# Human papillomavirus (HPV) prevalence in Oropharynx squamous cell carcinomas(OPSCC) in Brazil: a systematic review with meta-analysis

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## ABSTRACT

**Background:** Oropharynx squamous cell carcinomas (OPSCC) are an important public health problem. Our study aimed to conduct a systematic review with a metanalysis of the human papillomavirus (HPV) prevalence in OPSCC in Brazil.
The aim of our study was to conduct a systematic review with metanalysis about the level of Knowledge of the relation between human papillomavirus (HPV) and OPSCC among university students
**Methodology:** we conducted a systematic review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched MEDLINE/PubMed, SCOPUS, EMBASE and Lilacs for articles published up to March 2023.
**Results:** A total of 260 studies were retrieved with our search strategy, in addition, we included 3 articles manually. After removing duplicate articles, 156 studies remained. Reading the titles and abstracts of these studies, 34 studies were eligible to read the full article. After reading the full text of the selected articles, we excluded 21 articles for reasons such as: no access to the full text (n = 2), literature reviews, systematic reviews, case studies (n = 3), conference proceedings, thesis (n = 6), studies with few participants (n = 2) and studies that did not address the topic (n=8). There were 13 studies left that were included in this systematic review.
**Conclusion:** This study revealed a pooled prevalence of 18% of HPV in OPSCC in Brazil



*Keywords: prevalence, head and neck cancer, oral and oropharyngeal cancer, oropharyngeal neoplasms, HPV, head and neck neoplasms, brazil*




## 1. INTRODUCTION

"Oropharynx squamous cell carcinomas(OPSCC) are an important public health problem. Drinking, smoking and human papillomavirus (HPV) infection are considered important risk factors in OPSCC" [1-3]. "However, in recent decades, the prevalence of HPV in these tumors has increased globally, especially in more developed countries" [3]. The incidence of HPV in oropharyngeal tumors varies according to the population studied and the methodology applied in its detection [4,5]. The explanation for this is because in developed countries the population could have a greater number of sexual partners who practice oral sex and thus these countries have a higher prevalence of the virus in oropharynx.

Several studies showed a high prevalence of HPV in OPSCC in developed countries. Three important studies reported the prevalence of HPV in oropharyngeal tumors in the USA; Chaturvedi et al., Anantharaman et al. and D'Souza et al. who found incidences of 44.1%, 59% and 72% respectively [3,6-7]. The study of Chaturvedi et al., 2011 brings an older series (1984-2004) which justifies the lower incidence identified among these 3 selected works [3]. In Sweden Nasman et al., studying 98 patients with OPSCC, found an incidence of HPV of 79% [8].

Regarding the prevalence of HPV in oropharyngeal tumors in developing countries most studies show low incidences of HPV in oropharyngeal tumors. López et al. studied 91 patients in Brazil and found an incidence of 6,6% [9]. Anantharaman et al. in 2017 compared cases from the USA, Europe and Brazil, finding in 171 cases in Brazil an incidence of only 4,1% [6]. Petito in 2017, studying 82 cases in Brazil, found an incidence of 25,6 % [10]. Another recent study in a developing country found in India an incidence of 22.8% of HPV in oropharyngeal tumors [11].

In south America. A systematic review with meta-analysis carried out by Oliveira AC et al. from 38 studies showed a prevalence of 17,9% in South America countries [12]. Few articles address the prevalence of HPV in oropharyngeal tumors in Brazil. In addition, these studies were carried out with different, methodology making their comparison difficult. Another point at issue is that the number of patients used in each study is limited. So far, there is no systematic review addressing the prevalence of HPV in the oropharynx in Brazil.

Understanding the HPV prevalence in OPSCC in Brazil will be useful to guide campaigns and public investments in the Brazilian population. Therefore, our study aimed to conduct a systematic review with metanalysis of the HPV prevalence in OPSCC in Brazil.

## 2. MATERIAL AND METHODS

### 2.1 Searching strategies

We conducted a systematic review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. We searched in MEDLINE/PubMed, SCOPUS, EMBASE and Lilacs for articles published up to March 2023. The following terms were used to search in the titles, abstracts, and keywords: (“HPV” OR “papillomavirus” OR “papillomaviridae”) AND (“oropharynx” OR “oropharyngeal” OR “tongue” OR “mouth” OR “oral” OR “oral cavity”) AND (“cancer” OR “tumor” OR “neoplasms” OR “carcinoma squamous cell”) AND “Brazil”

### 2.2 Inclusion criteria

We searched for articles reporting the prevalence of human papillomavirus (HPV) in OPSCC in Brazil. We include articles in English, Portuguese, and Spanish. Any types of study designs were considered and no restriction on the publication date of the article.

### 2.2 Exclusion criteria

We exclude case reports, review articles, meta-analyses, and articles with incomplete information.

### 2.3 Selection of studies

Two researchers NAS and DGBS independently screened titles and abstracts for eligibility in the period from January to February 2023. Any discrepancies between all investigators were resolved by the third investigator (CCF).

### 2.4 Data extraction

Two investigators NAS and DGBS independently extracted the data from the selected studies and the data were reviewed by a third investigator. We use a form to extract the following data from each study: Author name, publication year, country, study design, population, aims, methods, main findings, and conclusions

### 2.5 Statistical analysis

All the statistical analyses for the meta-analysis were developed in R Studio software (version 4.2.2 and packages meta version 6.2-0 and metafor 3.8-0), with statistical significance at $p < 0.05$. The data extracted from the papers for the development of the forest plot are described in Table 1. To estimate the pooled prevalence of HPV the random effects method was used, with a 95% confidence interval [14]. The choice for using the R program, was due to the wide range of packages it makes available in its library (like the ones used in this meta-analysis), and due to the fact that it is free, different of programs like SPSS or SAS.

### 2.5 Quality assessment

The quality of the different papers included in this systematic review was evaluated following the checklist proposed by the Joanna Brigs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data [15]. The checklist contains 9 questions with four answering options including Yes, No, Unclear, and Not applicable; studies were characterized as follows: low risk of bias (> or = 70% of questions answered "yes") Moderate risk of bias (> or = 50% and 70% of questions answered "yes" and high risk of bias (50% of questions answered "yes"). In our review, 40 studies were considered as presenting low risk and 5 as moderate risk of bias as shown in table 2.

**Table 1 Characteristics of studies**

| Authors /year | Brazilian Region | Type of study | Site | Specimen | Detection method | No. of Cases | HPV positive/ no. of cases | Overall HPV positivity (%) |
|---|---|---|---|---|---|---|---|---|
| de Ferreira et al. (2021) | U | Across-sectional study | OP | FFPE | IHC | 252 | 81/252 | 32.1 |
| Petito et al. (2016) | CW | Retrospective study | OP* | FFPE | PCR | 43 | nov/43 | 25.6 |
| Piña et al. (2016) | U | Cross-sectional study | OP | FFPE | IHC | 13 | abr/13 | 30.8 |
| Pires et al. (2021) | U | Cross-sectional study | OP | FFPE | IHC | 254 | 79/254 | 31.9 |
| Cordeiro-Silva et al. (2012) | CW | Cohort study | OP* | FFPE and PE | PCR | 4 | 0/4 | 0 |
| Betiol et al. (2016) | SE | Cross-sectional study | OP | FFPE | PCR | 28 | abr/28 | 14.3 |
| Girardi et al. (2020) | SE | Retrospective cohort | OP | FFPE | IHC | 91 | 19/91 | 20.9 |
| Anantharaman et al. (2017) | U | case-control study | OP | FFPE | IHC and PCR | 171 | 7/171 | 4.1 |
| Buexm et al. (2020) | SE | Retrospective study | OP | FFPE | IHC and PCR | 346 | 21/346 | 6.1 |
| Carvalho et al. (2021) | SE | Retrospective cross-sectional study | OP | FFPE | IHC | 792 | 163/792 | 20.6 |
| López et al. (2014) | SE | Cohort study | OP* | FFPE | PCR | 91 | jun/91 | 6.6 |

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|---|---|---|---|---|---|---|---|---|
| Hauck et al. (2015) | SE | Cross-sectional study | OP* | FFPE | IHC | 71 | nov/63 | 17.5 |
| De Cicco et al. (2019) | U | Retrospective cross-sectional study | OP | FFPE | IHC and PCR | 215 | 127/215 | 59.1 |

S = South, SE = Southeast, N = North, NE = Northeast, CW = Central-West, U = Undefine

FFPE = formalin-fixed paraffin-embedded, FF = Fresh-frozen, EBC = Exfoliated buccal cells

OC = Oral Cavity, OP = Oropharynx, L = Larynx, HP = Hypopharynx, U = Unspecified

PCR = polymerase chain reaction, ISH—in situ hybridization, ICC = Immunocytochemistry and IHC = Immunohistochemistry

* In cases that included several sites, we considered only oropharyngeal cases

**Table 2** Risk of bias assessment according to the Joanna Briggs Institute critical appraisal tool for prevalence studies

| Authors/year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Total (%of "yes") | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| de Ferreira et al. (2021) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Petito et al. (2016) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Piña et al. (2016) | N | N | N | Y | Y | Y | Y | Y | Y | 66.69 | Moderade |
| Pires et al. (2021) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Cordeiro-Silva et al. (2012) | N | Y | N | Y | Y | Y | Y | Y | Y | 77.78 | Low |
| Betiol et al. (2016) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Girardi et al. (2020) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Anantharaman et al. (2017) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Buexm et al. (2020) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Carvalho et al. (2021) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| López et al. (2014) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| Hauck et al. (2015) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |
| De Cicco et al. (2019) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 100 | Low |

Note 1: Q1 = Was the sample frame appropriate to address the target population? - Q2 = Were study participants sampled in an appropriate way? - Q3 = Was the sample size adequate? - Q4 = Were the study subjects and the setting described in detail? - Q5 = Was the data analysis conducted with sufficient coverage of the identified sample? - Q6 = Were valid methods used for the identification of the condition? - Q7 = Was the condition measured in a standard, reliable way for all participants? - Q8 = Was there appropriate statistical analysis? - Q9 = Was the response rate adequate, and if not, was the low response rate managed appropriately?

Note 2: Y = yes; N = no; U = Unclear; NA = not applicable

## 3. RESULTS

### 3.1 Search results

A total of 260 studies were retrieved with our search strategy, in addition, we included 3 articles manually. After removing duplicate articles, 156 studies remained. Reading the titles and abstracts of these studies, 34 studies were eligible to read the full article. After reading the full text of the selected articles, we excluded 21 articles for reasons such as: no access to the full text (n = 2), literature reviews, systematic reviews, case studies (n = 3), conference proceedings, thesis (n = 6), studies with few participants (n = 2) and studies that did not address the topic (n=8). There were 13 studies left that were included in this systematic review. Figure 1 shows the flow of studies throughout the review. A summary of study characteristics is presented in Table 1.

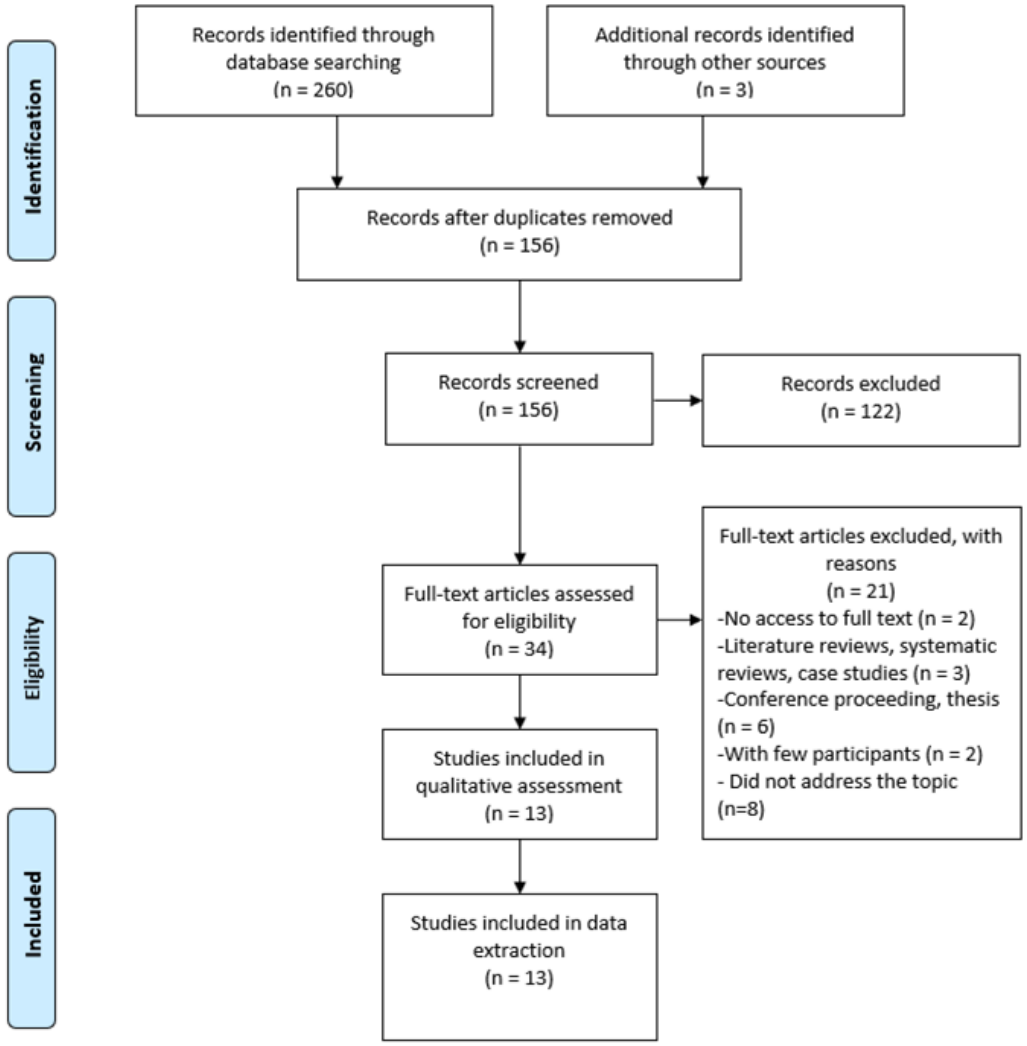


Fig. 1 PRISMA diagram of study identification and screening.



### 3.2 Characteristics of included studies

13 longitudinal studies with 2371 participants were included in this study [6, 9, 10,16-25]. These studies were conducted in different Brazilian regions, and most of the studies were carried out in the Southeast region. Table 1 shows the characteristics of the included studies. As depicted in Table 1, of the 13 articles included in this review, we have 5 cross-

sectional studies, 5 retrospective studies, 2 cohort studies and 1 case-control study. Among the studies included, two were from the Central-West region, six were from the Southeast, and five were from undefined region. Regarding the sample size of included studies, 04 is the smallest number of participants and 792 is the maximum number of participants (Table 1).

### 3.3 Meta-analysis of HPV prevalence in Oropharynx squamous cell carcinomas in Brazil

In our study, the prevalence of HPV range from 0.0 % to 59.0 %. The pooled prevalence for HPV in this study was 18% (95% CI, 11.0 % - 27.0 %) in OPSCC in Brazil. Figure 2 shows the forest plot illustrating the individual prevalence of each study and the pooled prevalence of this systematic review and meta-analysis



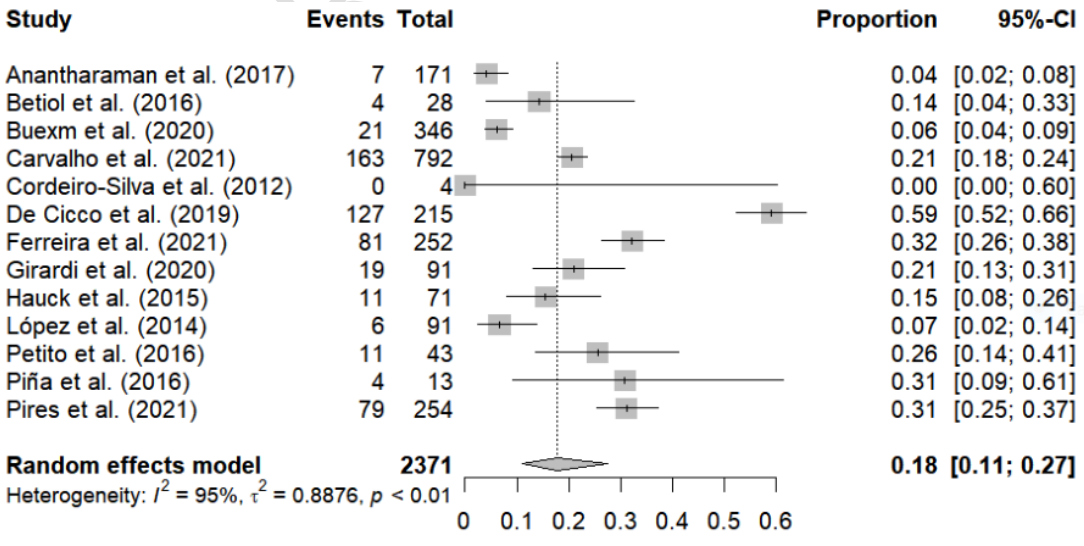

Fig. 2 Forest plot of a metanalysis of studies reporting prevalence of HPV infection in OPSCC in Brazil.

## 4. DISCUSSION

OPSCC were caused in the past due to smoking and alcohol consumption. However, nowadays many patients with oropharyngeal squamous cell carcinoma do not present with any of the aforementioned traditional risk factors. Several studies have correlated HPV as an etiological agent in many of these patients [26].

This is the first meta-analysis that explored the prevalence of HPV in OPSCC in Brazil. Our review included 13 studies that examined the prevalence of HPV in OPSCC in patients from Brazil. Based on 2371 cases, we found an overall prevalence of 18%. indicating a low level of HPV infection in OPSCC in Brazil.

It was observed that half of the studies brought a general prevalence of HPV without specified subtypes. In the rest of the studies , there was a specific evaluation, with hpv16 being the most cited, as in the study by Buexm et al., which brought all prevalent cases of hpv16, with 346 diagnoses. In the study by Anantharaman et al., 92% of the positive cases were for hpv16, 3.5% for hpv35, 2.7% for hpv18 and 1.5% for hpv33. In the study by Petito et al., the oral cavity and oropharynx were studied together, reaching results such as 33% of hpv16, 14% of hpv18, and the remainder divided among other subtypes. It was therefore inferred that the highest prevalence of HPV shown in the studies is due to hpv16, followed by hpvs 18 and 35.

Our systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [13] and we used the R studio software to perform the metaanalysis, which is a statistical software accepted worldwide by the scientific community.

Two studies indicated a worldwide prevalence of HPV in OPSCC: Termine et al. and that by Ndiaye et al., which indicated “a worldwide prevalence of 34.5% (95% CI; 28.4-40.6) and 29.5% (95% CI; 25.5- 33.6) respectively” [27, 28]. “Although the prevalence of HPV in oropharyngeal tumours varies according to the decade of study and the population studied. HPV prevalence in these tumours has been increasing globally and is more prevalent in developed countries than in developing ones” [3, 6]

In our metanalysis, we found an overall prevalence of 18%. Our data is concordant with Oliveira et al. who performed a meta-analysis with 38 studies that found an overall prevalence of HPV of 17.9% of oropharyngeal squamous cell carcinomas in South American patients [12]. Our data is also concordant with Petito et al. which studied 82 cases in Brazil and found an incidence of 25.6% [10]. This is explicated because developing countries generally exhibit lower incidences of HPV-related OPSCC than developed countries.

Our data are low compared with developed countries. The study of Mehanna evidenced that prevalence increased significantly in North America and Europe, before 2000 (50.7% and 35.3%, respectively, and after 2000: 69.7% and 73.1%, respectively [29]. For instance, Chaturvedi et al., Anantharaman et al. and D’Souza et al. reported incidences of 44.1%,

59% and 72%, respectively, in US casuistry [3,6,7]. Näsman et al. studied 98 patients with OPSCC in Sweden and found an HPV incidence of 79% [8].

It is important to know the general prevalence of HPV in OPSCC in the Brazilian population to better organize HPV prevention programs and educational measures. Prevalence studies are often used to devise public health actions and improve health services as well as serving as the first step to evaluate national control programs.

Our research has some limitations. Brazil is a large country, and the frequency of HPV in some locations has only been documented in a few studies or has not been published at all. As a result, the population included in our analysis may not be representative of the general population in Brazil. The large degree of variation among research may have an impact on the precise prevalence measured. The majority of the studies included in this evaluation were conducted in the South and Southeast. This was a foregone conclusion given that these are Brazil's most populous and economically developed areas. **5. CONCLUSIONS**

This study revealed a pooled prevalence of 18% of HPV in OPSCC in Brazil. This is the first study revealing the pooled prevalence of this virus in OPSCC in Brazil. Our data provide information to be used in HPV prevention policies and constitute a baseline for future studies involving HPV prevalence.

Due to the small number of studies on the presence of HPV in OPSCC in Brazil, it is necessary to carry out more randomized studies evaluating the prevalence of HPV in patients with OPSCC in Brazil.



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