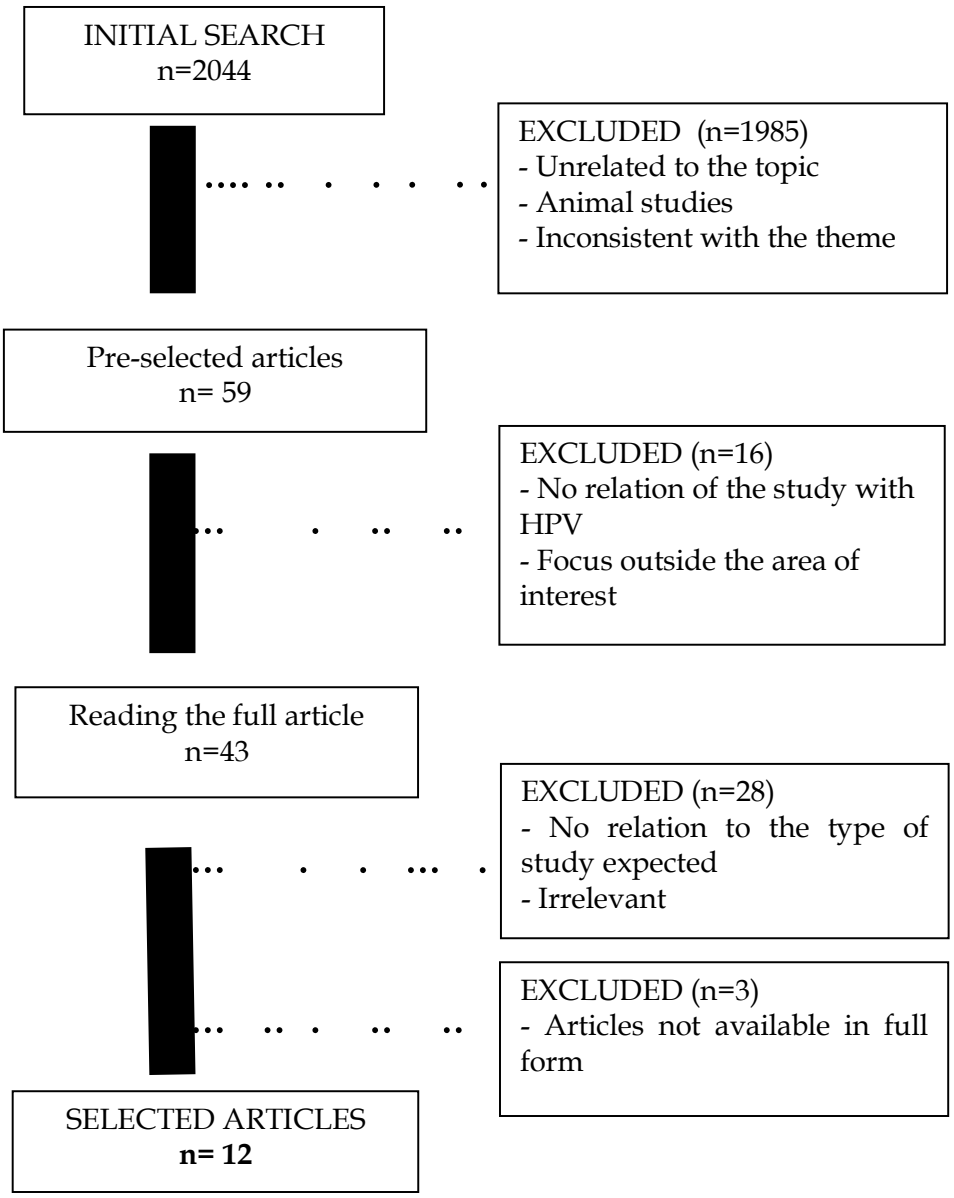

Figure 1 - Flowchart followed in the selection of articles.

The studies were carried out in several countries such as Japan, Thailand, Taiwan, Chile, China, Germany, Iran, Italy, England, United States and Denmark. Most studies were case control and used HPV DNA PCR to diagnose the infection. Of the selected articles, seven showed the occurrence of HPV in patients with oral cancer, however only two studies showed HPV as a possible etiology for oral cancer. The evaluation of article quality through STROBE showed that three articles were of intermediate quality and nine articles were of high quality (Table 1).

Table 1: Articles included in the study.

Author(s)/year	Place	Sample size	Methodology	Main findings	STROBE
Gan *et al*. (2014) [13]	China	200 cases and 68 controls	Case-control study carried out in patients with newly diagnosed CPB in the oral cavity between 2009 and 2013. PCR and direct sequencing were used to identify the types of HPV in the samples.	The presence of HPV DNA in CPB is not associated with the anatomical location of the tumor. HPV16 was detected in 39 of the 200 patients with CPB.	High quality
Krüger *et al.* (2014) [15]	Germany	88 patients	A cohort study analyzed HPV in patients with head and neck CPB treated at the Department of Oral and Maxillofacial Surgery at the Mainz University Medical Center. HPV status analysis was performed using DNA-PCR and p16 protein immunostaining.	The prevalence of cervical and oral CPB was positive for HPV in 6% of cases. In 3 patients, HPV 16/18 subtypes were found. There were no significant differences between HPV positive and negative patients in terms of age, sex, smoking and alcohol consumption, location.	High quality
Rushatamukayanunt *et al*. (2014) [16]	Japan	40 cases and 40 controls	Case control study with immunohistochemical analysis to detect p16INK4a and p53	HPV is less likely to cause CPB in young Japanese, and the p16INK4a expression level is not an appropriate substitute marker for HPV infection in CPB.	High quality
Simard et al. (2014)	Austria	118 cases and 100 controls	Case-control study of patients with oral leukoplakia or erythroplasia, who underwent surgical biopsy. HPV detection was performed by smear.	A significant association between the oral detection of high-risk HPV and the presence of leukoplakia / erythroplasia.	Moderate quality
Kouketsu *et al*. (2015) [17]	Japan	174 patients	Cohort study, assessed p16 levels by immunohistochemistry. In p16-CEC positive cases, the presence of HPV	HPV infection may play a minor role in oral oncogenesis in Japanese patients.	High quality

			DNA in situ through hybridization and HPV genotypes in real time through PCR were analyzed.		
Lee *et al.* (2015) [18]	Taiwan	1002 patients	Retrospective cohort study, carried out between 2004 and 2011, identifying tumor specimens through genotyping. PCR was used to diagnose HPV in specimens.	HPV infections are common in CPB in Taiwanese patients and predict 5 years of overall survival for these patients. If independently validated, our compound prognostic score with HPV16 infection can be useful for allocating patients with CPB to risk-adapted therapies.	High quality
Reyes *et al.* (2015) [19]	Chile	80 patients	Cohort study where demographic and clinical data were obtained directly from the patients' clinical record. The cases were confirmed histologically and the extraction of DNA and PCR for the presence of HPV.	HPV infection was detected at low prevalence in oropharyngeal and oral cancer in Chilean patients. HPV was present in 11% of cancers of the oral cavity. HPV-16 was the most prevalent genotype found in oral CPB with a higher prevalence in women, although they did not find any statistically significant association between presence and gender age, degree of differentiation for HPV.	High quality
Phusingha *et al*. (2016) [14]	Thailand	110 cases and 100 controls	Case-control study, where HPV infection was investigated by PCR using GP5 + / GP6 + primers, followed by HPV genotyping using reverse hybridization. Quantitative RT-PCR was used to assess transcription of the HPV oncogene. Exfoliated oral cells from cases	The prevalence of HPV in exfoliated cell samples from CPB cases and control groups was 29.7% and 13.0%, respectively, indicating a 2.82-fold increase in the risk of SCC in individuals infected with HPV.	High quality

			and controls were investigated for HPV infection.		
Ashraf *et al.* (2017) [20]	Iran	50 cases and 50 controls	Case-control study where DNA was extracted from blocks of tumor and non-tumor tissue. The detection of common HPV DNA by PCR and the high-risk genotypes, HPV 16 and HPV 18 was performed by conventional PCR.	lthough there was a significantly higher prevalence of HPV in oral tongue CPB, its association with carcinogenesis in this area requires further studies. None of the control group participants tested positive for DNA. HPV 16/18 genotypes were not detected in positive cases. No statistically significant association was found between HPV status and sex, age, tumor grade, tumor stage, or lymph node involvement.	High quality
Zammit et al. (2018)[21]	Italy	51 patients	Cohort study-Head and neck CPB biopsies were performed and RNA sequencing (RNA-seq) was performed. Tumors associated with HPV were determined using p16 staining of histological sections. Demographic data of the patient, including the location of the tumor in the oral cavity, and history of tobacco and alcohol use were correlated with genomic and transcriptomic analyzes.	In conclusion, HPV was shown to be an uncommon association with head and neck CPB with changes in transcriptional regulation TP53, being more common in smoking patients. Thus, HPV was not considered an etiological agent for head and neck CPB	Moderat e quality

Thorsteinsson et al. (2018) [22]	Denmark	334 patients	Cohort study Of the 334 HIV patients evaluated, 327 samples of oral lesions were obtained. Exfoliative cytology was performed in the oral cavity and HPV was analyzed using the CLART HPV2 assay (Genomica, Madrid, Spain)	It was not possible to state that HPV was a predictor of oral cancer due to the low prevalence of cases.	Moderate quality
Fakhry et al. (2019) 23	United States of America	396 patients	Cohort study with CPB patients from newly diagnosed oral cavity or oropharynx. Samples of oral rinse were prospectively collected at diagnosis and at the conclusion of primary therapy, in addition to weekly samples of oral washing during radiotherapy. The DNA of the tumor sample and the oral rinse were evaluated for 37 types of HPV, and the viral load was quantified by real-time PCR, specific for each type. The cancers were stratified by the tumor's HPV status, and HPV was classified as a tumor type whether identical to that detected in the tumor type or not.	Oral detection of HPV DNA in the diagnosis differed between patients with cancer HPV + and HPV -. Among patients with HPV + cancer, the category of advanced tumor in stage T3 or T4 was more prevalent, with a higher risk of death.	High quality

Hearnden et al. (2018)[24]	England	607 patients	Control case - mouthwash and oral gargle and for the detection of oral HR-HPV, in addition to the sample of buccal epithelial cells of the mucosa for the measurement of folate of buccal epithelial cells of the buccal mucosa. A blood sample was collected to measure folate in whole blood.	There was no association between the concentration of folate in whole blood and epithelial cell folate concentration and oral HR-HPV infection. This may indicate that there is no causal association between HPV and oral cancer.	High quality

HPV = human papilloma virus; DNA = deoxyribonucleic acid; PCR = polymerase chain reaction; CPB = squamous cell carcinoma; RNA- ribonucleic acid, HIV- human immunodeficiency vírus.

Discussion

In the present study, when analyzing, through a systematic review, the association between HPV and oral cancer, twelve articles were included in this review. Analysis of the studies showed that this association could not be determined, since a variety of factors may interfere with the study of HPV as a risk factor for oral cancer. Some studies[13-14] showed a relevance for the presence of HPV, considering it highly associated with oral cancer and an independent risk factor and even greater with the association of tobacco and alcohol, with HPV-16 being the most commonly found genotype.[14] The present study indicated that HR-HPV is strongly associated with Squamous Cell Carcinoma (SCC) and plays an important causal role in oral carcinogenesis.

The HPV present in oral cavity infection appears to vary from other regions of the head and neck and plays a minor role in oral carcinogenesis.[15, 21] In addition, little correlation between HPV and CPB was established and no significant difference was detected between HPV positive and negative patients for smoking and drinking habits, they have no obvious etiological factors for CPB in young people.[16, 23]

HPV can be obtained by using a fresh specimen[14-15,17-21], exfoliative cytology through mucosal brushing[16,22] and mouthwash[23-24], with no difference between the association of HPV and oral cancer and the method obtaining the virus.

Kouketsu et al.[17] suggest that there is no association of HPV as an exponent risk factor for CPB, requiring additional cellular changes for the CPB to occur. For Lee et al.[18], the molecular oncogenesis of HPV is significantly different from tobacco and alcohol, thus it is not an important etiologic agent, contributing only as an aggravating factor after exposure to tobacco and alcohol. These findings were similar to those by Reyes et al.[19] who indicated that there was no association with molecular changes related to the causal role of HPV.

Immunohistochemical measurements with the intention of evaluating the polymerase chain reaction (PCR) and direct sequencing were used to identify the types of HPV in different studies.[20,23] In the study by Gan et al.[13], the authors

performed PCR with GP5 + / GP6 +, with DNA samples collected from patients' fresh tissues. The authors found a higher prevalence rate of HPV infection in cases than in controls (27.5% versus 2.9%, respectively).

Rushatamukayanunt et al.[16], also using an immunohistochemical study to detect the presence of p16INK4a and p53 in CPB of young Japanese patients, found that p53 combined with p16INK4a profiles was significantly correlated with alcohol consumption in younger patients, but the level of protein expression was not an appropriate substitute marker for HPV infection in CPB, demonstrating little relevance of HPV in CPB in a young Japanese population.

Krüger et al.[15], using a methodology similar to the study by Rushatamukayanunt et al. 16, also studied the presence of viral DNA separating them by strains of HPV, and immunostaining of the p16 protein and the results that were positive for HPV was about 6% (five patients) and in three of them the HPV subtypes 16 and 18 were found. However, of the three HPV positive cases (60%) were smokers and three of the HPV positive patients (60%) were alcoholics, corroborating the findings of Rushatamukayanunt et al.[16], where the authors concluded that HPV plays a minor role in oral cancer carcinogenesis. There was no statistically significant difference between the group with high-risk HPV 16 and 18 and negative HPV.

Similar to the findings of other studies[13,15-16], Kouketsu et al.[17], in a case-control study, studied the expression of tumor suppressor p16 protein in Japanese patients. In total, 174 specimens of SCC were examined for p16 levels by immunohistochemistry, and p16-SCC positive cases were analyzed for HPV DNA through in situ hybridization and HPV genotypes in real time PCR. The results observed in the study showed an immunoreactivity for p16 with various levels of p16 expression observed in the cells and cytoplasms of CPB cells in 13.8% of cases of HPV infection. According to the authors, these results were similar or slightly lower than those observed in previous studies, concluding that HPV infection may have a minor role in oral oncogenesis in Japanese patients.

Retrospective cohort studies were carried out, respectively in Taiwan, Chile and Japan.[17-19] The studies used different sample sizes (1002, 80 and 174, respectively). The sample size of the study by Lee et al.18 justified the fragmentation of the cohort into two: "2004 cohort" (from 2004 to 2007) and "2008 cohort" (from 2008 to 2011). The cohort was divided according to the presence or absence of risky oral habits, and the prognostic impact of HPV infections associated with risky oral habits was also assessed. The results of the study showed a global prevalence of HPV infections of 19%, with a higher occurrence of oncogenic HPV (16%). The authors concluded that patients without risky oral habits and HPV infections showed a worse prognosis than those without evidence of HPV infections. No significant association was found between overall survival and any HPV infection, however, additional univariate analysis with stratified data revealed that, among patients with advanced CPB (stage III / IV), the presence of HPV16 infection was associated with a prognosis. adverse to survival.[18]

For Reyes et al.[19], disagreeing with Lee et al.[18], the HPV prevalence in CPB of Chilean patients was 11% and no association with molecular changes in the expression of p16, p53, pRb and Ki-67 using immunohistochemistry was related to the causal role of HPV in oral cancer.

The case-control study by Phusingha et al.[14], conducted in northeastern Thailand, used exfoliated cells samples, unlike other studies in which tissue samples were assessed.[13-17] In addition, Phusingha et al.[14] investigated HPV infection through genotyping using reverse hybridization, unlike all other studies included in this review. The study also concludes that high-risk HPV-16 was the most common genotype and was detected in both CPB cases and control groups and that HPV infection plays an important role in oral carcinogenesis in northeastern Thailand.

O HPV composes a heterogeneous group with more than 100 viral types and their variants with modification of up to 10% of the original viral genome, with HPV genotypes 16/18, considered to be high risk, the types most commonly related to oral malignancies.[6] In the present study most of the studies included analyzed genotypes 16 and 18, however, in a study carried out in Iran with 100 samples in formalin-embedded and paraffin-embedded tissue blocks, equally divided into 50 cases and 50 controls, found seven cases (14%) of individuals in the case group with positive results for HPV and no individual in the control group with positive results for HPV. In addition, HPV genotype 16/18 was not detected among the seven positive cases. The study then concluded that for the studied population, the possible environmental and host genetic factors should be considered more relevant than HPV infection. [20]

Conclusion

Based on the results obtained in the present study, it is possible to conclude that it is possible to identify the presence of HPV in some cases of oral cancer, however, it was not possible to associate its presence with the etiology of oral cancer, being important for other studies to be carried out with the verification of the best association.

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