

Review Article

Volume 4 Issue 3 - April 2024
DOI: 10.19080/JTMP.2023.04.555640

J Tumor Med Prev

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Relationship of HPV with Laryngeal Cancer: A Systematic Review

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Submission: April 10, 2024; **Published:** April 22, 2024

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Summary

The Human Papilloma Virus (HPV) is responsible for causing an infection capable of contaminating the skin and mucous membranes of men and women, presenting wart-like lesions in the injured regions. HPV is recurrently detected in patients with laryngeal cancer, which is head and neck cancer, which represents 1.2% of all malignant diseases. The present study seeks, through a systematic review, to find out which subtypes of HPV are most common and their relationship with the development of laryngeal cancer. Therefore, articles published in full from 2012 onwards in the English language, which addressed the proposed topic, were included in the study. Of the 107 articles initially selected, 33 were read in full and 30 were properly included in this review, covering fifteen different countries. The articles pointed out the most oncogenic HPV subtypes described in the literature: HPV-16, HPV-18, HPV-31 and HPV-33. The most used method for identifying HPV in laryngeal cancer in the studies analyzed was the identification of HPV DNA, through quantitative PCR measurement. Of the 30 articles analyzed, 18 specified how many patients were male and how many were female. Of these 18 studies, 1,928 patients were evaluated, 1,574 were male, corresponding to 81.63% of cases, thus observing a notable prevalence in the corresponding public.

Abstract

The Human Papillomas Virus (HPV) is responsible for causing an infection capable of contaminating the skin and mucous membranes of men and women, presenting wart-like lesions in the injured regions. The Human Papillomas Virus (HPV) is responsible for causing an infection capable of contaminating the skin and mucous membranes of men and women, presenting wart-like lesions in the injured regions. HPV is recurrently detected in patients with laryngeal cancer, which is a head and neck cancer, which represents 1.2% of all malignant diseases. The present study seeks, through a systematic review, to know the prevalence of HPV and its relationship with the development of laryngeal cancer. Thus, of the 107 articles first selected, 33 were read in full and 30 were properly contemplated in this review, which pointed out the most oncogenic HPV subtypes described in the literature: HPV-16, HPV-18, HPV-31 and HPV- 33. The most used method for the identification of HPV in laryngeal cancer in the analyzed studies was the identification of HPV-DNA, through the measurement of quantitative PCR. Of the 30 articles analyzed, 18 specified how many patients were male and how many were female. Of these 18 studies, 1,928 patients were evaluated, 1,574 were male, corresponding to 81.63% of the cases, thus observing a significant prevalence in the corresponding public.

Keywords: Human Papillomavirus (HPV); Alpha papillomavirus; Laryngeal neoplasms; Genotypes; Retinoblastoma protein

Abbreviations: HPV: Human Papillomas Virus; QUIPS: Quality in Prognosis tool was used Studies; PCR: Polymerase Chain Reaction; PNI: National Immunization Program; WHO: World Health Organization

Introduction

Cancer is considered a global public health problem, representing the second largest cause of death on a global scale, being responsible for 9.6 million deaths in 2018. Statistically, one in every six deaths occurs due to this disease [1]. Among head and neck neoplasms, laryngeal cancer represents around 25% of malignant tumors that affect this area and 1.2% of all types of cancer [2]. Laryngeal cancer affects the region responsible for

housing the vocal cords, being a major influence on the patient's quality of life [3]. This type of cancer can spread by direct extension to adjacent regions, through metastases, especially in cervical lymph nodes [4]. The occurrence of laryngeal cancer is prevalent in men [5] and can affect any of the three anatomical parts of the organ: supraglottis, glottis and subglottis [6]. The most affected site is the glottis, on the true vocal cord [7].

History taking and physical examination are essential to evaluate the clinical picture of patients with laryngeal cancer. Initial symptoms, such as odynophagia and hoarseness, may indicate the location of the tumor [8]. For proper diagnosis and staging, tests such as indirect and direct laryngoscopy are performed. Diagnostic confirmation is made through direct laryngoscopy with biopsy, and naso laryngoscopy can be used when necessary [9]. Therapeutic options for laryngeal cancer include radiotherapy, chemotherapy and surgery, and can be used alone or in combination, depending on the stage and individual characteristics of the patient, seeking a cure or improving quality of life, with a combination of two or more therapeutic methods reserved for special cases or when the objective is palliative [10,11].

Among the most common etiologies are smoking and alcoholism. However, human papillomavirus (HPV) infection has been the target of several studies, demonstrating a significant role in the development of laryngeal cancer [12-14]. HPV is a sexually transmitted virus, which causes infection in the skin and mucous membranes, and leads to the appearance of papillomatous warts in the affected areas. The virus can manifest itself as low risk or high oncogenic risk. The main types of HPV with low oncogenic risk are HPV-6 and HPV-11, being responsible for benign lesions. Among the HPV genotypes with high oncogenic risk, the ones most commonly related to the development of malignant tumors are HPV-16 and HPV-18 [15,16]. Molecular evidence links the presence of HPV in head and neck neoplasms, causing the inactivation of the tumor suppressor proteins p53 and retinoblastoma [11]. Considering a possible relationship between HPV infection and the development of laryngeal cancer, it is extremely important to analyze the incidence of the HPV virus in this type of cancer. This assessment is important, as demonstrating the relationship between HPV and laryngeal cancer, it is essential to carry out awareness and prevention campaigns, including vaccination, avoiding an increase in the number of cases and complications caused by this etiology. Therefore, this systematic review aims to understand and report the most common HPV subtypes and their relationship with the development of laryngeal cancer.

Methodology

The review systematic in the literature is of a basic, exploratory and descriptive nature, with a qualitative approach and retrospective bibliographic procedure, being carried out in accordance with the methodological recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma). The search for articles was carried out in December 2022, using electronic databases PubMed and Science Direct. To search the databases, the descriptors "HPV" OR "human papillomavirus" OR "high-risk human papillomavirus" OR "alpha papillomavirus" AND "laryngeal cancer" OR "squamous neoplasms cancer of larynx", the search being carried out in the title and abstract fields. The study included articles published in full from 2012 onwards in English, which

addressed the incidence and relationship of HPV in laryngeal cancer. Review articles (narrative, integrative and systematic) and in vitro and animal research articles, book chapters, theses, dissertations, conference annals, reports were excluded from the study. technical and ministerial documents.

Experimental Design

Initially, duplicate articles were identified through a double-blind search and analysis. Next, the title and summary of the studies were evaluated, adopting the inclusion and exclusion criteria and the approach to the research topic. Subsequently, the articles were read in full, and those that did not agree with the theme or that did not meet the criteria required for this review were discarded. To assess quality and risk of bias, the Quality in Prognosis tool was used. Studies (QUIPS), which analyzes articles in the following way: participation in the study, abandonment of the study, evaluation of the result, clarity and objectivity of the study and analysis statistics, and in the end the articles can be classified as having low, moderate or high risk of bias [17].

Results

Research results and risk of bias and quality of studies

107 articles were found in the two databases, 65 studies in the PubMed database and 42 in Science Direct. Of these, five were duplicates, leaving 102 articles for analysis. After evaluating the articles by their title and summary, applying the inclusion and exclusion criteria, 33 articles remained that fit the theme. After reading the 33 articles in full, three were discarded, as they did not address the theme proposed in this systematic review. Therefore, 30 articles were selected and qualified by the QUIPS platform for the necessary data collection. The research design is presented in Figure 1. The QUIPS instrument was used to assess the quality and risk of bias of the articles chosen for evaluation, as shown in Table S1. No articles were excluded from the systematic review, as none presented a high risk of bias.

General information about the selected studies

The 30 articles selected for this review were published between 2012 and 2022, with their main characteristics and results in Table 1 [18,19]. Of the 30 articles, six were carried out in the United States (#4, #10, #14, #20, #23, #29), four in Mexico (#13, #16, #19, #30), three in Poland (#7, #17, #22), two in Japan (#1, #24), two in Turkey (#9, #21), two in Italy (#3, #12), two in China (#27, #28) and the other countries with a study, Egypt (#2), Lithuania (#5), Sweden (#6), Spain (#11), Colombia (#25), Brazil (#15), Iran (#26) and Germany (#18). One of the studies (#8) was carried out in Europe and America in general. The most used method for identifying HPV in laryngeal cancer in the studies analyzed was the identification of HPV DNA, using the quantitative Polymerase Chain Reaction (PCR) technique, being used in 26 articles (#1, #3, #4, #5, #6, #7, #8, #9, #10 #11,

#12, #13, #14, #15, #17, #18, #19, #20, #21, #22, #23, #24, #25, #26, #27, #30). The detection of HPV DNA can be done by hybrid capture, in situ hybridization and genotyping. These 26 articles used the genotyping method, a technique that has advantages, as it detects a higher number of HPV types [20]. Another technique used in three articles (#2, #16, #28) was immunostaining, an

indirect technique for detecting HPV in laryngeal tumors. The 30 articles reviewed included studies on the type of squamous cell carcinoma, that is, squamous cell carcinoma. Of these, only two articles (#7, #10) observed the occurrence of invasive squamous cell carcinoma, with extra laryngeal involvement, the others demonstrated squamous cell carcinoma in situ.

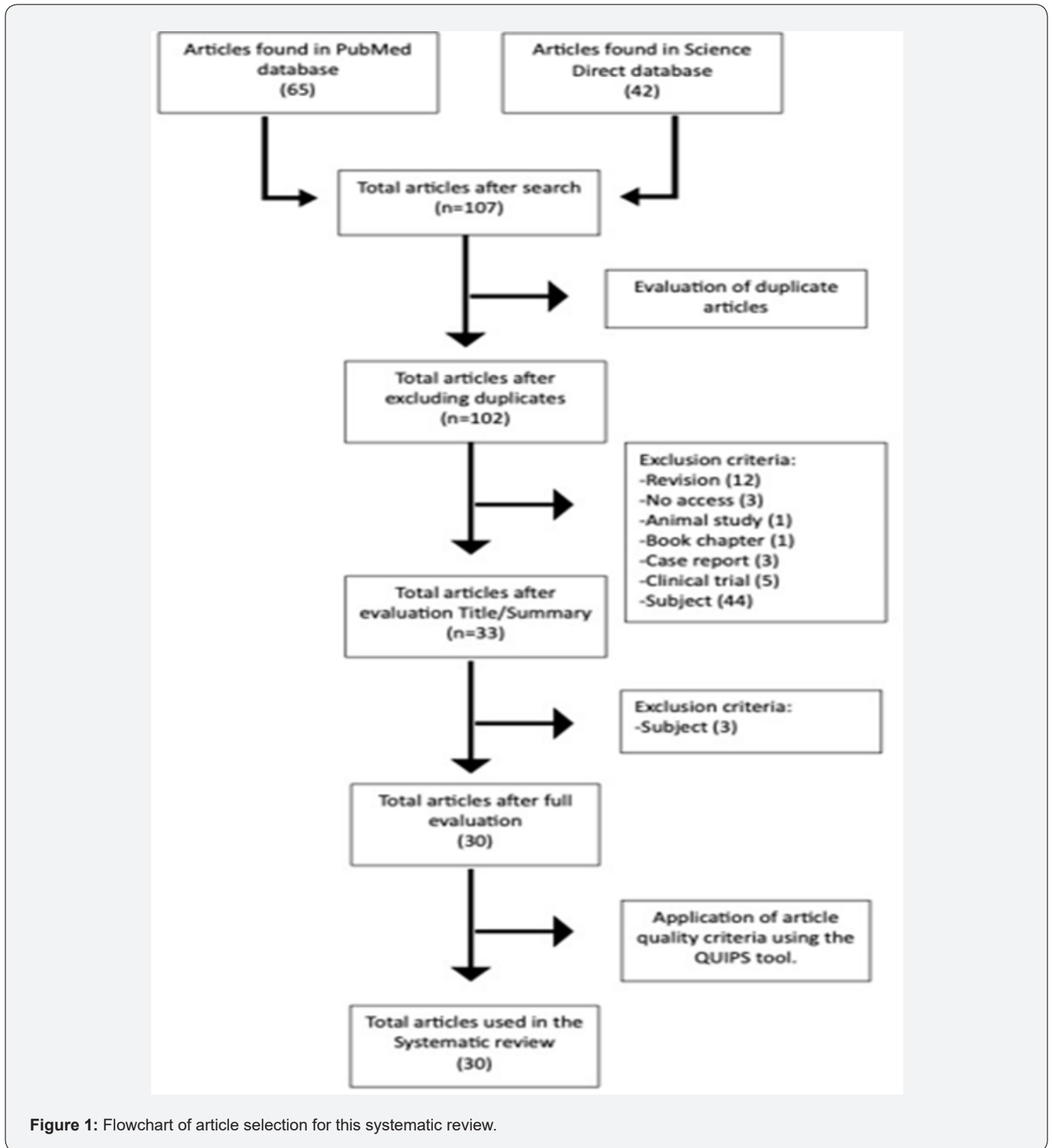


Figure 1: Flowchart of article selection for this systematic review.

Table 1: General results of the articles analyzed.

No.	Ref	Country	Main Results
#1	Kyeong A, et al., [18].	Japan	Of the 88 patients with CL, there were 16 (18.2%) cases positive for HR-HPV, two (2.3%) cases positive for low-risk HPV (HPV-6) and five (5.7%) positive cases for p16. All p16-positive cases contained HR-HPV DNA. Regarding the types of HR-HPV, thirteen patients had HPV-16 and one patient had HPV-33.
#two	Gomaa MAM, et al., 2017.	Egypt	Among the patients in the study, nine (18%) had positive immunostaining for HPV-16. The correlation between HPV-16 positivity and the age of affected patients is presented. The patient's smoking rate and amount of alcohol consumption were not significantly correlated with HPV-16 positivity.
#3	Gallus R, et al., 2022.	Italy	Among the 80 cases tested for HPV DNA, seven (8.75%) tested positive for HR-HPV16 DNA. Detection of HPV DNA was not associated with differences in overall survival (OS) (p =0.64 in Log-Rank), relapse-free survival (RFS) (p =0.86 in Log-Rank), or survival disease-specific disease (DSS) (p =0.93 in Log-Rank).
#4	Hughes RT, et. al., 2019.	USA	In total, 279 patients with laryngeal/ hypopharyngeal SCC were identified, the majority of whom were male (79%), Caucasian (81%). Of 94 patients with known HPV status, 82 were classified as negative and twelve were classified as positive.
#5	Stumbrytė-Kaminskie Ė A, et. al., 2020.	Lithuania	After HPV detection, viral infection was found in 42.86% (21 of 49) of all LSCC cases. Viral genotyping showed that HPV-16 was the dominant type (17 of 21 cases, 80.95%) in HPV-positive tumor samples; In several cases, the HPV-18 type was detected (three of 21 cases, 14.9%) and in one case double infection was observed.
#6	Schindele A. et. al., 2022.	Sweden	9% of samples (3/33) were positive for high-risk HPV-16 and overexpressed p16. A total of 14% (11/78) of samples overexpressed p16.
#7	Mucha-Matecka A. et. al., 2021.	Poland	All patients were diagnosed with squamous cell carcinoma, including three cases (22%) of low-grade (G1) cancer; 35 cases (58%) of intermediate-grade (G2), and, finally, twelve cases (20%) of cancer. high grade (G3). Among the 60 patients analyzed, assessment of the status and type of HPV-16 infection was possible for 59 patients; for one patient, no DNA was obtained during the extraction process.
#8	by Sanjosé S, et. al., 2019.	Europe And America	The prevalence of HPV for all types combined was 3.5% in laryngeal cancer. HPV-16 was the dominant type in HPV-related cancers in all regions. Within oropharyngeal cancer from 78.1% (Americas) to 94.7% (Asia and Oceania), in oral cavity cancer 90.9% (Americas and Europe), and in laryngeal cancer 0.0% (Africa based on small number of samples) to 58.3% (Europe).
#9	Onerc Celebi O, et. al., 2018.	Türkiye	Tumor location included the supraglottis (p=58 [70.7%]) and the glottis (p=24 [29.3%]). In total, five (6.1%) patients were clinically stage II, 38 (46.3%) were stage III, and 39 (47.6%) were stage IV.
#10	Hernandez BY, et. al., 2014.	US	HPV DNA was detected in 21% of laryngeal cancer cases. Carcinogenic HPV types were detected in 26 of 31 HPV-positive tumors. The carcinogens HPV-16 and HPV-33 were the most commonly detected genotypes. Other carcinogenic genotypes included HPV-18, HPV-31, HPV-35, HPV-39, HPV-51, and HPV-66. HPV was detected in 30% of advanced-stage cancers and 17% of early-stage cancers (p = 0.07).
#11	Chen WC, et. al., 2017.	Spain	Twenty-six cases were p16+ (16.8%) and 19 cases were PCR+ (12.3%). HPV+ tumors were predominantly located in the oropharynx (42.1%, p=0.017) and tended to be more frequent in males, with a higher incidence in younger patients.
#12	Allegra E, et. al., 2021.	Italy	Expression of nuclear p16 in tumor cells was detected in 20 of 74 (27.02%) laryngeal carcinomas, with all cases showing high expression of p16 (IRS > 10).
#13	Vazquez-Guillen JM R, et. al., 2018.	Mexico	HPV DNA was detected in 93 (47.7%) specimens. HPV-11 was the most common with 68 cases (73.1%) and HPV-52 was the most common HR-HPV found with 51 cases, which corresponds to 54.8% of all samples positive for HPV.
#14	Stephen JK, et. al., 2012.	US	Of the 79 primary LSCC, 38 were early stage, 40 late stage, and one unknown stage. HPV-16 was detected in 21/77 (27%) patients. HPV correlated with gender (p=0.02).
#15	Brito C, et. al., 2022.	Brazil	HPV analyzes demonstrated that half of the samples were positive for the virus. High oncogenic risk types 16, 45 and 33 were observed in the majority of patients (68.3%). Type 6, a low- risk HPV, was found in one patient. HPV-16 was the most prevalent type in this cohort (p=22, 53.65%).

#16	Peralta R, et. al., 2018.	Mexico	HPV-16 was the only type detected in the LSCC samples. This set allowed detection of HPV DNA in 20% of LSCC samples (6/30).
#17	Janecka-Widła A, et. al., 2020.	Poland	Active HPV infection was detected in 20.65% of patients. HPV-16 was dominant (81.25%) followed by HPV-35 (9.38%) and double infections with HPV-16 and 35 (6.25%) or HPV-35 and 18 (3.12%) .
#18	Kühn JP, et. al., 2021.	Germany	For oropharyngeal cancer cases, p16 showed the highest significance in predicting outcome. Oropharyngeal cancers had the highest percentage of p16-positive cases (54%), followed by oral cavity cancers (47%), hypopharyngeal cancers (39%), and laryngeal cancer.
#19	Villagómez -Ortíz VJ, et. al., 2016.	Mexico	The distribution by clinical stage of the disease at diagnosis was: 17 patients in clinical stage IV, eleven patients in stage III, ten patients in stage II and seven in stage one. HPV infection was detected in two patients (4.4%), both diagnosed with laryngeal cancer. The viral subtype detected in both patients was type eleven;
#20	Hernandez, et al., 2016.	US	Tumor tissue specimens from 101 of 148 cases from previous analysis confirmed as sufficient for immunohistochemistry included for study not present. A total of 19 (18.8%) cases remained classified as unspecified SCC and one case was small cell carcinoma.
#21	Dogantemur, et al., 2018.	Türkiye	Polyclonal HPV positivity was detected in eleven (12.2%) of the 90 cases. Of these eleven cases, HPV 16 was positive in six, HPV-18 in four and HPV-16 and 18 were positive in one. In 18 (20%) of the cases, p16 was positive. Six of the cases (6.6%) were positive for HPV and protein16. In cases where protein 16 alone or HPV and protein 16 were co-positive. Although life expectancy above five years was numerically higher in HPV and protein 16 positive cases, this was not statistically significant.
#22	Drop, et al., 2017.	Poland	Men (87.7%) with smoking problems (70.6%) and alcohol abuse (59.6%) prevailed in the studied group. Single HPV infection was more frequent in oral cavity cancer (44.5%), while EBV infection was more frequent in oropharynx cancer (57.1%).
#23	Vera Cruz, et al., 2020.	US	The results showed the presence of HPV in 72.4% of the sample (21 cases). All types of HPV were evaluated.
#24	Matsusaki et al.,	Japan	The LPH for low-risk HPV was applied to all 144 patients, and the high-risk HPV was additionally applied to 121 of the 144 patients. PCR was applied to 94 of the 144 patients. LPH detected low-risk HPV-DNA in 23 patients (one cancer and 22 papillomas) and high-risk HPV-DNA in three patients (one cancer and two papillomas). PCR detected HPV-6 and HPV-11 in the papilloma group, while it detected HPV-31 in a patient with laryngeal cancer and a patient with a precancerous lesion.
#25	Quintero, et al., 2013.	Colombia	The overall prevalence of HPV was 18.9%. HPV was found in 23.9%, 17.5% and 13.3% of oral cavity, larynx and oropharynx cases, respectively. Among HPV-positive cases, 82% were HPV-16 and 18% were HPV-18. No other HPV genotypes were identified. The majority of patients were male.
#26	Roshan, et al., [19].	Will	82 laryngeal specimens from 60 patients with laryngeal SCC as a case group and 22 patients with benign laryngeal conditions and without laryngeal SCC were examined for the presence of HPV-16/18 or HHV-8 DNA using PCR.
#27	Xu, et al., 2014.	China	The overall prevalence of HPV DNA was 4.9% (33/674) in LSCC patients and 0% (0/674) in control cases in our series (p<0.01). In 33 HPV-positive patients, 28 (84.8%) were HPV-16, two (6.1%) were HPV-18 and one (3.0%) each HPV-31, HPV-45 and HPV-33 positive.
#28	Chen, et al., 2017.	China	The prevalence of HPV (all types) was higher in cases than in controls 21 (7.0%) versus ten (3.3%). The risk of LSCC associated with HPV-16 DNA positivity was even higher in patients aged 55 years or younger, never smokers, and never drinkers.
#29	Bates, et al., 2019.	US	In multivariate analysis, HPV-negative status (HR = 1.42, p=0.02) and receipt of CRT (HR = 1.34, p=0.01) were associated with worse OS when compared to positive patients for HPV and patients receiving TL, respectively. HPV-16 and HPV 18 were the most prevalent in the study.
#30	Ortíz, et al., 2016.	Mexico	The association between laryngeal squamous cell carcinoma and HPV occurred in two patients, representing an overall prevalence of 4.4% in our population and 10% for laryngeal tumors. The samples were positive for HPV 18, 16, 11 and 6.

Incidence of HPV subtypes in laryngeal cancer

Table 2 was developed with the aim of recording the most prevalent HPV types identified during the systematic review. Thus, it was observed that among the HPV subtypes with high oncogenic risk, HPV-16 was mentioned in 28 articles (93.33%), followed by HPV-18, with 14 mentions (46.66%). Types 31 and

33 were evaluated in five articles each (8.33%). Subtypes 35, 45, 51, 52 and 66 were mentioned three times each (2%). HPV-39 and 56 appeared in two articles (3.33%). Regarding low-risk or non-oncogenic subtypes, HPV-6 and HPV-11 were mentioned in only four studies (6.66%).

Table 2: Number of articles per type of HPV identified in laryngeal cancer.

Types of HPV	Articles	Total Articles
HPV – 6	#15; #23; #24; #30	4
HPV – 11	#9; #13; #24; #30	4
HPV – 16	#1, #2, #3; #4; #5; #6; #7; #8; #9; #10; #11; #12; #14; #15; #16; #17; #18; #19; #20; #21; #22; #23; #25; #26; #27; #28; # 29; #30	28
HPV – 18	#5; #9; #10; #11; #17; #18; #19; #21; #23; #25; #26; #27; #29; #30	14
HPV – 31	#10; #18; #23; #24; #27	5
HPV – 33	#1; #15; #18; #23; #27	5
HPV – 35	#10; #17; #23	3
HPV – 39	#10; #18	two
HPV – 45	#15; #18; #27	3
HPV – 51	#10; #18; #23	3
HPV – 52	#13; #18; #23	3
HPV – 56	#18; #23	two
HPV – 66	#10; #18; #23	3

Most common HPV subtypes by country

Table 3: HPV subtypes by country/region.

Country	HPV subtype
Germany	16
Brazil	6, 16, 33, 45
China	16, 18, 31, 33, 45
Colombia	16, 18
Egypt	16
Spain	16
US	16, 18, 31, 33, 35, 39, 51 and 66
Will	16, 18
Italy	16, 52, 56, 58
Japan	6, 11, 16, 31, 33
Lithuania	16, 18
Mexico	11, 16, 52
Poland	16,18, 35
Sweden	16
Türkiye	16, 18
Europe and America	16

In Table 3, the different types of HPV analyzed in the selected articles are listed, taking into account the geographic location by

country or region of the sample examined. In all 15 countries in which the studies were carried out, the presence of HPV-16 was unanimous, followed by HPV-18, which, in turn, was found in seven countries.

Prevalence of HPV by sex

Of the 30 articles analyzed, 18 specified how many patients were male and how many were female (#2, #5, #7, #8, #9, #10, #11, #12, #13, #14, #15, #17, #18, #19, #24, #26, #29, #30). Of these 18 studies, 1,928 patients were evaluated, 1,574 were male, corresponding to 81.63% of the cases analyzed, thus observing a significant prevalence in the corresponding public. Among these articles that reported the population to be predominantly male, only three of them also possessed age information (#2, #12, #18), establishing an average of 60 years. The remaining articles did not distinguish patients between men and women.

Discussion

Among head and neck cancers, laryngeal cancer corresponds to around 1% of malignant lesions in cancers in general, nationally, not taking into account skin tumors, both melanomas and non-melanomas (GLOBOCAN, 2020). Laryngeal cancer affects the region responsible for housing the vocal cords. This type of cancer can spread by direct extension to adjacent regions, through metastases, especially in cervical lymph nodes [4].

HPV has been recognized as a risk factor for the emergence of oropharyngeal carcinomas due to the increase in the number of lesions in individuals who are not among the groups that have well-established carcinogenic factors for the development of neoplasms, such as smoking and alcohol consumption (Chen et al., 2006).

According to Zorzanelli et. al [11], squamous cell carcinoma is the histological type with the highest incidence among laryngeal neoplasms. This fact was widely observed in the 30 articles analyzed, all of which referred to squamous cell carcinoma. Molecular tests are significantly useful for detecting HPV infection by allowing the identification of the type of HPV, its viral load and evaluation of protein expression. carcinogenic. PCR, used in 26 of the 30 articles analyzed in this review, is a nucleic acid synthesis technique in which a specific segment of virus DNA is replicated and represents a method sensitive for detection of HPV. As in the review article by Aimagambetova & Azizan [21], who analyzed 39 articles referring to the methods used to detect HPV in laryngeal cancer in Kazakhstan, with the prevalence of the quantitative PCR method through genotyping, as observed in this systematic review. HPV are a group of viruses that can be classified into high-grade HPV and low-grade HPV, based on their oncogenic potential. High-grade ones, such as types 16 and 18, are considered more invasive and are associated with a greater oncogenic potential (TOMMASINO, 2013).

The relationship between high-grade HPV and the development of cancer is related to the action of its main oncogenes, which interact with cellular proteins, p53 and Rb (retinoblastoma protein) (TOMMASINO, 2013). The p53 protein plays an important role in regulating the cell cycle and suppressing tumors. High-grade HPVs have a protein called E6, which has the ability to bind to p53 and inactivate it. This compromises the cell's ability to repair DNA damage and increases the risk of malignancy. Furthermore, high-grade HPVs have the E7 protein, which interacts with the Rb protein. Rb, in turn, acts as a tumor suppressor, controlling the cell cycle and preventing uncontrolled cell proliferation [22]. The interaction between the E7 protein and Rb leads to the inactivation of Rb, allowing HPV-infected cells to divide uncontrollably and promoting the development of cancer. Low-grade HPV, such as types 6 and 11, have less oncogenic potential and are more associated with the development of benign lesions [22]. HPV-16 is considered the most prevalent subtype in relation to laryngeal neoplasia. A study carried out by Barros [23] shows a strong association between HPV-16 infection and the development of squamous cell carcinomas of the larynx.

Although it is less common compared to HPV-16, HPV-18 has also been detected in some cases of laryngeal cancer. This subtype is generally associated with other types of neoplasms, such as cervical cancer and anal cancer (ROSHAN, 2013). With the aim of preventing the incidence of HPV infection, the nonavalent HPV vaccine offers protection against nine types of HPV viruses: 06, 11,

16, 18, 31, 33, 45, 52 and 58. These types of viruses have been identified as highly prevalent in the studies mentioned in this review. On the other hand, the quadrivalent vaccine, used in the National Immunization Program (PNI), protects only against types 06, 11, 16 and 18, leaving additional types of viruses unprotected: 52, 33, 31, 58 and 45. Since 2014, the quadrivalent HPV vaccine is offered free of charge by the Unified Health System (SUS) for girls aged 9 to 14 and boys aged 11 to 14. Quadrivalent vaccine is the most used in Latin America, according to the WHO (2019). In Africa, HPV vaccination can vary between different countries and regions of the continent. However, the most commonly used vaccine is the quadrivalent, due to its more affordable price when compared to the nonavalent. Organizations, such as the World Health Organization (WHO) and UNICEF, also play an important role in HPV vaccination on this continent, seeking to protect the most vulnerable populations and reducing the burden of HPV-related diseases. Both the quadrivalent and nonavalent vaccines are widely used in the United States and Canada, as well as Europe [1].

In relation to the studies observed, it was found that HPV-16 was the HPV subtype most observed in laryngeal cancer in population studies in Latin America, North America, Africa, Europe and Asia. Among men, the highest incidence rates were observed in Central and Eastern Europe, the Caribbean and Southern Europe; among women, laryngeal cancer was more common in the Caribbean and North America (FERLAY et al., 2020); [24]. The incidence of HPV infections can vary between men and women, as there are differences in exposure and immune response to the virus. However, it is important to highlight that HPV is a sexually transmitted infection that affects both sexes.

In women, HPV is best known for being associated with the development of cervical cancer, the estimated number between 2023-2025 is 7840 new cases. It is estimated that the vast majority of cervical cancer cases (estimated number between 2023-2025 is 15.38 cases per 100,000 women) are caused by persistent HPV infection. In addition to cervical cancer, HPV may also be related to the development of other types of cancer, such as vaginal, vulvar, anal and oropharyngeal cancer [25]. In men, HPV can cause genital warts, as well as being associated with other types of cancer, including penile, anus and oropharyngeal cancer. Although men do not develop cervical cancer, they can carry the virus and transmit it to their sexual partners. It is important to highlight that HPV infection is common in both sexes and can occur at any age after the start of sexual activity [26].

Although HPV infections are more common in women, the occurrence of papillomavirus laryngeal neoplasia in men is significantly higher. The estimated number of new cases of laryngeal cancer for Brazil, between 2023 and 2025, is 7,790 cases, corresponding to an estimated risk of 3.59 per 100,000 inhabitants, with 6,570 cases in men and 1,220 cases in women. These values correspond to an estimated risk of 6.21 new cases

for every 100,000 men and 1.09 for every 100,000 women [25]. Therefore, it is extremely important to raise awareness about HPV vaccination in men as a preventive measure not only for HPV infections, but also for the development of laryngeal cancer and other types of cancer related to the virus. There are some reasons that may contribute to this difference between men and women. The main form of HPV transmission is through sexual contact [27]. Men, in general, tend to have more sexual partners throughout their lives than women [28] which increases their exposure to the virus and, consequently, the risk of infection.

Furthermore, according to Abreu [29], some risk behaviors, such as smoking and alcohol consumption, are associated with an increased risk of HPV-related laryngeal cancer. Such behaviors are more frequent in men, which may contribute to the higher incidence of this form of cancer in this group. It is worth mentioning that a survey carried out by the Center for Disease Control and Prevention, suggests that men may have a less efficient immune response to HPV compared to women. This may result in greater persistence of virus infection and, consequently, a greater risk of developing cancer [30]. Commonly, vaccination against HPV has been emphasized mainly for women, due to the association between HPV and cervical cancer. However, it is essential to recognize that HPV also affects men and is linked to a variety of cancers, including laryngeal cancer [31]. Vaccination in men can help prevent the spread of the virus, protect against HPV complications and reduce the risk of developing laryngeal neoplasia. By getting vaccinated, men contribute to reducing the transmission of the virus, protecting themselves and their sexual partners [32].

Therefore, awareness of the importance of HPV vaccination in men should be promoted through public health campaigns, education in schools, information in doctors' offices, and dissemination of accurate information about the benefits of vaccination [33-45]. Therefore, it is important to highlight that knowledge about the different subtypes of HPV plays a fundamental role in the adoption and development of more effective prevention and treatment approaches for HPV infections. These measures have the potential to reduce morbidity and mortality associated with the development of cancer, including laryngeal cancer (WHO, 2019). Understanding which HPV subtypes are most frequently linked to laryngeal cancer allows us to target prevention strategies, such as vaccination against high-risk subtypes [46-55]. Furthermore, early identification of the presence of the virus, through screening and diagnostic tests, allows timely and adequate treatment of precursor lesions, thus reducing the risk of progression to invasive cancer [56-62].

Conclusion

This systematic review, using appropriate search criteria, found 30 articles related to HPV subtypes at high risk for developing laryngeal cancer [63-68]. After analyzing the articles,

it is concluded that, in general, the most common HPV subtypes in laryngeal neoplasms are HPV 16, 18, 31, 33, 35, 45, 51, 52, 66, 39 and 56. Therefore, it is clear that research into the types of HPV that are most strongly associated with the development of laryngeal cancer is extremely important to support public health policies. The analysis of studies in this review plays a crucial role in identifying the main HPV subtypes found in a given region, allowing the development of prevention strategies, especially in the context of vaccination. The implementation of public health policies based on epidemiological evidence, such as vaccination against the most prevalent HPV subtypes, can have a significant impact on reducing morbidity and mortality associated with laryngeal cancer. Furthermore, awareness of the importance of early diagnosis and adequate treatment of precursor lesions can contribute to earlier detection and a better prognosis.

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Table S1: Risk and bias assessment of selected articles (QUIPS tool).

Participation in the study	Friction between studies	Prognostic factor measurement	Measurement of results	Confounding bias across studies	Statistical analysis and results	General
+	+	+/-	+	+	+	+
+	+	+/-	+/-	?	+/-	+/-
+	+	-	+/-	?	+	+
+	?	+/-	+	+	+	+
+/-	+	+	+	?	+	+
+	?	+/-	+/-	?	+/-	+/-
+/-	-	+/-	-	+	+	+/-
+/-	+	+	+	+/-	+	+
+	+	+	+	?	+	+
+	+	+/-	+	+	+	+
+/-	-	+/-	+	?	+/-	+/-
+	+	+/-	+	+	+/-	+
+	+	-	+/-	+	+	+/-
+/-	+	-	+	+	+	+
+	-	+	+	?	+	+
+	+	+	+	+/-	+	+
+	+	+/-	+	-	+	+
+/-	+/-	-	+	+	+	+/-
+	?	+/-	+	-	+/-	+/-
+/-	+	+	+	?	+/-	+
+	-	+	+/-	+	+/-	+/-
+	+	+	+	+/-	+	+
-	-	+	+	+	+	+/-
+	+/-	+	+	+	+	+
+	+	?	+	+/-	+	+
+/-	-	+	-	+	+	+/-
-	?	+	-	+/-	+	+/-
-	+	+	+	+	+	+
+	?	+	+	?	+	+
+	-	+/-	+	+/-	+	+/-



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DOI: [10.19080/JTMP.2024.04.555640](https://doi.org/10.19080/JTMP.2024.04.555640)

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