

Relationship of human papilloma virus (HPV) infection with the presentation of squamous cell carcinomas from regions of the oropharynx

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ABSTRACT

Human papilloma virus (HPV) is classified as a sexually transmitted disease, in which this double-stranded DNA virus is often associated with cervical cancer. However, in more recent studies, this virus has also been associated with oropharyngeal squamous cell carcinoma (OSCC). Therefore, this systematic review aims to show the relationship between HPV and CCEO. Thus, Pubmed, The Cochrane Library, Bioone, Lilacs and Scielo databases were used with articles published between January 2010 and June 2020 encompassing publications in Portuguese, Spanish and English, respecting the inclusion and exclusion criteria. A total of eleven articles that presented a relationship with oropharyngeal infection and HPV were considered eligible. Despite the high number of articles found by the search for the association between HPV and neoplasms in different regions of the body, it was possible to understand the association between CCEO and the infection caused by HPV, through a PRISMA stratification model. Thus, it was demonstrated, in addition to the presence of this association, the need for faster, more accessible and effective diagnostic methods for the correct presentation of pathology and etiological factor.

Keywords: Human papillomavirus, Squamous cell carcinoma, Oropharynx, Oral cavity.

INTRODUCTION

Human papillomavirus (HPV) is a sexually transmitted disease caused by a virus of the Papillomaviridae family¹, in which these are double-stranded DNA viruses capable of infecting exposed epithelia². HPV virus is one of the most common sexual diseases diagnosed in American contexts³. The nomenclature of this pathology is directly associated with the verrucous lesions it causes, which are called papillomas³. Its infection is commonly associated with the beginning of sexual life and in young people, being considered the virus with the highest sexual contamination present¹.

Previously, HPV was considered a disease that affected only the region of the cervix, and is still considered the main cause of cervical cancer. However, since 1983 it has also been considered as the cause of other pathologies associated with the head and neck region².

This, in turn, is classified as a high-risk and low-risk virus for oncogenesis^{1,4}, but it also has a numerical structure classification in which more

than 200 different strains can be verified, 40 of which are capable of infecting the genital mucosa and 9 of those capable of causing cancer⁵. Among them, we highlight HPV types 16 and 18, which are the ones that present the highest pathological risk. HPV-16 has a greater pathological capacity, being associated with oropharyngeal squamous cell carcinoma (OSCC), with emphasis on oropharyngeal squamous cell carcinoma (OSCC)⁶⁻⁹. These pathologies were previously more associated with patients who had a history of smoking and alcoholism, but recently studies have shown that there is a link between HPV³. This type of occurrence is presented not only by HPV identification tests such as p16IK4a, but also by the reduction in the level of tobacco consumers in recent decades⁶.

In this context, HPV has acquired increasing relevance as one of the causative agents of this subset of head and neck neoplasms and, consequently, diversifying the clinical history and risk factors associated with the increase in cases, thus presenting an important correlation with the increase in the prevalence of HPV³.

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When the study on squamous cell carcinoma (SCC) is expanded, which is responsible for 90% of all malignant neoplasms in the head and neck region, it is possible to find pathophysiological relationships between it and HPV². This pathology affects in particular males aged between 30 and 60 years predominantly^{3,9}.

Therefore, this study intends to analyze the association between head and neck carcinoma and the infection caused by HPV.

METHOD

Ethic

The present study does not require an informed consent form (ICF) and was not submitted to the Ethics Committee of the institutions involved due the fact that it is a systematic review, exclusively with published articles.

Search strategy and inclusion criteria

The present systematic review followed the structure proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA model, which consists of a checklist with 27 items and a flowchart of 04 steps, aiming at the transparency of the systematization and reducing biases in data analysis, in order to give a good quality to this research

Searches were carried out from the following electronic databases by the four authors using the following search tools: Pubmed, The Cochrane Library, Bioone, Lilacs (Latin American and Caribbean Health Sciences) and Scielo. The research carried out a data collection with articles published in these databases between January 2010 and June 2020 with publications in Portuguese, Spanish and English. We used a broad search strategy to avoid publication-related errors and to evaluate research focused only on oropharyngeal and nasopharyngeal neoplasms caused by HPV and for that, the following steps were followed: Formulation of the guiding question, evaluation and selection of studies,

analysis and synthesis of the material found and description of the results.

From this, the following keywords were used "cancer" and "HPV" and "epidemiology" and "squamous cell carcinoma" and "oropharynx" and "hypopharynx" and "rhinopharynx" and "mole palate" and "mouth" and "early detection" and "squamous cell carcinoma" and "oral squamous cell carcinoma" and "oropharyngeal squamous cell carcinoma" ("cancer" and "HPV" and "epidemiology" and "squamous cell carcinoma" and "oropharynx" and "hypopharynx" and "rhinopharynx" and "soft palate" and "mouth" and "early detection" and "squamous cell carcinoma" and "head and neck squamous cell carcinoma" and "oral squamous cell carcinoma" and "oropharyngeal squamous cell carcinoma" and "squamous cell carcinoma" and "head and neck" and "epidermoid" and "oral cavity"). The reference lists of articles subsequently selected were manually analyzed by the researchers.

Exclusion criteria

Articles for which it was not possible to obtain versions in Portuguese, English or Spanish were excluded from the search. Those that did not contain sufficient data on the relationship between HPV and oropharyngeal neoplasms, repeated publications, articles using animal models exclusively, pediatric population, articles that did not have HPV and oropharyngeal neoplasms as their objective.

Extraction of articles

The articles were collected by the four authors using forms created for this purpose and tabulation of data. The forms were divided into two in which the first was used to survey the number of articles found in which the keywords for research and the number of the article found in different databases are inserted.

The second form was used to analyze the references, authorship, methodology presented and the researcher's analysis of the article.

Discrepancies that emerged were resolved by discussion and consensus of researchers.

Survey of articles

Initially, 26,169 articles were identified in the PUBMED, LILACS, BIOONE, COCHRANE and SCIELO databases later after removing the duplicates and a total of 15,173 articles were found, then the titles were analyzed, a total of 10,996 articles were selected, of these 218 were selected for abstract reading and, then, 40 of them for full reading, which were divided by year of publication, later on type of article and methodology presented. After their analytical

reading, 11 were chosen because they present data and information to answer the guiding question of the review. The selected texts were later submitted to thematic analysis.

The distribution of bibliographic references in the databases allows thematic analysis consistent in a method for identifying and analyzing pattern records from data, organizing them and describing them in detail. However, a theme should not be considered just because it is present at a certain frequency in the material obtained, but because of the researcher's interpretation.

These themes must be analyzed in different ways by the researcher aiming at a better way of interpreting and adapting the guiding question.

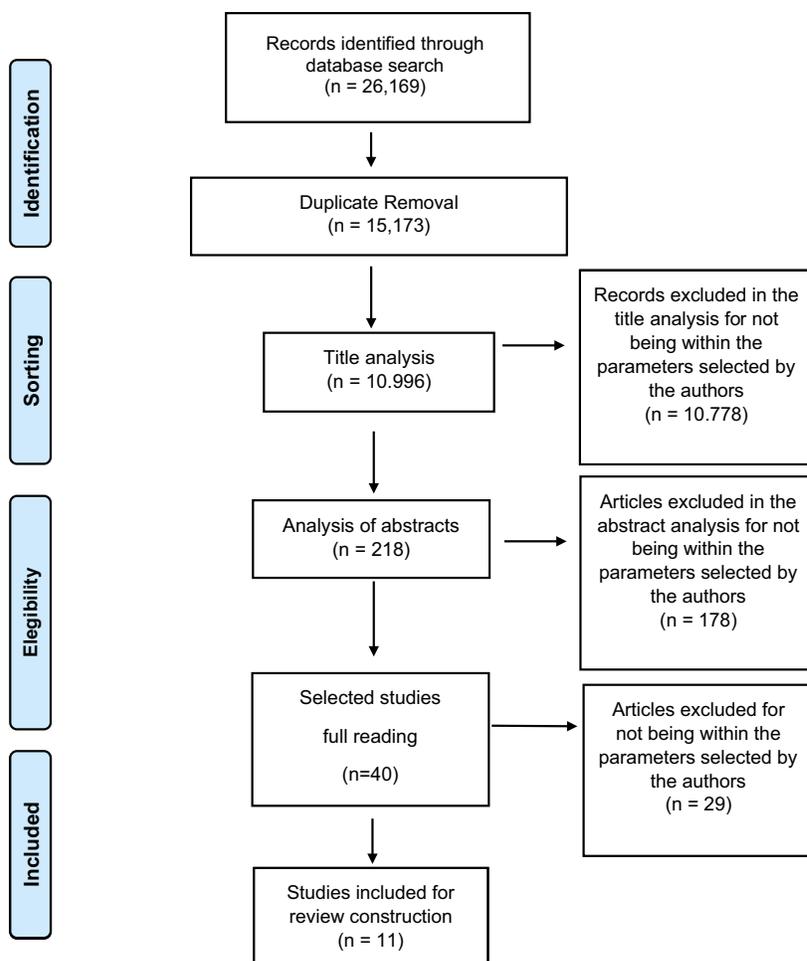


Figure 1: Organizational chart referring to the selection process of articles for systematic review based on the PRISMA method.

Table 1

Distribution of bibliographic references obtained from the PUBMED, LILACS, BIOONE, COCHRANE and SCIELO databases according to the selected keywords, Brazil, 2020.

SEARCH THERMS	PUMED	LILACS	BIOONE	COCHRANE	SCIELO
CANCER / HPV / ORAL SPINOCELLULAR CARCINOMA	1	25	0	0	3
CANCER / HPV / HEAD NECK SQUAMOUS CELL CARCINOMA	9	24	4	141	10
CANCER /HPV / OROPHARYNGEAL SPINOCELLULAR CARCINOMA	0	7	0	0	0
CANCER/ HPV / SPINOCELLULAR CARCINOMA	2	74	0	0	6
CANCER/ HPV/ OROPHARYNGEAL SQUAMOUS CELL CARCINOMA	627	17	4	90	7
CANCER/ HPV/ RHINOPHARYNX	77	0	0	0	0
CANCER/ HPV/ SUQAMOUS CELL CARCINOMA	4849	112	5	5	30
CANCER/HPV/ EPIDEMIOLOGY	132	130	0	0	23
CANCER/HPV/ HYPOPHARYNX	137	3	0	0	0
CANCER/HPV/ MOUTH	743	20	3	46	2
CANCER/HPV/HEAD AND NECK	1	0	0	0	5
CANCER/HPV/ SQUAMOUS CELL CARCINOMA	2	74	0	1	19
CANCER/HPV/SPINAL CELL CARCINOMA OF HEAD AND NECK	0	15	0	0	1
CANCER/HPV/ORAL CAVITY	0	4	0	0	3
CANCER/HPV/SQUAMOUS CELLS	1	0	0	0	28
CANCER/HPV/EARLY DETECTION	2425	0	5	126	37
CANCER/HPV/EPIDEMIOLOGY	6550	132	5	2	25
CANCER/HPV/EPIDERMIOID	3	75	0	0	3
CANCER/HPV/ EPIDERMIOID	3	78	0	0	4
CANCER/HPV/HEAD AND NECK	2162	39	6	226	15
CANCER/HPV/HYPOPHARYNX	0	4	0	0	0
CANCER/HPV/ORAL CAVITY	430	4	4	53	1
CANCER/HPV/ORAL SQUAMOUS CELL CARCINOMA	127	37	2	67	23
CANCER/HPV/ OROPHARYNX	6	32	0	0	12
CANCER/HPV/OROPHARYNX	933	28	2	3	6
CANCER/HPV/SQUAMOUS CELL CARCINOMA	3821	112	5	247	68
CANCER/HPV/SQUAMOUS CELLS	386	2	6	276	29
TOTAL	23427	1048	51	1283	360

Source: The author (2020)

Table 2

Total articles found in relation to selected databases, Brazil, 2020.

DATABASES	QUANTITY
PUMED	23427
LILACS	1048
BIOONE	51
COCHRANE	1283
SCIELO	360
TOTAL	26169

Source: The author (2020)

Table 3

List of conclusions of each article selected for analysis, Brazil, 2020.

Nº	TITLE	YEAR	DATABASES	COUNTRY	METODOLOGY	ARTICLE ANALYSIS
1	Human papillomavirus-associated head and neck cancer: oncogenic mechanisms, epidemiology and clinical behaviour	2015	Pubmed	United Kingdom	Quantitative	The study presents the physiological and pathophysiological relationships present in the infection of the HPV virus to regions of the body with the possibility of infection and metastasis, has good demonstration of the viral and cellular mechanism in how to enter the cell, as well as its interaction with the cell nucleus for the propagation of the virus. virus.
2	Knowledge of Pregnant Adolescents about Human Papillomavirus	2019	Scielo	Brazil	Quantitative	Article in which epidemiological data of pregnant women with HPV are analyzed, as well as their relationship of knowledge about the virus. It is a quantitative study of descriptive character with application on an outpatient basis about pregnant adolescents and their level of knowledge about HPV. The study also presents important epidemiological data on the conditions of these pathologies present in Brazil.
3	Cáncer orofaríngeo y virus del papiloma humano en cabeza y cuello: relaciones fisiopatológicas y epidemiológicas	2018	Scielo	Costa Rica	Qualitative	A study about the pathophysiology of the HPV virus seeking to evaluate the forms of infection and contagion of the virus and its internal protein structure. The article reports the epidemiological and serological characteristics of the pathology, guiding the relationship between infection and disease involvement.
4	A pilot study to compare the detection of HPV-16 biomarkers in salivary oral rinses with tumour p16INK4a expression in head and neck squamous cell carcinoma patients	2016	Pubmed	United States	Quantitative	Detection of HPV-16 DNA in salivary mouthwash has been shown to be indicative of HPV status in HNSCC patients and could potentially be used as a diagnostic tool in addition to current methods.
5	Prevalence of Human Papillomavirus Types and Variants and p16(INK4a) Expression in Head and Neck Squamous Cells Carcinomas in São Paulo, Brazil	2016	Pubmed	Brazil	Quantitative	In summary, it was observed that in our population the overall prevalence of HPV is lower than that reported in developed countries, although HPV-16 was the most prevalent viral type.
6	Virus Papiloma Humano en Cáncer Oral y Orofaríngeo. Revisión de la Literatura	2015	Scielo	Chile	Qualitative	The relationship between HPV and oral and oropharyngeal SCC, according to the most recent studies, is presented as a current reality and should be classified as a different entity from conventional SCC.

(Continuação)

Tabela 3*(Continuação)*

Nº	TITLE	YEAR	DATABASES	COUNTRY	METODOLOGY	ARTICLE ANALYSIS
7	Prevalence of oral and oropharyngeal human papillomavirus infection in Brazilian population studies: a systematic review	2015	Scielo	Brazil	Quantitative	The healthy Brazilian population has a very low rate of oral HPV infection. Other groups, for example, patients at risk or their partners, immunodeficient patients, patients with oral lesions and patients with SCC of the oral cavity or oropharynx who are at increased risk of HPV infection.
8	Human papillomavirus in oral cavity and oropharynx carcinomas in the central region of Brazil	2016	Scielo	Brazil	Quantitative	The results obtained in the present study, regarding the presence of high-risk genotypes for HPV16 and HPV18, highlighted the importance of HPV vaccination in the control of carcinomas of the oral cavity and oropharynx.
9	Current understanding of the mechanism of HPV infection	2012	Pubmed	United States	Qualitative	This article promotes an understanding of human papillomavirus (HPV) infection that can contribute to the development and evaluation of strategies to prevent infection from HPV, the causative agents of essentially all cervical cancers, various other carcinomas, and cutaneous/mucosal papillomas.
10	Advanced carcinoma of the oropharynx: survival analysis comparing two treatment modalities	2020	Scielo	Brazil	Quantitative	In conclusion, the two treatment protocols, surgery, radiotherapy and chemotherapy, radiotherapy, were equally efficient in the treatment of advanced squamous cell carcinoma of the oropharynx, considering that both promoted similar and disease-free survival rates.
11	An update on oral human papillomavirus infection	2013	Pubmed	India	Quantitative	The article presents the relationship between HPV and orogenic sex and its vertical transmission and high-risk sexual behavior. HPV is most strongly related to couples who have had oral sex. The spectrum of manifestations of HPV infection ranges from focal epithelial hyperplasia, oral lichen planus, squamous papilloma, and squamous cell carcinoma variant.

Source: The author (2020)

After analyzing the articles, the following lines of conclusion were found: Existence of an increase in oropharyngeal neoplasms related to the presence of HPV.

Furthermore, studies have demonstrated the association between human papillomavirus and oropharyngeal squamous cell carcinomas through HPV-16⁵ variants.

Most patients with HPV-associated oropharyngeal carcinoma have immunohistochemical sensitivity related to type p16, which is strongly related to CCEO^{6,8,9}. The diagnosis occurs in young people considerably compared to patients without detectable infection by HPV¹, while the average of oropharyngeal and oral cavity carcinomas without HPV association is over 60 years old, occurring more

frequently in individuals with risky sexual behavior, not smokers or light smokers and non-alcoholics⁹.

Despite the evaluation made with epidemiological data found in the articles, it is also possible to find different types of HPV carriers, including pregnant adolescents who had a low level of knowledge about the virus, its means of infection or prevention¹. These data are in agreement with the presentation made in different studies and reviews, where participants tested positive for the presence of HPV and the possibility of infection both orally and cervically^{8,4}.

In this sense, another fundamental aspect to be highlighted is the sex ratio of the detected cases. In oropharyngeal tumors, there is a predominance of males, but in those associated with HPV, this male prevalence tends to decrease.

As a result, among the articles analyzed, studies that seek to evaluate the presence of HPV in patients with lesions in the oropharynx region were verified, relating the presence of carriers, immunodeficiencies and tests to identify the type of virus present in the region of the oral cavity^{6,3}.

There is also the presence of articles that demonstrate the direct physiological and pathophysiological relationship between HPV contamination and the oropharynx regions, demonstrating in a judicious and profound way the mechanism of cellular infection, oral contamination^{12,3}.

Thus, the selected articles presented a good foundation in the decision of a plausible result from the experiences reported in these studies.

DISCUSSION

HPV has been studied as a disease pathogen for over 40 years, and its connection with lesions of the head and neck region was initially proposed in 1983, at the same time head and neck carcinomas were related to lesions in the same region².

When evaluating the epidemiology of neoplasms in the head and neck region, we observed that in countries like India, with one of the largest populations in the world, an incidence of 190,732 cases and a prevalence of 398,757 of these pathologies. Even with the current worldwide

trend of reducing tobacco consumption, recent studies lead to an understanding of the present relationship of HPV in the emergence of CCEO¹⁰.

Pathologically, HPV presents an interesting mechanism of infection, always aiming to be located in regions with exposed mucosa, the recognition and understanding of the pathophysiological mechanism between the oropharyngeal mucosa and the causative agent are considered of fundamental importance for the health professional, because it is an increasingly emerging disease in the world population³.

This, in turn, belongs to the family of double-stranded deoxyribonucleic DNA viruses, without capsid and presenting DNA in a circular structure with the ability to transmit without massive changes in the genetic chain. Thus, the virus has its genetic material wrapped in two circular proteins, called L1 and L2 and having its genome with the possibility of encoding proteins 'Early' or E1, E2, E4, E5, E6, E7^{2,3,11}.

Initially, the virus penetrates the basal layer of the epithelium, requiring a break in tissue prone to micro trauma, for example, oral cavity, oropharynx and genital regions, if there is no such break, HPV does not reach its site of action. After reaching the target cell, the viral DNA inoculates the nucleus, where it can remain in an episomal or resting state, or enter an active transcriptional state. Furthermore, HPV does not encode the proteins that carry out the transcription of its genome, thus, it is dependent on the host cell to carry out its mitosis. The protein contents of HPV are the main oncogenic factors responsible for malignancy, mainly proteins E6 and E7. These proteins, in turn, block the action of tumor suppressor genes, which would be the activation of some cytological defense mechanisms, such as apoptosis. Thus, the process of carcinogenesis caused by HPV occurs, which is a disorganized process of mitosis by atypical cells that is normally characterized in its macroscopic form by verrucous lesions in the area of infection called "condyloma acuminatum"².

Under normal conditions, the tumor suppressor gene called retinoblastoma (Rb) remains in a hypophosphorylated condition that prevents the release of the E2F transcription factor, managing to prevent cell proliferation and the advancement of

the cycle. However, the E7 protein has the function of inactivating the Rb, promoting the overexpression of the p16^{INK4a} gene that alters the G1-S phase and releases the E2F and, thus, the multiplication of the invading gene occurs ^{2,8}.

The E6 protein has the potential to bind to the tumor suppressor gene called p53 and promote an intervention, through the ubiquitin-ligase enzyme. Thus, it alters the G1 phase and inhibits histone acetyltransferases, which is one of the main mechanisms of p53 defenses against oncogenes. This reduces the cellular response to p53 and allows an increase in viral replication, facilitating the initiation and progression of cancer¹².

Since the first recognized case of HPV infection, there has been an exponential increase in its incidence due to changes in sexual behavior in society. Thus, the need for preventive measures against HPV, such as the vaccine, has become essential. A priori, in 2014, in Brazil, the vaccination campaign against HPV began, called the National Immunization Program, with the vaccine being the only method with scientific evidence for the prevention of HPV. This vaccination plan at the first moment of the campaign consisted of 3 doses: the 1st, 2nd dose after one month of the first and 3rd dose six after the first. After that, there were some changes to the 2016 schedule, the 2nd dose was no longer needed, as studies showed that the antibody response was no different for girls who received the 1st, 2nd and 3rd doses when compared to those who had received only the 1st and the last dose. Therefore, the 2nd phase started to focus on age (between 9 and 13 years old) and the number of doses (1st and last, 6 months later). In addition, the vaccine is effective, safe and, above all, the main way to prevent the 4 types of HPV 6, 11, 16, 18, with types 16 and 18 present in 70% of cervical cancers, and types 6 and 11 present in 90 % of cases of genital warts^{1,12}.

Thus, considering the various oropharyngeal pathologies existing in the literature over the years, only the clinical manifestation of a lesion is not considered a diagnostic confirmation, but the suspicion may appear according to the characteristic of the lesion. The most effective method of proving HPV-16 infection is the expression of the p 16 gene, which is found in

the DNA of the virus. Patients carrying CCEO with HPV-16 have the DNA of the virus detected from the salivary oral rinse. Another relevant factor for these patients is the staging, which is performed using the TNM method, according to the anatomical location where the lesion was removed, with the objective of allowing the professional to know the severity of the case and, thus, to elaborate a strategy of management for each patient⁶.

CONCLUSION

This review made it possible to confirm the present relationship between HPV and CCEO, aiming to seek more recent studies that carefully analyze the current forms of infection, pathophysiology, diagnosis and prevention. In addition, it made it possible to explain different points of view on the cytological mechanisms of infections caused by the HPV virus. The present study also identified the need for an increase in research aimed at rapid and accurate diagnostic methods, as well as an increase in epidemiological studies of the neoplasms presented and their causative agents as a way of improving the application and guidance of public policies for prevention and treatment.

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SPECIFIC CONTRIBUTION OF EACH AUTHOR

All authors will contribute to the development and interpretation of the data that made up the submitted study, including:

- Substantial contribution to study design or data interpretation;
- Participation in the drafting of the draft version;
- Participation in the review and approval of the final version;
- Compliance to be responsible for the accuracy or completeness of any part of the study.

FUNDING SOURCES

None.

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Editor:
Prof. Dr. Paulo Henrique Manso

Received: mar 14, 2021
Approved: aug 18, 2022
