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Prevalence and genotype distribution of human papillomavirus (HPV) in penile cancer in Brazil

Prevalência e distribuição genotípica do papilomavírus humano (HPV) EM câncer de pênis no Brasil

Prevalencia y distribución del genotipos del virus del papiloma humano (VPH) en el cáncer de pene en Brasil

Eduarda de Soares Libânio[1], Júlia Holer Naves Ribeiro[1], Antonio Marcio Teodoro Cordeiro Silva[1], Luana Gomes Alves[2], Megmar Aparecida dos Santos Carneiro[3], Vera Aparecida Saddi[1].

ABSTRACT

Objective: To estimate the prevalence and genotypic distribution of Human Papillomavirus (HPV) in penile cancer in Brazil. **Methods:** This is a systematic review and meta-analysis of studies published from 2000 to 2021, that investigated the prevalence and genotypic distribution of HPV in penile cancer in different geographical regions in Brazil, using molecular methods. The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO), conducted in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analysis Statement (PRISMA) and the quality of included studies was assessed by the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. **Results:** 15 studies were included, comprising 1,250 cases. The combined prevalence of HPV in penile cancer was 52.0% and the highest prevalence was observed in the Northeast region (79%), followed by the North region (54%), Southeast (44%) and Central-West region (31%). HPV16 was the most prevalent genotype, followed by HPV6, HPV11, HPV18, HPV51, HPV59, HPV74, HPV31, HPV35 and HPV68. **Final considerations:** Our results confirm the association of HPV with penile cancer and highlight the presence of viral genotypes not covered by the tetravalent prophylactic vaccine distributed by the public health system in Brazil.

Keywords: Penile neoplasms, Human papillomavirus, Prevalence, Types of HPV.

RESUMO

Objetivo: Estimar a prevalência e a distribuição genotípica do Papilomavírus humano (HPV) no câncer de pênis no Brasil. **Métodos:** Trata-se de uma revisão sistemática e metanálise sobre os estudos que investigaram a prevalência e a distribuição genotípica do HPV no câncer de pênis em diferentes regiões do Brasil, usando métodos moleculares, no período de 2000 a 2021. A revisão foi cadastrada no International Prospective Register of Systematic Reviews (PROSPERO), conduzida de acordo com o Preferred Reporting of Systematic Reviews and Meta-Analysis Statement (PRISMA) e a qualidade dos estudos incluídos foi avaliada pelo Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. **Resultados:** 15 estudos foram incluídos, totalizando 1.250 casos. A prevalência combinada do HPV no câncer de pênis foi de 52,0% e a maior prevalência foi observada na região Nordeste (79%), seguida da região Norte (54%), Sudeste (44%) e Centro-Oeste (31%). O HPV16 foi o genótipo mais prevalente, seguido pelo HPV6, HPV11, HPV18, HPV51, HPV59, HPV74, HPV31, HPV35 e HPV68. **Considerações finais:** Nossos resultados confirmam a associação do HPV ao câncer de pênis e destacam a presença de genótipos virais não contemplados pela vacina profilática tetravalente distribuída pelo sistema público de saúde no Brasil.

Palavras-chave: Neoplasias penianas, Papilomavirus humano, Prevalência, Tipos de HPV.

[1] Pontifícia Universidade Católica de Goiás (PUC-GO). Goiânia - GO.
[2] Associação de Combate ao Câncer em Goiás (HAJ-ACCG). Goiânia - GO.
[3] Universidade Federal de Goiás (IPTESP-UFG). Goiânia - GO.

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RESUMEN

Objetivo: Estimar la prevalencia y distribución genotípica del Virus del Papiloma Humano (VPH) en el cáncer de pene en Brasil. **Métodos:** se trata de una revisión sistemática y metanálisis de estúdios, publicado entre 2000 y 2021, que investigaron la prevalencia y distribución genotípica del VPH en el cáncer de pene en regiones de Brasil, utilizando métodos moleculares. La revisión fue registrada en el International Prospective Register of Systematic Reviews (PROSPERO), realizadas de acuerdo con el informe Preferred Reporting of Systematic Reviews (PRISMA) y la calidad de los estudios incluidos fue evaluada por la Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. **Resultados:** Se incluyeron 15 estudios, totalizando 1.250 casos. La prevalencia combinada del VPH en el cáncer de pene fue del 52,0% y la mayor prevalencia se observó en la región Nordeste (79%), seguida de la región Norte (54%), Sudeste (44%) y Centro-Oeste (31%). El VPH16 fue el genotipo más prevalentes, seguido del VPH6, VPH11, VPH18, VPH51, VPH59, VPH74, VPH31, VPH35 y VPH68. **Consideraciones finales:** Nuestros resultados confirman la asociación del VPH con el cáncer de pene y resaltan la presencia de genotipos virales no cubiertos por la vacuna profiláctica tetravalente, distribuida por el sistema de salud público de Brasil.

Palabras clave: Neoplasias del pene, Virus del papiloma humano, Predominio, Tipos de VPH.

INTRODUCTION

Penile cancer (PC) is a rare neoplasm, with about 36,068 new cases and 13,211 deaths recorded worldwide in 2020 (BANDINI M, et al., 2022). In Brazil, in 2022, 1,933 new cases and 463 deaths from PC were estimated, with a standardized incidence of 1.3 cases/100,000 inhabitants (PORTAL DA UROLOGIA, 2022). High incidence rates of PC are observed in the North and Northeast regions, with the state of Maranhão accounting for one of the highest incidences in the world, around 6.1/100,000 inhabitants (KORKES F, et al., 2020; VIEIRA CB, et al., 2020). The large number of PC cases in these regions corroborates the relationship with low socioeconomic status and low human development index (SOARES A, et al., 2020). From a clinical point of view, PC evolves as a palpable, visible, and painless lesion and the main complaints include discharge, bleeding, and bad odor, especially when there is a delay in diagnosis and treatment. In uncircumcised patients, the foreskin can hide the lesion, which progresses through the skin (HELD-WARMKESSEL J, 2012; KORKES F, et al., 2020). The lesions evolve with changes in the color of the glans, in the form of a wound, persistent ulcers and tumors on the glans, foreskin, body of the penis and inguinal nodes (HELD-WARMKESSEL J, 2012).

Squamous cell carcinoma is the most common histological type of PC and grows on the surface of the mucosa, predominantly on the glans (35-48%) or on the inner foreskin (13-21%) (THOMAS A, et al., 2021). CP is a serious disease that compromises the function of the member and, in some cases, results in mutilation of the penis. It can also progress with regional metastases in the inguinal and/or pelvic nodes that affect the function of the lower limbs (KORKES F, et al., 2020; SOARES A, et al., 2020; THOMAS A, et al., 2021). Distant metastases are rare and occur when the disease is already in more advanced stages (BERRIDGE C and GODDARD J, 2020). The age groups most affected by PC are the fifth and sixth decades of life (MEDEIROS-FONSECA B, et al., 2021; THOMAS A, et al., 2021) and the main risk factors include a history of sexually transmitted infections (STIs), with emphasis on human papillomavirus (HPV) infection, phimosis, smoking, immunosuppression, chronic inflammation and, mainly, lack of genital hygiene (HELD-WARMKESSEL J., 2012; SOARES A, et al., 2020; THOMAS A, et al., 2021).

Poor hygiene is an important risk factor for CP, as it facilitates the retention of scaly cells, urine and smegma in the glans. Smegma appears because of the bacterial action on the squamous cells of the preputial sac and appears to be involved in the carcinogenic process, as it produces chronic irritative effects (KORKES F, et al., 2020; MEDEIROS-FONSECA B, et al., 2021). Neonatal or early childhood circumcision helps to protect against PC, as it is preventing genital infections and facilitating adequate genital hygiene (KORKES F, et al., 2020; SOARES A, et al., 2020). HPV is an important risk factor for PC and several studies investigate the prevalence and distribution of HPV in these tumors. A global study evaluated PC samples obtained from 25 countries and demonstrated the presence of HPV DNA in 33.1% of invasive PC, with a predominance of HPV16, followed by HPV6, HPV35, HPV45 and HPV33 (ALEMANY L, et al., 2016). A meta-analysis included

52 studies on patients from different countries, demonstrating a combined HPV prevalence of 50.8% in PC, with HPV16 predominating, followed by HPV6, HPV18 and HPV11 (OLESEN TB, et al., 2018).

In Brazil, a meta-analysis evaluated the prevalence of HPV DNA in genital cancers, demonstrating a combined prevalence of HPV of 42.0% in PC, with the highest prevalence of HPV16, followed by HPV18, HPV11, HPV6 and HPV45 (DE PEDER LD, et al., 2018). HPV infection is an important risk factor for the development of PC, and prophylactic vaccines, which efficiently protect against some types of HPV, might also provide effective protection against PC (LAURENT JS, et al., 2018). Three main vaccines are used to prevent HPV infection around the world. The bivalent vaccine, which protects against HPV 16 and 18; the quadrivalent vaccine, which protects against HPV 6, 11, 16 and 18; and the nonavalent vaccine, which protects against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. Since the vaccine offered by Brazilian's Unified Health System (SUS) is the quadrivalent, its effectiveness in preventing HPV-related PC is questionable, given that research indicates a more widespread and varied genotypic distribution of HPV in these malignancies (DE PEDER LD, et al., 2018; OLESEN TB, et al., 2018).

To develop public strategies for the prevention and treatment of PC as well as to inform and motivate the male population to follow vaccination schedules, knowledge of the prevalence of HPV DNA and the genotypic distribution of the virus in different Brazilian geographic regions is crucial. In addition, to evaluate, in the medium and long term, the effectiveness of anti-HPV vaccines in Brazil, it is necessary to know the prevalence of infection in different geographic regions, as well as the distribution of genotypes in the Brazilian population. Thus, this study evaluated, through a systematic literature review and meta-analysis, the prevalence and genotypic distribution of HPV in PC in different regions of Brazil. The data gathered from this study might be used to design methods to assess the efficacy of anti-HPV vaccines in Brazil as well as to plan future research on PC prevention.

METHODS

This systematic review and meta-analysis investigated the prevalence and genotypic distribution of HPV in PC in patients from Brazil. The study protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under number CRD42021270411. The review was conducted in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analysis Statement (PRISMA) and the quality of the studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (MUNN Z, et al., 2015). The articles were searched in the PubMed and Scielo databases, on August 4, 2021, using the search descriptors (MeSH): Penile cancer AND Prevalence AND Human Papillomavirus; Penile cancer AND Human Papillomavirus AND Genotype; Penile Intraepithelial Neoplasia AND prevalence AND Human Papillomavirus; Penile Intraepithelial Neoplasia AND Human Papillomavirus AND genotype; "NOT ("review" OR "letter" OR "meta-analysis" OR "case report").

The included studies were published between January 2000 and August 2021. Initially, the titles and abstracts were read independently by two researchers (ESL and JHNR) and classified for full reading and data extraction. In cases of disagreement or discrepancy between the two reviewers, a third analysis (VAS) was performed. The inclusion criteria comprised: (1) studies on PC; (2) human studies; (3) epidemiological studies of HPV prevalence in PC; (4) studies that evaluated HPV genotypes in PC, using molecular techniques such as polymerase chain reaction (PCR), reverse hybridization and gene sequencing; (5) studies completely available in the databases; (6) primary and descriptive studies; (7) articles that presented a clearly described methodology; (8) studies with consistent objectives in relation to the methodology and results presented; (9) studies in Portuguese, English, Spanish and French.

Quality of primary studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (MUNN Z, et al., 2015), which includes nine criteria organized in a table, equivalent to nine points. After complete reading and evaluation, the selected studies were categorized into low quality (score less than 5 points), moderate quality (5 - 7 points) and high quality (greater than 8

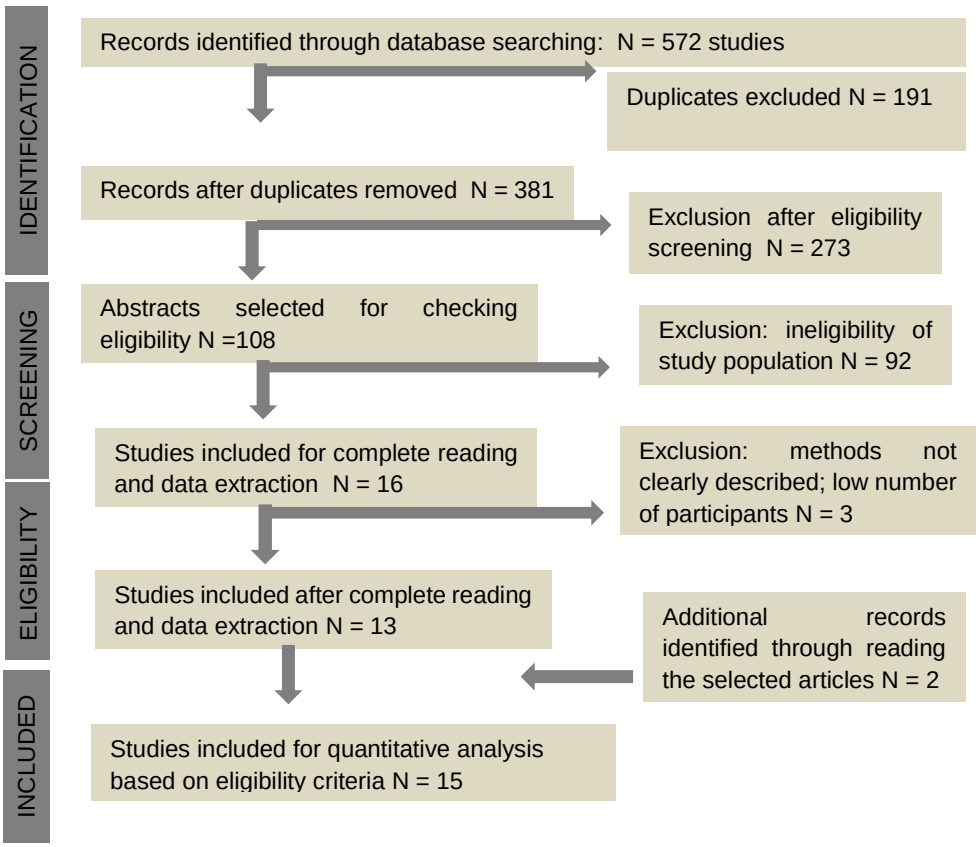
points). The quality of the studies was assessed independently by two authors, based on contingency tables previously assembled (**Appendix 1**).

Data extracted from the studies included: title, authors, geographic region, case series studied, age of participants, molecular methods for HPV detection and analysis, HPV prevalence and prevalence of genotypes identified in the PC studies. Prevalence data were tabulated to determine the combined prevalence of HPV and the main genotypes detected in the studies. The extracted data was used to carry out a meta-analysis. In this context, they were combined with the application of the generalized linear mixed model (GLMM), which considers random effects, in addition to the usual fixed effects. To assess the heterogeneity of the studies, the chi-square (Chi^2), Tau^2 and I^2 tests were applied. For all tests, a significance level of 5% (p-value<0.05) was adopted. Statistics and graphs were carried out using RStudio software.

RESULTS

The initial search carried out on PubMed resulted in 572 studies published between 2000 and 2021. After reading the titles and abstracts, 464 studies were excluded. Among those excluded, 191 were duplicate titles in the lists from the search with each set of descriptors and 380 did not meet the inclusion criteria proposed by this review and meta-analysis. On the other hand, 108 titles were included after the initial reading. After careful reading, based on the inclusion criteria, 16 studies were considered for full reading and 13 studies that analyzed the detection and genotypic distribution of HPV in PC samples in Brazil were included. After reading the selected articles, two other studies that had not been included in the initial search were included because they met the eligibility criteria established in this review. Therefore, 15 studies were selected and included for the composition of this review and meta-analysis. Figure 1 shows the flowchart for identification, selection, and inclusion of studies.

Figure 1 - Flow chart of the study selection.



Fonte: Libânio ES, et al., 2024.

The included studies covered four geographic regions of Brazil and the majority were carried out in the Southeast region, with nine studies (752 patients), followed by the Northeast region, with three studies (186 patients), the North, with two studies (129 patients) and the Midwest, with one study (183 patients). The largest series included 183 PC patitens from the Central-West region (ARAÚJO LA, et al., 2018) and the smallest series included 44 PC patients from the Southeast region (KUASNE H, et al., 2015). HPV detection and genotyping in the studies included in this meta-analysis used molecular methods for detecting HPV DNA, such as polymerase chain reaction (PCR) with type-specific primers, dot blot hybridization, RFLP (Restriction Fragment Length Polymorphism), PCR followed by reverse hybridization (INNO-LiPA and LCD-Array HPV 3.5 kit by Chipron), RT-qPCR, Nested PCR, real-time PCR, microarray, LCD-array, and PapilloCheck (**Table 1**).

Table 1 - Description of the studies included in the metanalise.

Reference	Country Region	HPV Detection Method	Objectives of the Study	Number of Patients N	Age Range (years)	HPV Prevalence (%)
Bezerra et al., 2001.	Southeast	PCR and Dot Blot	To evaluate the prevalence of HPV in PC and association with clinical characteristics and patient prognosis.	82	27-77	30.5%
Bezerra et al., 2001.	Southeast	PCR	To evaluate the prevalence of HPV and genotype distribution in 60 Squamous Cell Carcinomas and 11 Verrucous Carcinomas and the association with clinical characteristics and patient prognosis.	71	27-77	29.6%
Scheiner et al., 2008.	Southeast	PCR and RFLP	To investigate the prevalence of HPV and genotype distribution in CP patients from Rio de Janeiro, Brazil	80	36-86	72.5%
Afonso et al., 2012.	Southeast	Type specific PCR and RFLP	To investigate the prevalence of HPV and genotype distribution in CP patients from two hospitals in Rio de Janeiro, Brazil.	135	21-87	60.7%
Calmon et al., 2013.	Southeast	PCR and Reverse Hybridization	To identify differentially expressed genes in high-risk HPV-positive and negative CP patients.	47	31-95	48.9%
Fonseca et al., 2013.	North	PCR	To evaluate the prevalence of HPV and genotype distribution in CP and association with histological type, clinical aspects, and prognosis.	82	22-91	60.9%
Busso-Lopes et al., 2015.	Southeast	Real Time PCR	To evaluate the prevalence of HPV and genotype distribution in CP and potential molecular aspects of the tumours.	46	-	34.8%
Kuasne et al., 2015.	Southeast	Real Time PCR and Microarray	To evaluate the prevalence and genotype distribution of HPV in CP and potential epigenomic and transcriptomic markers associated with prognosis.	44	24-92	38.6%
Souza et al., 2015.	Northwest	Nested PCR	To evaluate the prevalence of HPV and genotype distribution in CP and association with clinical and histological aspects.	76	26-97	63.1%
Termini et al., 2015.	Southeast	PCR and Reverse Hybridization	To evaluate the prevalence of HPV and genotype distribution in CP and the association of SOD2 expression and prognostic aspects.	125	-	20.6%
Afonso et al., 2017.	Southeast	Type specific PCR, RFLP,	To investigate the prevalence of HPV and EBV in PC and the asscoiation with p16INK4a methylation status and clinical aspects.	122	26-92	64.8%

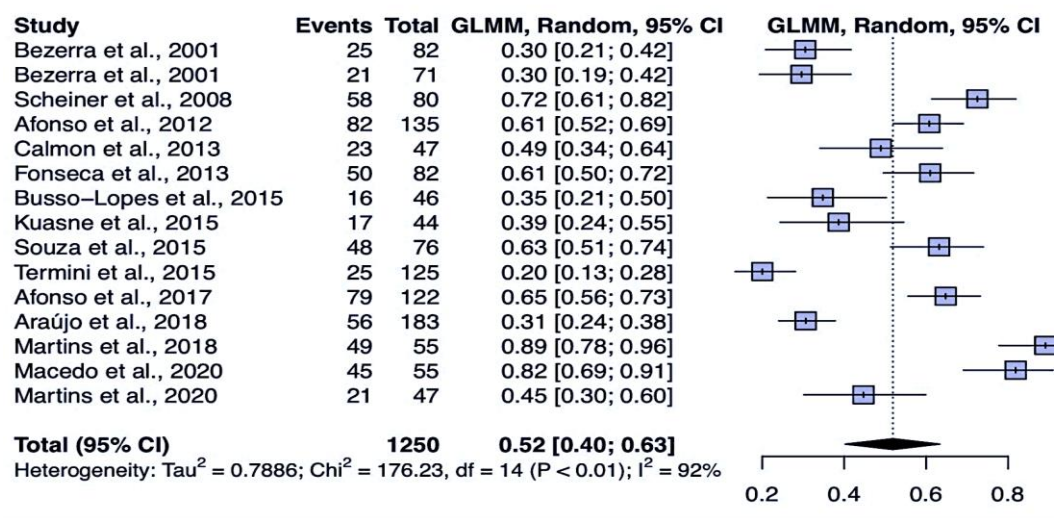
		and LCD-Array				
Araújo et al., 2018.	Midwest	PCR and Reverse Hybridization	To estimate the prevalence of HPV and genotype distribution in CP and association with p16INK4a expression, clinical and histological aspects.	183	-	30.6%
Martins et al., 2018.	North East	Nested PCR	To evaluate the prevalence of HPV and genotype distribution in CP and association with clinical, prognostic and histological aspects.	55	17-61	89.1%
Macedo et al., 2020.	North East	PCR, Type specific PCR tipo específica and DNA sequencing	To evaluate the prevalence of HPV, genotype distribution and association with copy number variation of selected genes in CP patients from a high incidence region in Brazil (Maranhão).	55	23-103	81.8%
Martins et al., 2020.	North	Real Time PCR (16+18) and PapilloCheck	To investigate the expression of p16INK4a and the presence of HPV and EBV infection CP patients from the Amazon region.	47	20-90	45.0%

Fonte: Libânio ES, et al., 2024.

Studies investigating the HPV prevalence and genotyping in PC in Brazil included a total of 1,250 patients, of which 615 were positive for HPV. The combined prevalence of any HPV genotype in PC was 52.0% (95% CI: 40.0 - 63.0%; I^2= 92.0%), as shown in (**Figure 2**). The combined prevalence of any HPV genotype in PC for each Brazilian geographic region is shown in (**Figure 3**). The combined prevalence of any HPV type was 79.0% (95% CI: 64.0 - 89. 0%; I^2= 84.0%) in the Northeast region, 54.0% (95% CI: 43.0 - 65.0%; I^2= 68.0%) in the North, 44% (95% CI: 32.0- 0.56%; I^2=92%) in the Southeast, and 31% (95% CI: 24.0 - 38.0%; I^2 not applicable) in the Central-West region (**Figure 3**). Given that HPV16 and HPV18 are the most prevalent high oncogenic genotypes in HPV-associated cancers in the world, as well as those commonly included in the anti-HPV vaccines, the prevalence of these two genotypes was also combined in this study.

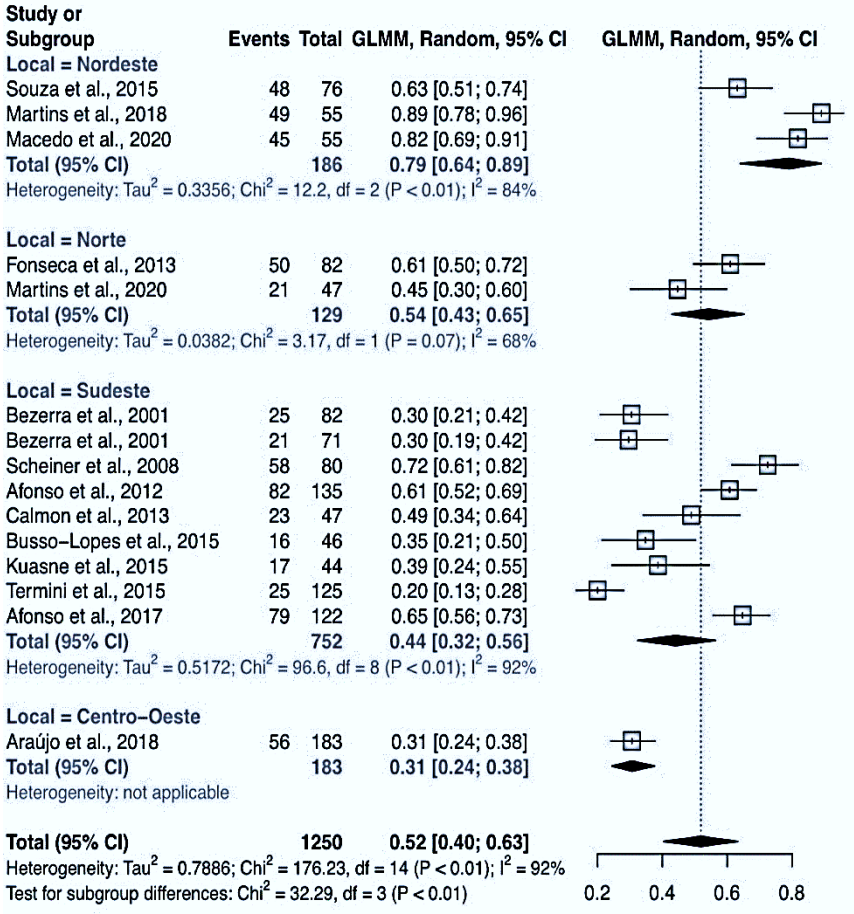
The combined prevalence of HPV16 was 48.0% (95% CI: 36.0-61.0%; I^2= 84%), while the combined HPV18 prevalence was 7.0% (95% CI: 4.0-10.0 %; I^2= 46%) (**Figure 4a and 4b**). According to this meta-analysis, HPV16 was the most prevalent genotype in PC in Brazil, with a combined prevalence of 48.0% (95% CI: 36.0-61.0%; I^2= 84%), followed by HPV6 (8.0%) (95% CI: 4.0-15.0%; I^2=75%); HPV11 (8.0%) (95% CI: 3.0-17.0%; I^2= 89%); HPV18 (7.0%) (95% CI: 4.0-10.0%; I^2= 46%); HPV51 (6.0%) (95% CI: 3.0-12.0%; I^2=0%); HPV59 (6.0%) (95% CI: 2.0-21.0%; I^2=70%); HPV74 (6.0%) (95% CI: 2.0-17.0%; I^2= 61%); HPV31 (5.0%) (95% CI: 3.0-8.0%; I^2= 21%); HPV35 (5.0%) (95% CI: 3.0-10.0%; I^2= 19%); and HPV68 (5.0%) (95% CI: 1.0-27.0%; I^2= not applicable) (**Figure 5**). The genotypic distribution of the 10 most prevalent HPV genotypes in PC in Brazil is shown in **Figure 5**.

Figure 2- Forest Plot showing the combined prevalence of any HPV genotype in PC to the geographic region.



Fonte: Libânio ES, et al., 2024.

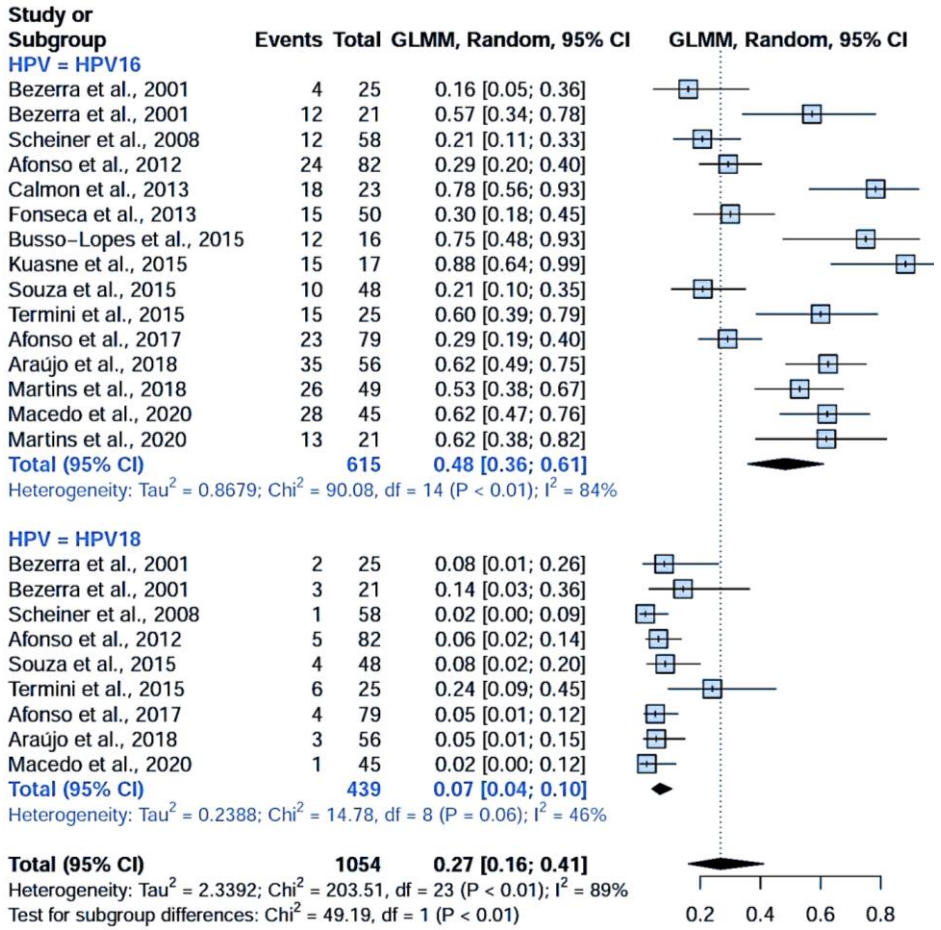
Figure 3 - Forest Plot showing the combined prevalence of HPV in PC according obtained from Brazilian studies



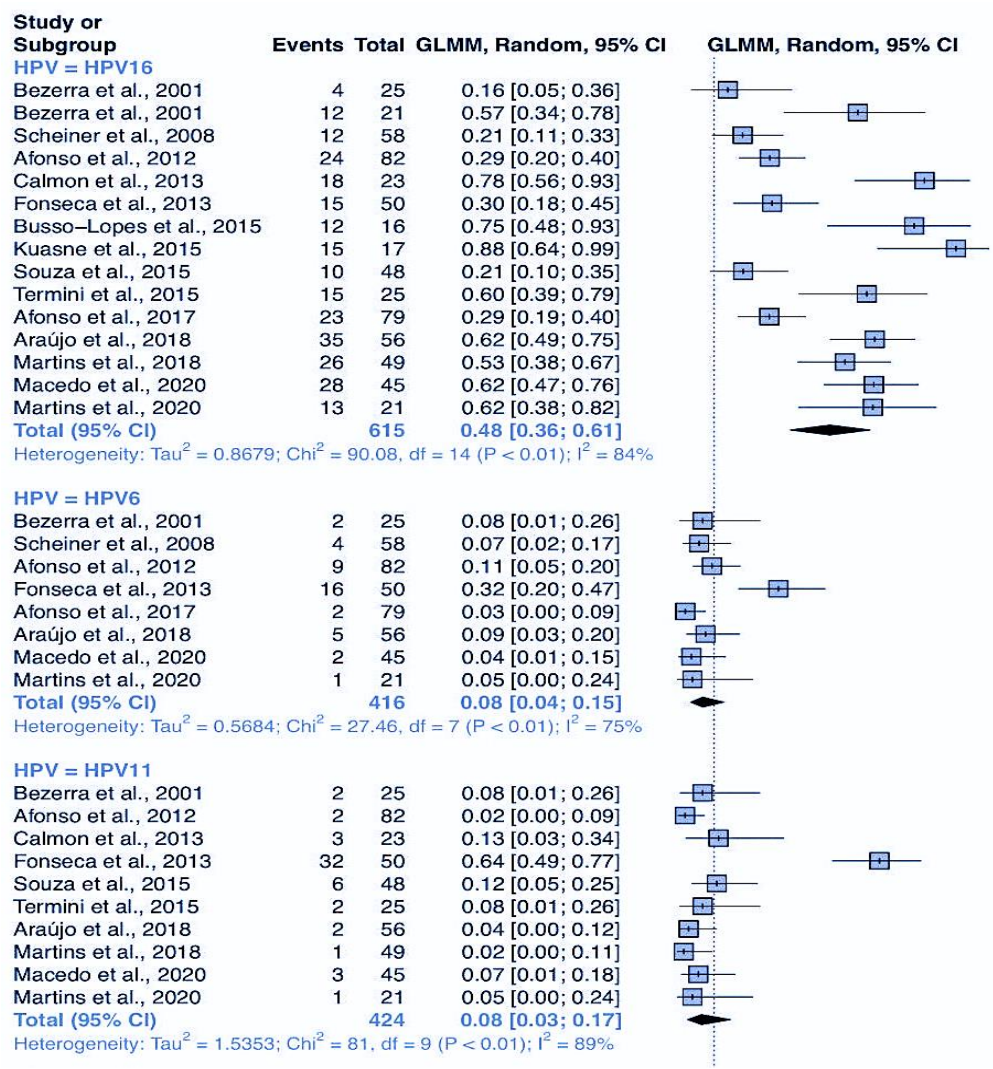
Fonte: Libânio ES, et al., 2024.

Figure 4 - Forest Plot showing the combined prevalence of HPV16 and HPV18 in PC patients in Brazil.

A)

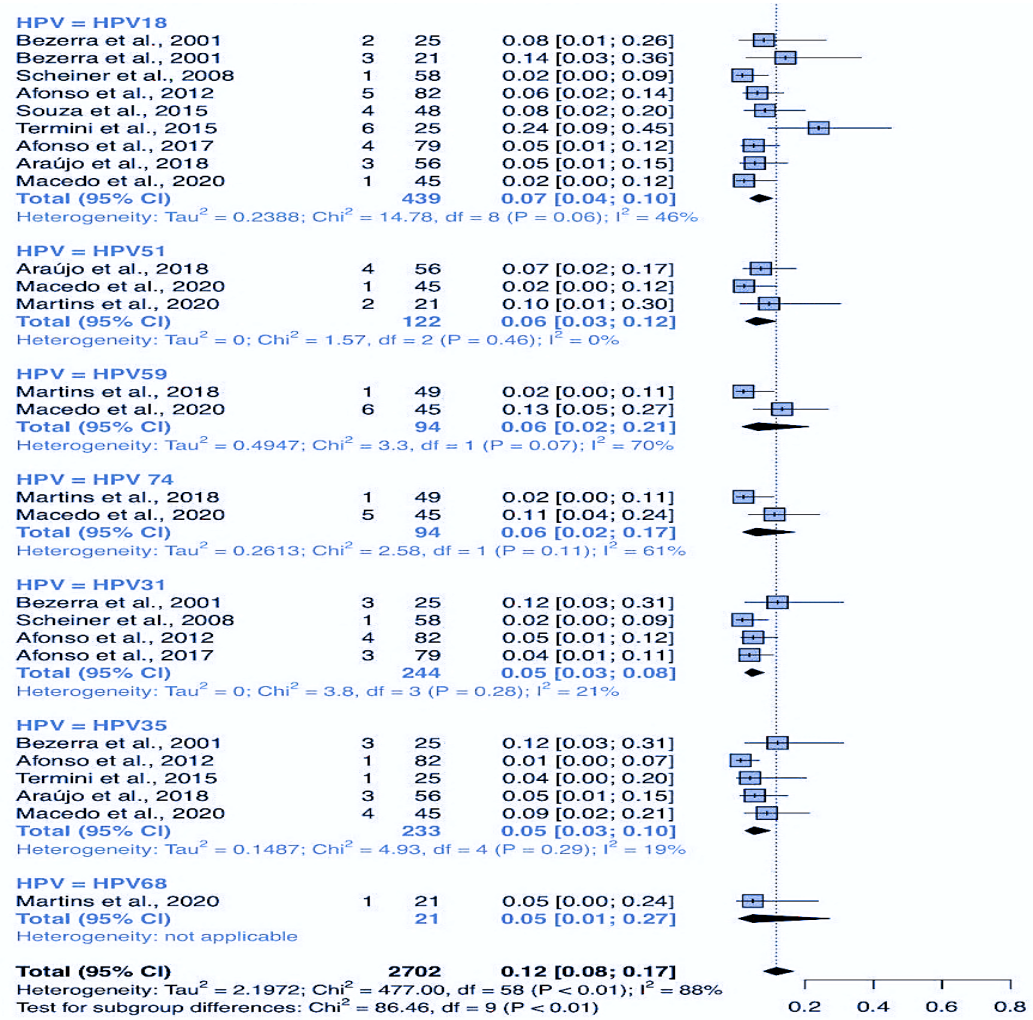


B)



Fonte: Libânio ES, et al., 2024.

Figure 5 - Forest Plot showing the combined prevalence of other HPV genotypes detected in PC in the Brazilian studies.



Fonte: Libânio ES, et al., 2024.

DISCUSSION

This meta-analysis included 15 studies that evaluated the prevalence of HPV DNA and the genotypic distribution of the virus in 1,250 PC patients in Brazil. More than half, 615 cases, were HPV DNA positive, resulting in a combined prevalence of any HPV of 52.0% (95% CI: 40.0 - 63.0%). Our results corroborate the important contribution of HPV to the development of PC in different regions of Brazil, as the combined prevalence ranged from 31.0% (95% CI: 24.0 – 38.0%), in the Central-West, to 79. 0% (95% CI: 64.0 - 89.0%), in the Northeast of the country, a region described with the highest incidence rates of PC in the world (VIEIRA CB, et al., 2020). A previous meta-analysis (DE PEDER LD, et al., 2018) evaluated the prevalence of HPV DNA in genital cancers in Brazil and demonstrated a combined prevalence of HPV in PC of 42.0% (95% CI: 32.0 - 55 .0%). This prevalence is slightly lower than that found in our study, however, the previous meta-analysis included only eight studies published in the period from 2008 to 2015, considering 320 patients, the majority from the Southeast and Northeast regions of the country.

Another meta-analysis (OLESEN TB, et al., 2018), conducted from 52 studies from several countries, analyzed 4,199 patients with PC and demonstrated a combined HPV prevalence of 50.8% (95% CI: 44.8 – 56 ,7), with the highest prevalence of HPV in PC being found in patients from South America, reaffirming the results found in our study. Since Brazil is a country of continental dimensions, discrepancies between the combined HPV prevalence values in PC were expected. The highest combined prevalence rates were identified in the Northeast region (79.0%) (95% CI: 64.0 - 89.0%) and in the North region (54.0%) (95% CI: 43.0 - 65. 0%). This variability can be explained by socioeconomic differences that reflect differences in the incidence of PC and the prevalence and distribution of HPV within Brazil. The Northeast and North regions are considered the poorest regions of the country and have higher incidences compared to the more economically developed regions (VIEIRA CB, et al., 2020).

High rates of HPV infection in the general population are also described in the North and Northeast regions of Brazil (WENDLAND EM, et al., 2020). HPV16 and HPV18 are described as the most prevalent genotypes in HPV-associated cancers (BRUNI L, et al., 2023), however, in PC, this prevalence appears to be different. An international retrospective study demonstrated that five most prevalent HPV genotypes in PC were HPV16 (62.9%), HPV6 (3.6%), HPV35 (2.7%), HPV45 (2.7%) and HPV59 (1.2%), with HPV18 in sixth position (1.2%) (ALEMANY L, et al., 2016), while another meta-analysis showed that HPV16 was the most prevalent type in PC (68.3%) , followed by HPV6 (8.1%), HPV18 (6.9%), HPV11 (5.4%) and HPV33 (2.2%) (OLESEN TB, et al., 2018). The meta-analysis previously conducted on Brazilian patients showed that HPV16 was also the most prevalent type in PC (51.0%), followed by HPV6 (17.0%), HPV11 (15.0%), HPV18 (8.0%) and HPV45 (6.0%) (DE PEDER LD, et al., 2018).

According to our results, HPV16 was the most prevalent genotype in PC in Brazil, with a combined prevalence of 48.0%, followed by HPV6 (8.0%), HPV11 (8.0%), HPV18 (7, 0%) and HPV51 (6.0%). Variations in the genotypic distribution of HPV in PC are observed in different studies. Although HPV16 is the most prevalent genotype in the whole world, low oncogenic risk HPV, such as HPV6 and HPV11, presented considerable proportions, both in our meta-analysis as in others mentioned above.

Two carcinogenesis pathways are described for PC, one associated with HPV infection and the other independent of HPV. In penile carcinoma associated with HPV infection, the viral oncoproteins, E6 and E7, expressed by high-risk HPV, are implicated in the inactivation of two tumor suppressor proteins, p53 and retinoblastoma protein (pRb), resulting in increased cell proliferation, resistance to apoptosis and loss of cell differentiation (MEDEIROS-FONSECA B, et al., 2021). In the HPV independent pathway, it is believed that chronic inflammation, resulting from prolonged exposure to smegma, progresses to irritative precursor lesions, which also evolves to neoplasia. In these circumstances, damaged cells release reactive oxygen and nitrogen species (ROS/RNS), which are implicated in the genesis of mutations and the progression of cancer (MACEDO J, et al., 2020).

The World Health Organization recommends classifying penile squamous cell carcinoma into HPV-related carcinomas and non-HPV-related carcinomas, as well as their special subtypes with distinct clinicopathological

and molecular relevance. However, studies are needed to investigate the value of HPV as a prognostic marker in penile carcinomas (CUBILLA AL, et al., 2018). The absence of histological subclassification for penile squamous cell carcinomas and the uneven distribution of HPV-positive and HPV-negative cases according to patients age group are two important limitations of the studies included in our meta-analysis. Moreover, a thorough description of infections with multiple genotypes is absent in the included studies. Our investigation was further complicated by the finding that only two studies examined the prevalence and genotypic distribution of HPV in penile intraepithelial neoplasia (PIN) (SILVA RJC, et al., 2017; SUDENGA SL, et al., 2017). Twelve PIN samples were examined in total by the two studies, and every one of them tested positive for HPV DNA. Although HPV6 was also found in four cases, HPV16 was the most common genotype in both investigations. We chose not to include this variable in our meta-analysis due to the paucity of research on HPV genotyping in penile intraepithelial neoplasia in Brazil.

In addition to providing a reliable and updated estimate with many PC cases for a single country, this study also provided a combined picture of the genotypic distribution and prevalence of HPV in Brazilian PC patients. The HPV vaccine, available in the Unified Health System in Brazil, is the quadrivalent vaccine that protects against the HPV6, HPV11, HPV16 and HPV18, thus, it is believed that a significant portion of penile cancers could be prevented through this vaccine. The National Health Surveillance Agency (ANVISA, 2017) has approved the nonavalent vaccine, which protects against genotypes 31, 33, 45, 52, and 58 in addition to the four genotypes. Therefore, our data suggests that the nonavalent vaccine should provide additional protection against CP in Brazil, highlighting the significance of its use.

Understanding the prevalence and genotypic distribution of HPV in PC in Brazil enables more tailored and efficient interventions to be planned based on the specific requirements of each region in the country. Given the high prevalence of HPV in those tumors and the most prevalent HPV genotypes found in the present meta-analysis, it is possible to hypothesize that the nonavalent prophylactic vaccine may increase protection against CP. However, educational measures, including genital hygiene, the need for circumcision and adherence to the existing vaccination program will certainly have a relevant impact on fighting this cancer. In addition, research on the relationship between HPV and PC in Brazil must be conducted throughout the entire country, including the South, to gather more comprehensive data. Studies that assess the genotype distribution across patient age groups and histological types should also be conducted.

CONCLUSION

In Brazil, HPV was found on 52% of PC. The highest combined prevalence of HPV in PC was observed in the Northeast region (79%), followed by the North region (54%), Southeast region (44%) and Central-West region (31%). HPV16 was the most prevalent genotype, followed by genotypes 6, 11, 18, 51, 59, 74, 31, 35 and 68. The genotypic distribution of HPV in PC is like that observed in other countries. The tetravalent prophylactic vaccine against HPV, available in the Unified Health System in Brazil, offers protection against a significant portion of penile cancers, however, the nonavalent prophylactic vaccine may increase protection against CP.

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