

The relation between human papillomavirus (HPV) and oropharynx cancer: state of the art

A relação entre o papiloma vírus humano (HPV) e o câncer de orofaringe: estado da arte

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ABSTRACT

Objective: To analyze, through literary research, the relation between oropharynx squamous cell carcinoma (SCC) and Human Papillomavirus (HPV), as well as associated epidemiological data and prognosis. **Methods:** This is a narrative review of literature, with investigation on *PubMed*, *LiLACS*, *Scielo* and *BVS* bases, as well as free search, from June/2021 to February/2022. The DeCS/MeSH descriptors used in Portuguese and English were: “HPV”, “*Papillomavirus humano*”, “Human Papillomavirus”, “*Carcinoma de Células Escamosas Orofaríngeo*”, “Oropharyngeal squamous cell Carcinoma” and “*Carcinoma Escamocelular*”. After all the refinement

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steps through the application of inclusion and exclusion criteria, a total of 26 studies were selected. **Results:** Oropharyngeal cancer is related to HPV-positive patients, and its incidence is higher in men. It presents a growing increase in young adults. However, the prognosis and survival rates are favorable. **Conclusion:** There is a growing relation between oropharynx SCC and HPV in young and adult males, which emphasizes the importance and need for efforts to improve diagnosis, treatment, and prevention of new cases. Further studies are needed to determine the epidemiological impact and this relation in the long term.

Indexing terms: HPV. Human Papillomavirus. Oropharyngeal squamous cell carcinoma. Carcinoma, squamous cell.

RESUMO

Objetivo: Analisar por meio de busca literária, a relação entre o Carcinoma de células escamosas (CEC) de orofaringe e o Papilomavírus Humano (HPV), bem como dados epidemiológicos associados e o prognóstico.

Métodos: Tratou-se de uma revisão narrativa da literatura, com levantamento nas bases *Pubmed*, *LiLACS*, *Scielo* e *BVS*, além de livre busca, no período de Junho/2021 a Fevereiro/2022. Os descritores DeCS/MeSH utilizados em português e inglês foram: “HPV”, “Papillomavirus Humano”, “*Human Papillomavirus*”, “Carcinoma de Células Escamosas Orofaríngeo”, “*Oropharyngeal squamous cell Carcinoma*”, “Carcinoma de Células Escamosas Oral”, “*Oral squamous cell Carcinoma*”, “Neoplasias Orofaríngeas” and “*Oropharyngeal neoplasms*”. Após todas etapas de refinamento mediante aplicação dos critérios de inclusão e exclusão, um total de 26 estudos foram selecionados. **Resultados:** O câncer de orofaringe possui relação com pacientes positivados para o HPV e sua incidência é maior em homens. Apresenta crescente aumento em adultos jovens, todavia, o prognóstico e as taxas de sobrevivência são favoráveis. **Conclusão:** Há uma relação crescente do CEC de orofaringe e o HPV em jovens e adultos do sexo masculino, o que enfatiza a importância e a necessidade de se obter esforços para melhorar o diagnóstico, o tratamento e a prevenção de novos casos. Novos estudos são necessários com o objetivo de determinar o impacto epidemiológico e essa relação a longo prazo.

Termos de indexação: Papillomavirus humano. Carcinoma de células escamosas de cabeça e pescoço. Carcinoma de célula escamosas.

INTRODUCTION

Cancer is defined as a set of malignant diseases that manifest themselves through disordered cell division, characterized by their ability to spread and invade tissues and organs. Oropharyngeal neoplasia is a type of malignant tumor that affects the tongue's root, posterior one-third, tonsils, soft palate, as well as the posterior pharyngeal wall [1].

According to Globocan statistics, more than 98,412 cases of oropharyngeal cancer were diagnosed in 2020 in both sexes, with 48,143 deaths reported [2]. In Brazil, the estimated number of new cases emergence from 2020 to 2022 was 11,200 among men, and 4,010 among women [3]. According to the Brazilian National Cancer Institute (INCA), in 2020, oral cavity cancer had a high prevalence in males, being the fifth most common type of malignant tumor among this population. Concerning oropharyngeal cancer, that represents about 15-20% of aerodigestive tract cancers in both sexes [4].

Human Papillomavirus (HPV) is a DNA virus from the papillomavirus family, classified as one of the most common microorganisms, considering a worldwide epidemiological analysis. HPV is the responsible agent for this kind of sexually transmitted infection, which is part of an extensive viral family of considerable importance, due to its clinical manifestations in the head and neck regions, as well as its notorious participation in the development and evolution of malignant lesions. This agent is detected in about 25% of

cancers occurring in the oropharynx, also representing a proportion of 4% to 61% of neoplasms in the oral cavity [5,6].

Genetic sequencing analyses have shown, through genomic differentiation, more than 200 types of HPV detected. Among those types, the ones associated with higher incidence of cancer are HPV-16 and HPV-18, present in approximately 70% of cases of malignant cervix neoplasms, as well as those in other body parts, especially vulva, vagina, penis and oropharynx [4]. Globocan results showed that HPV DNA was found in 35% to 50% of cases, being divided into two groups according to oncogenic potential: low and high risk [2,4].

Oropharynx Malignant neoplasm has a different tumoral behavior compared to other types of cancer, and its aggravation is directly related to the primary HPV infection. That happens basically because persistent oncogenic infections may turn primary injuries into squamous cell carcinoma (SCC), and, however harmful this situation may be, determining a favorable prognosis depends on diagnosis and treatment in early stages [7].

It's essential / necessary to determine the importance of the relation between HPV and oropharyngeal cancer, since there is high incidence of cases, especially among young individuals. In specific terms, this virus is responsible for 71% and 51.8% of all oropharyngeal SCCs in The United States and The United Kingdom, respectively [8].

Since it is a cancer which presents not only aggressive characteristics but also high occurrence in young patients, we consider important studying it for better understanding and clarification of the relation between HPV and oropharynx SCC. Thus, this study aimed to analyze, through literary research, the relation between these two entities, as well as the associated epidemiological data and the prognosis of this condition.

METHODS

The methodology strategy defined for this narrative review consisted of a literary search for articles carried out on the database of the National Center for Biotechnology Information (PubMed), Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific Electronic Library Online (SciELO) and Virtual Health Library (VHL), between June 2021 and October 2022, using the crossing through Boolean operators AND and OR of the following Portuguese and English DeCS/MeSH descriptors: "HPV", "*Papillomavirus Humano*", "Human Papillomavirus", "*Carcinoma de Células Escamosas Orofaringeo*", "Oropharyngeal squamous cell Carcinoma", "*Carcinoma de Células Escamosas Oral*", "Oral squamous cell Carcinoma", "*Neoplasias Orofaringeas*" and "Oropharyngeal neoplasms".

Papers selection was based on articles whose titles addressed HPV and its relation with oropharyngeal cancer. First, abstracts available in established databases were collected. After titles and abstracts initial reading process, journals that evidenced the main subject of this paper were selected according to the following inclusion criteria: relevance for the subject, papers written in English, Portuguese, or Spanish, which presented their respective abstracts on specific search platforms, and published in the last 10 years. Periodicals that did not fit those criteria were excluded from the research, as well as monographs, dissertations, theses and letters to the editor.

After the initial refinement stage, 1,488 articles were found in PubMed, 22 in LILACS, 2,491 in BVS, and 33 in SciELO, totaling 4,034 publications. In an attempt to obtain a greater scientific base, it was

decided to carry out a free search through the analysis of references used in the articles initially selected on the platforms, and also on institutional websites related to the subject, 9 additional works were found through this search, which totaled 4,043 studies. After reading the papers in full, following the inclusion and exclusion criteria, 26 articles were included in this study (chart 1).

Chart 1. Database search strategy.

Data base	crossing of descriptors DeCS/MeSH	Selected sample	Excluded sample	Final sample
PUBMED	"HPV" AND "Oropharyngeal squamous cell" OR "Human Papillomavirus" AND "Oropharyngeal neoplasms"	1.488	1.474	14
SCIELO	"HPV" AND "Oropharyngeal squamous cell" OR "Human Papillomavirus" AND "Oropharyngeal neoplasms" AND "Oral squamous cell Carcinoma"	33	31	2
LILACS	"HPV" AND "Oropharyngeal squamous cell" OR "Human Papillomavirus" AND "Oropharyngeal neoplasms"	22	22	0
BVS	"HPV" AND "Oropharyngeal squamous cell" OR "Human Papillomavirus" AND "Oropharyngeal neoplasms"	2.491	2.490	1
FREE SEARCH	-	9	0	9
TOTAL	-	4.043	4.017	26

State of art

Clinical and histopathological characteristics of Oropharynx SCC

There is high incidence of oropharynx SCC all over the world population, and according to the location where it occurs, it presents different biological behavior [9]. Generally, it is characterized as a well-differentiated tumor with high occurrence of lymph node metastasis [8,10]. The most predominant subsites are in the tonsils and the root of the tongue, comprising 96% of oropharyngeal neoplasms. The most common symptom is sore throat, dysphagia, odynophagia, besides otalgia [8].

Bearing in mind that most head and neck SCC have their origin in oral cavity and oropharynx squamous cells, it is worth highlighting their histopathological characteristics. Most oral carcinomas are identified as the conventional well-differentiated keratinizing type. Thus, head and neck SCC is a malignant epithelial tumor with squamous cell differentiation characterized by keratin formation. Biopsy studies have shown that this type of neoplasm ranges from well to moderately differentiated, demonstrates moderate to severe peritumoral inflammatory infiltrate, and an expansive or infiltrative pattern of invasion, regardless the site of involvement. It is urgent to point out that, despite this type of SCC typically occurs with keratin,

HPV was associated as a risk factor for non-keratinizing SCC of the head and neck in the tonsillar (oropharynx and oral cavity) and nasosinusal areas [11].

Oropharyngeal carcinoma is a disease that is conventionally associated with exposure to tobacco and alcohol, and currently has been associated with HPV. Tobacco remains a critical factor for the response to treatment and survival of patients with SCC in this region who are positive for HPV. It is noteworthy that the interaction between smoking, HPV infection and carcinogenesis is complex and multifactorial. Data from the survey by Elhalawani et al. [12] suggest that although survival is strongly impacted by virus infection, exposure to tobacco also plays a very important role, although a determinant relation between these two factors has not been established.

Regarding gender, higher rates of occurrence are found among men, with a frequency four times higher than among women. Sexual behavior, such as the practice of oral sex, and the number of partners observed among men, may be a risk factor responsible for the high incidence of HPV-related neoplasms among the concerned population. However, there has been a growing increase in diagnoses among the female population. It may also be related to changes in sexual behavior, which has become closer to that one typical of men. In Europe, this increase has generated less negative impact, since it was found that female gender is associated with higher survival rates after oropharynx SCC diagnosis, regardless they have or not been infected by HPV [13,14]. Table 1 exemplifies the worldwide distribution of oropharyngeal cancer between females and males.

The increase of oropharynx SCC incidence in the last two decades has caused great damage to health systems due to the increase in amount of resources needed for patients care. This situation is aggravated by late diagnosis, high numbers in recurrence and progression of the disease, which leads to lower overall survival [10].

Table 1. Incidence of oropharyngeal cancer in men and women by world region (2020 estimate).

Area	Number of cases among women	Number of cases among men	Total cases
World	19.367	79.045	98.412
Africa	749	2.164	2.913
Americas	4.139	18.771	22.910
Asia	7.579	34.597	42.176
Europe	6.717	22.522	29.239
Oceania	183	991	1.174
Total	38.734	158.090	196.824

Note: adapted from Bruni et al., 2022 [15].

General characteristics of HPV virus

HPV is a small, non-enveloped virus which has circular double-stranded DNA genomes which lives in cutaneous and mucosal epithelium. It can be present in five genera (Alpha, Beta, Gamma, Mu and Nu),

most of which belong to the genera Alpha-HPV, Beta-HPV and Gamma-HPV [5,16]. The progression of the infection begins in the circular genome, which consists of six regions (E1, E2, E4, E5, E6 and E7), where eight genes are encoded. In addition, access to the basal lamina through the action of the L1 and L2 capsid proteins, and DNA replication by E1 and E2 proteins in the middle layers of the epithelium [5,17,18], take place. After initial replication, the DNA copy number is kept stable and viral genomes replicate with cellular DNA [5]. HPV infection may occur in two ways: the productive one, which has the life cycle interrupted, making the occurrence of cancer null; and the unproductive, also called abortive or transformative, which has a normal life cycle, with a high risk of cancer development [5,8].

According to the World Health Organization (WHO), 14 types of high-risk HPV in the mucosa are currently classified: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 [8]. Low-risk types such as HPV-6, 11, 42, 43 and 44 are found in benign lesions. HPV-6 and HPV-11 are usually present in anogenital warts. HPV-16 and HPV-18 are found in cases of high-grade squamous intraepithelial lesions and in cervical carcinomas [8,17]. In a study carried out with tumor samples, it was found that HPV-16 is the high-risk type with the highest prevalence (16%) for the SCC development [19].

It is known that HPV-16 and HPV-18 may play important roles in the development of some cells malignancy. However, it is necessary to establish a direct relation between these two subtypes and performance in the oncogenic development of oral cavity neoplasms. Despite being the second most common type of HPV, HPV-18 was found less frequently in oral cavity SCC cases, than in cervical adenocarcinomas ones. Furthermore, when analyzing the prevalence between HPV-16 and HPV-18, it was revealed that subtype 18 may not favor the development of oropharynx SCC, due to its affinity with glandular tissue. Therefore, HPV-16 was considered positive for SCC in this region, with a predominant manifestation among 21 to 44 year-old people [20].

Relation between SCC of the oropharynx and HPV

Oropharyngeal cancer and its relation with HPV demonstrate molecular, clinical, and epidemiological evidence. Thus, the manifestation of cancer in this region is marked by oral infection acquired by HPV, due to the non-complete elimination of the virus, allowing the appearance of neoplasia [17].

Regarding patients with positive SCC and HPV, it was observed that the number of cases increasingly encompasses adult patients of advanced age, in which most of those involved are under 65 years old, with an average age at diagnosis, around 61 years old. In the United States, the diagnosis reached the highest numbers among individuals between 60 and 64 years old. These data may also be related to the increase in unprotected sexual activity among the elderly [8,13].

The human oral cavity contains a diverse community of approximately 700 microbial species, many of which may contribute to carcinogenesis. HPV infection coincides with the presence of certain bacteria, such as *Streptococcus anginosus*, *Prevotella melaninogenica* and *Fusobacterium naviform*, which may be associated with dysbiosis and correlate with oral carcinogenesis. Furthermore, poor oral health increases the risk of HPV infection and may contribute to SCC of the oropharynx related to this virus [14,21].

During the carcinogenic progression of positive HPV to cancer, the viral oncogenes E6 and E7 are mainly responsible for its pathogenesis [8]. E6 gene is determined by its association with tumor protein 53 (p53), which has the function of paralyzing cells in G1. E7 gene, on the other hand, is directly linked to tumor suppressors of retinoblastoma protein (pRb), causing the cell to enter the S phase and, consequently,

causing the inactivation of those proteins. Thus, the oncogenic potential results in changes such as tumor cell proliferation, apoptosis and malignancy progression [18,22]. In addition to those proteins, p16 acts to inhibit the cell cycle and is responsible for the diagnosis of positive HPV due to the presence of a clinical biomarker [8].

Treatments available for those diagnosed with SCC are established according to tumor staging, being classified as type I, II, III or IV. Staging in clinical practice is of paramount importance for the patient's prognosis, since it is based on tumor diameter and the occurrence of regional or distant metastasis. Treatment involves surgical excision, radiotherapy and chemotherapy, which may or may not be associated to each other [8].

Patients with oropharyngeal carcinoma diagnosed with HPV have a favorable prognosis and survival rates, with an overall average of three years, compared to those negative for HPV [18]. This is due to the fact that, generally, the HPV-negative patient is usually an alcohol and tobacco user, that is, he is in the constant presence of carcinogenic metabolites, with a consequent increase in genetic alterations [21,22].

HPV-related malignant tumors are more sensitive to radiotherapy. According to the study by Kimple et al. [23], cell lines from infected cancer patients showed significantly greater sensitivity to radiation. Furthermore, the research also demonstrated that, clinically, those patients had a faster response to treatment, which means that the tumor immune response is faster in HPV-positive cells than in HPV-negative cells.

Epidemiological aspects and future perspectives

While the occurrence of SCC in the head and neck region in developed countries has been decreasing due to the probable reduction in smoking, the rates of oropharynx SCC (root of the tongue and tonsils) related to HPV have increased, which raises a concern regarding its future control. In addition, literature demonstrates a high incidence of SCC in that region among male population [14].

Descriptive analysis by age showed that the highest concentration of deaths, considering both sexes, occurred in the group aged from 50 to 59– with an annual average of 1.02 deaths per 100,000 inhabitants, followed by the group aged from 60 to 69 (0.87/100,000 inhabitants/year). Regarding the analysis according to race/color, the highest mortality rate was identified in the black race/color, with 3.39 deaths per 100,000 inhabitants. Next, there is white race/color (3.36/100,000 inhabitants/year) [4].

On the other hand, even in view of the results presented, it is known that oropharyngeal cancer related to HPV typically affects white men with higher economic status [8,18]. However, socioeconomic factors, opportunities to access health services for early diagnosis and treatment, as well as the quality of the treatment offered, are also related to survival rates. Therefore, it is not difficult to understand the result of these mortality rates, since socioeconomic inequality in Brazil are deeply marked by the ethnic-racial component [4]. Table 2 shows average mortality due to oral and oropharyngeal cancer, according to sex, anatomical position and race/color.

Vaccination is the safest and most effective method for preventing HPV infection, resulting in significant reduction in the occurrence of benign and malignant lesions due to its high relation with these neoplasms. Therefore, vaccination should be reinforced among young people and adults, especially adolescents, who will probably be protected during their first sexual contact. It is interesting to point out that the vaccine is usually quadrivalent, being effective for HPV 6, 11, 16 and 18. In addition, it is approved for both sexes, aged 9 to 26 years, with administration in three doses [5, 8].

It is understood that prophylactic vaccination can prevent HPV infection and mass immunization can reduce the risk of infection in both men and women. However, only vaccinating women will hardly be effective in extinguishing the risks of infection by the virus in both populations, that is why it is important to highlight the need of vaccinating male population. According to Brazilian Health Ministry, only in the year 2022, there was an expansion regarding the age of the male population that can be immunized against the virus, with the inclusion of boys aged 9 and 10. Then, vaccination was extended to both sexes between the ages of 9 and 14 [24].

It is noteworthy that HPV vaccination campaigns started late in Brazil, covering female population only in 2016 [25] and the male in 2017 [26]. Besides, it is urgent to point out that immunization in the private system has high prices, which makes its access difficult to most disadvantaged population.

Table 2. Average adjusted mortality rates for oral and oropharyngeal cancer (per 100,000 inhabitants) according to sex, anatomical location and race/color in Brazil, in years from 2000 to 2013.

Variable	Global	Men	Women
Anatomical location			
Language Basis	0.283	0.498	0.082
Palate	0.169	0.248	0.095
tonsils	0.112	0.195	0.034
Oropharynx	1.108	1.947	0.322
Race/Color			
White	3.355	5.632	1.221
Black	3.385	5.441	1.459
Dun/Brown	2.275	3.565	1.067
Yellow	1.402	2.341	0.522
Indigenous	0.883	1.355	0.442

Note: adapted from Cunha et al. [4].

CONCLUSION

In recent years, due to the progressive increase in cases of malignant oropharynx tumors, there has been recognition of the direct and growing relation between SCC in this region and HPV in young people and adults, especially males, which emphasizes the importance and need of increasing efforts for diagnosis, treatment, and prevention of new cases. New studies are needed in order to determine long-term epidemiological impact of oropharynx SCC related to HPV.

Collaborators

LP Cunha and EG Conceição, analysis, conceptualization, first version writing, methodology, investigation, data acuration. MVC Marques and MF Souza, methodology and final version approval (review and edition). JSV Néri and JBL Dantas, project management, supervision, final version approval (review and edition). All authors: validation and design.

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