

## Research Article

# Human papillomavirus Prevalence and Genotyping in Penile Squamous Cell Carcinoma Patients

Walna Luisa Barros Ramos<sup>1</sup>, Ana Paula Almeida Cunha<sup>1</sup>, Lucas Henrique de Lima Costa<sup>1</sup>, João Paulo Castello Branco Vidal<sup>1</sup>, Vandilson Pinheiro Rodrigues<sup>3</sup>, Luciane Maria Oliveira Brito<sup>1,2</sup> and Flávia Castello Branco Vidal<sup>1,3</sup>

<sup>1</sup>Tumors and DNA Bank of Maranhão, Federal University of Maranhão, Brazil

<sup>2</sup>Medicine III Department, Federal University of Maranhão, Brazil

<sup>3</sup>Department of Morphology, Federal University of Maranhão, Brazil

**\*Corresponding author**

Flávia Castello Branco Vidal, Tumors and DNA Bank of Maranhão, Federal University of Maranhão, São Luís, Rua Coelho Neto, 311 Centro, CEP: 65020-140, Brazil, Tel: 55-98 21091273; Email: flavidal@hotmail.com

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**Abstract**

**Objective:** To evaluate the prevalence of human papillomavirus (HPV) infection in penile carcinomas in São Luís, Brazil, and to correlate the virus presence to histopathological factors.

**Methods:** This was a prospective analytical study of 29 patients submitted to partial and total penectomy surgery. Data were collected through a survey and medical record analysis. Tumor samples were collected during surgeries and DNA extraction was performed. PCR-Nested technique was used for viral DNA amplification, with PGMYO9/11 and GP+5/+6 primers. Automated sequencing analyses were made in order to genotype the HPV types.

**Results:** The mean age of the patients was  $63.2 \pm 17.3$ . Population consisted of a low educated and low socioeconomic status man (82.8%), illiterate (55.2%). Most of the men (62.1%) had not been circumcised, had never used a condom (72.4%), and 51.7% reported the occurrence of some previous sexually transmitted disease (STD). The most prevalent type of lesion was ulcerative (51.7%) and the glans was affected in 93.1% of the cases. HPV presence was detected in 72.4% of the cases and the oncogenic risk HPV 16 was the most prevalent (55.6%). Statistical difference was observed in the correlation between HPV status and previous STD ( $p = 0.03$ ).

**Conclusion:** Various risk factors for penile cancer were observed like absence of circumcision, no use of condom and high prevalence of HPV. The high prevalence of HPV and high-risk types suggest the need for further action to prevent the spread of HPV among the population.

**INTRODUCTION**

Penile cancer is a rare disease with 26 000 new cases occurring worldwide annually [1]. In Western Europe, represents 0.3 to 0.6% of malignant tumors, while in Africa incidence reaches 10% of all malignant cancers affecting men. In Brazil, penile cancer represents 2% of the total, with the highest prevalence being observed in the North and Northeast regions [2].

Human Papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide [3]. Studies show that 30% of the world's sexually active population is infected with HPV, and about 500,000 new cases are detected per year, with 70% being found in developing countries [2]. This virus has been recognized as one of the possible causes of penile carcinoma, but its role in the development of the disease and its correlation with the prognosis, remain unclear [4,5]. Besides HPV infection, known risk factors for the development of penile cancer include poor hygiene, phimosis, smoking, low

socioeconomic status, a history of genital warts and/or other sexually transmitted diseases and risky sexual behavior [4].

A recent study pointed out that the state of Maranhão has the highest incidence of penile cancer in Brazil and globally [2]. The aim of the present study was to describe socioeconomic variables, sexual behavior, clinical and histopathological aspects of penile epidermoid carcinoma patients from Maranhão state, Brazil. We also performed HPV genotyping as it is an important epidemiological data for evaluating the efficacy of screening programs and campaigns, recently extended to the male population in Brazil. Statistical analysis was performed to detect a possible association between the variables and HPV presence.

**MATERIALS AND METHODS****Patients**

A prospective cross-sectional study was carried out between the years 2015 and 2017 in a cancer reference hospital in the

State of Maranhão, Brazil. A convenience sample of twenty-nine patients who submitted to partial or total penectomy surgery participated in the study. A survey was conducted with these patients to collect sociodemographic and personal history data. Clinical and histopathological data were collected from medical records.

In accordance with the provisions of the Declaration of Helsinki for research involving human, the study was approved by the Committee of Ethics and Research of the Federal University of Maranhão. Informed consent was obtained from all individual participants included in the study.

### HPV detection

During the surgical procedure, fragments of tumor tissue were collected and sent to the Tumors and DNA Bank of Maranhão laboratory. The DNA of the samples was extracted through the Dneasy Blood and Tissue kit (QIAGEN Ltd, UK). PCR-Nested technique was used for viral DNA amplification, with PGMY09/11 primers in the first round, and with GP+5/+6 primers in the second round. Visualization of the amplified products was performed using 1.5% agarose gel electrophoresis. DNA-HPV positive samples were submitted to automated sequencing in a 3500 Series Genetic Analyzer (ThermoFisher, MA, USA), performed with the ET Dye Terminator Cycle Sequencing kit (GE Healthcare, UK) according to the manufacturer's suggested protocol.

### Statistical analysis

The dependent variable was represented by HPV detection (absence or presence), while the independent variables included age, socioeconomic characterization, behaviors, hygiene habits, clinical and histopathological parameters.

The descriptive statistics of the data were initially performed using measures of frequency, mean and standard deviation. The chi-square or Fisher's exact test was used to compare the distribution of categorical variables between groups with absence or presence of HPV. The Spearman coefficient ( $R_s$ ) was used to analyze the correlation between the ordinal grading variables of the neoplastic lesion (Jackson, Broders and Component T of the TNM scale). The level of significance was 5% ( $p \leq 0.05$ ). Statistical analysis was performed with the SPSS program (version 17.0, IBM, Chicago, IL, USA). The level of significance was 5% ( $p \leq 0.05$ ).

## RESULTS

Table 1 describes socioeconomic variables and life style behavior of patients with penile epidermoid carcinoma in São Luís, Brazil, and its relationship between HPV detection. The total subjects in this study were 29 with the mean age of  $63.2 \pm 17.3$ . Most of the patients were over 60 years of age (69%) (Table 1). The older patient was 97 and the younger was 23 year old. The studied population consisted of a low educated and low socioeconomic status man with an income of up to 1 minimum Brazilian wage (82.8%) (less than \$260 dollars), were illiterate (55.2%), 62.1% was brown color, and 79.3% lived in municipalities in the interior of Maranhão. Also in Table 1, 69% of the patients were in a consensual relation, 62% of the patients were smokers or former smokers and 62.1% were drinkers

or former drinkers. There were no association between HPV presence and the socioeconomic and life style behavior variables.

Table 2 displays the distribution of variables related to sexual behavior. As shown, 62.1% patients had not been circumcised, 72.4% had never used a condom, and 51.7% reported the occurrence of some previous sexually transmitted disease (STD). The majority of patients (55.1%) reported performing genital hygiene. Thirteen patients (44.9%) reported that their first sexual relation was before 18 years and 62.1% declare ten or more sexual partners during life. Statistical difference was observed in the correlation between HPV status and previous STD ( $p = 0.03$ ). Patients who reported previous STD were more likely to have HPV.

Table 3 shows penile lesions localization. Most patients (51.7%) exhibited more than one affected region, with the glans involved in 93.1% of the patients. HPV presence was not correlated with lesion localization or number of affected sites.

All tumors histological subtype was epidermoid carcinoma. Table 4 shows a higher frequency of the ulcerated lesion type (41.4%). Most of the tumors had no perineural (96,6%) or angiolinfatic invasion (86,2%). The well differentiated tumors (grade I) identified in this work, according to Broder's classification, were the most prevalent (41,4%). According to staging of Jackson most tumors were stage I and II (27,6%). TNM staging demonstrated a prevalence of T1 lesion (27,7%). HPV presence was not correlated with any of the clinical and histopathological variables.

The presence of HPV was confirmed in 21 (72.4%) patients out of the 29 patients comprising the sample. Furthermore, viral types were identified in 45% of the patients through the automated sequencing technique. Type 16, considered to be a high oncogenic risk, was found in 55.6% of the patients, followed by types 45 (11.1%), 6 (11.1%), 52 (11.1%), and 33 (11.1%).

## DISCUSSION

Our results reveal that 69% of the penile cancer patients were older than 60 years. This is consistent with previous studies showing that penile cancer incidence is higher in men in the sixth decade of life [3]. Comparable results have been found in studies by Favorito [6], Hernandez [7], Chaux [8], Sousa [9] and Chalya [10]. In contrast, in a single study by Slaoui [11] a mean age for the incidence of penile cancer was reported as below 60 years of age.

In this study, 79.3% of the patients lived in municipalities in the interior of Maranhão. This observation supports the study of Chaux [8] who identified a high incidence (83%) of men with penile cancer residing outside the major centers. The results can be explained due to the delay in seeking of medical care from men living outside the major centers, because of the greater difficulty in accessing health services. Educational levels, family income, and marital status were also evaluated in the socio-demographic survey. A prevalence of illiterate men with a family income of up to one minimum wage was observed. Again, this is consistent with previous studies, showing that neoplasia affects mainly men from lower socio-economic classes and with a lower level of education [7,11-13]. Hernandez [7], reported a higher penile

**Table 1:** Relation between HPV detection, socioeconomic variables, and life style behavior of 29 patients with penile epidermoid carcinoma in São Luís, Brazil.

Variables	Total n (%)	HPV		p value
		Absent n (%)	Present n (%)	
<b>Age group</b>				0.37
< 60 years	9 (31)	1 (11.1)	8 (88.9)	
≥ 60 years	20 (69)	7 (30.0)	13 (70.0)	
<b>Income</b>				1.00
> 1 minimum wage	7 (17.2)	2 (28.6)	5 (71.4)	
≤ 1 minimum wage	22 (82.8)	6 (27.3)	16 (72.7)	
<b>Education</b>				0.99
Illiterate	16 (55.2)	5 (31.2)	11 (68.8)	
≤ 8 years of schooling	11 (34.5)	3 (27.3)	8 (72.7)	
> 8 years of schooling	2 (10.3)	0 (0)	2 (100)	
<b>Race</b>				0.99
White	5 (17.2)	1 (20)	4 (80)	
Brown	18 (62.1)	5 (27.8)	13 (72.2)	
Black	6 (20.7)	2 (33.3)	4 (66.7)	
<b>Place of residence</b>				0.64
Capital	6 (20.7)	1 (16.7)	5 (83.3)	
Interior	23 (79.3)	7 (30.4)	16 (69.6)	
<b>Relationship</b>				0.30
Single	3 (10.3)	0 (0)	3 (100)	
Consensual union	20 (69)	4 (20)	16 (80)	
Divorced	2 (6.9)	1 (50)	1 (50)	
Widow	2 (6.9)	1 (50)	1 (50)	
Not informed	2 (6.9)	-	-	
<b>Smoking</b>				0.64
No	11 (38.0)	2 (18.2)	9 (81.8)	
Former smoker	13 (44.8)	4 (30.8)	9 (69.2)	
Current smoker	5 (17.2)	2 (40)	3 (60)	
<b>Drinking</b>				0.68
No	9 (31)	2 (33.3)	6 (66.7)	
Former drinker	14 (48.3)	4 (28.6)	10 (71.4)	
Current drinker	4 (13.8)	0 (0)	4 (100)	
Not informed	2 (6.9)	-	-	

Probability value calculated using Fisher's exact test. \*Statistically significant differences ( $P < 0.05$ ).

cancer incidence in municipalities where less than 75% of the population completed high school, in comparison with patients living in communities with higher education levels. Torbrand [14] suggested that a low educational level is associated with an increased risk of developing invasive penile cancer.

Regarding life style behavior, most patients in this study (62%) reported using tobacco and 62.1 referred alcohol using at some point in their lives. Daling [15] demonstrated the relationship between tobacco use and the risk of developing penile cancer, where active smokers and former smokers showed, respectively, a probability 2.3 and 1.9 times higher of developing cancer. A 1.5

times higher risk of in situ penile cancer development and a 4.5 times higher risk of invasive cancer development was observed among current smokers in that same study. Wanick [16] showed that tobacco use was observed in 75% of cases of invasive penile cancer. A high incidence was also found in the work of Chaux [8] (76%) and Koifman [12] (56.5%) of the patients diagnosed with penile cancer reported the use of tobacco. The use of alcohol and/or other drugs can lead to a promiscuous sexual behavior witch can increase the chance of HPV infection and is also associated with increased risk of penile cancer [8].

In our study, it was observed that 62.1% of the patients had

**Table 2:** Relation between HPV detection and variables related to sexual behavior of 29 patients with penile epidermoid carcinoma in São Luís, Brazil.

Variables	Total n (%)	HPV		P value
		Absent n (%)	Present n (%)	
<b>Circumcision</b>				1.00
No	18 (62.1)	4 (27.8)	14 (72.2)	
Yes	3 (10.3)	1 (0)	2 (100)	
No information	8 (27.6)	-	-	
<b>Condom use</b>				0.09
Always	1 (3.5)	0 (0)	1 (100)	
Sometimes	7 (24.1)	0 (0)	7 (100)	
Never	21 (72.4)	8 (38.1)	13 (61.9)	
<b>Previous STD and/or genital warts</b>				0.03*
No	8 (27.6)	4 (50)	4 (50)	
Yes	15 (51.7)	1 (3.4)	14 (93.3)	
No information	6 (20.7)	-	-	
<b>Genital hygiene</b>				0.27
No	7 (24.1)	3 (42.9)	4 (57.1)	
Yes	16 (55.1)	2 (12.5)	14 (87.5)	
No information	6 (20.7)	-	-	
<b>Age of first coitus</b>				0.10
< 18 years	13 (44.9)	1 (7.7)	12 (92.3)	
≥ 18 years	7 (24.1)	3 (42.9)	4 (57.1)	
No information	9 (31)	-	-	
<b>Number of sexual partners during life</b>				0.62
< 10	8 (27.6)	1 (12.5)	7 (87.5)	
≥ 10	18 (62.1)	5 (27.8)	13 (72.2)	
No information	3 (10.3)	-	-	

Probability value calculated using Fisher's exact test. \*Significant differences (P < 0.05).

**Table 3:** Relationship between HPV detection and penile lesion clinical variables of 29 patients with penile epidermoid carcinoma in São Luís, Brazil.

Variables	Total n (%)	HPV		P value
		Absent n (%)	Present n (%)	
<b>Lesion area</b>				
Glans				0,467
Yes	27 (93,1)	9 (33,3)	18 (66,7%)	
No	2 (6,9)	0 (0)	2 (100)	
Foreskin				0,335
Yes	13 (44,8)	3 (23,1)	10 (76,9)	
No	16 (55,2)	6 (37,5)	10 (62,5)	
Corpus				0,081
Yes	6 (20,7)	0 (0)	6 (100)	
No	23 (79,3)	9 (39,1)	14 (60,9)	
<b>Number of affected regions</b>				0.449
One	14 (48,3)	5 (35,7)	9 (64,3)	
More than one	15 (51,7)	4 (26,7)	11 (73,3)	

Probability value calculated using Fisher's exact test. \*Statistically significant differences (P < 0.05).

not been circumcised. In a study by Koifman [12] performed in Brazil, the absence of circumcision was also common. The presence of phimosis and exuberant prepuce make it difficult to expose the glans and conduct adequate cleansing of the genital region, thus influencing the development of penile cancer [8]. The incidence of penile cancer in countries with higher levels of neonatal circumcision, such as Israel, is extremely low and may reach rates below 1% [13]. A systematic review analyzing the effect of circumcision on penile cancer confirmed its beneficial effect when performed before 18 years of age compared to an increased risk of developing such cancer when carried out during adulthood [17].

A worrying result of our study was the high prevalence (72.4%) of patients who had never used a condom and admitted previous sexually transmitted infection (51.7%). The majority

also has their first coitus before 18 years old and had more than 10 sexual partners during life. These data represents a promiscuous sexual behavior of patients that may increase the chance of HPV infection and other etiological conditions that favors penile cancer [18]. Other studies also reported increased promiscuous sexual behaviour and history of sexually transmitted infections among penile cancer patients [4,8].

Statistical analysis showed a significant ( $p = 0.03$ ) relation between previous reported STD and HPV presence. A common risk factor for penile cancer includes a clinical history of sexually transmitted diseases such as gonorrhoea, Chlamydia, and/or syphilis [6]. It is known that some sexually transmitted infectious agents, such as Chlamydia trachomatis and Herpes simplex, cause local inflammation, and could contribute to HPV infection and cervical lesion progression [19,20]. The relation between

**Table 4:** Relationship between HPV detection and histopathological lesion variables of 29 patients with penile epidermoid carcinoma in São Luís, Brazil.

Variables	Total n (%)	HPV		P value
		Absent n (%)	Present n (%)	
<b>Ulcerated lesion</b>				0.323
Absent	9 (31.0)	2 (22.2)	7 (77.8)	
Present	12 (41.4)	5 (41.7)	7 (58.3)	
No information	8 (27.6)	-	-	
<b>Wart lesion</b>				0.592
Absent	17 (58.6)	6 (35.3)	11 (64.7)	
Present	4 (13.8)	1 (25.0)	3 (75.0)	
No information	8 (27.6)	-	-	
<b>Perineural invasion</b>				0,689
Absent	28 (96,6)	9 (32,1)	19 (67,9)	
Present	1 (3,4)	0 (0)	1 (100)	
<b>Angiolinfatic invasion</b>				0,364
Absent	25 (86,2)	7 (28,0)	18 (72,0)	
Present	4 (13,8)	2 (50,0)	2 (50,0)	
<b>Broders' Classification</b>				0,073
Grade I	12 (41,4)	6 (50,0)	6 (50,0)	
Grade II	7 (24,1)	0 (0)	7 (100)	
Grade III	4 (13,8)	2 (50,0)	2 (50,0)	
No information	6 (20,7)	-	-	
<b>TNM staging</b>				1,000
T1	8 (27,7)	2 (25,0)	6 (75,0)	
T2	7 (24,1)	2 (28,6)	5 (71,4)	
T3	5 (17,2)	2 (40,0)	3 (60,0)	
No information	9 (31,0)	-	-	
<b>Staging of Jackson 1966</b>				0,161
Stage I	8 (27,6)	2 (25,0)	6 (75,0)	
Stage II	8 (27,6)	2 (25,0)	6 (75,0)	
Stage III	2 (6,9)	2 (100)	0 (0)	
No information	11 (37,9)	-	-	

Probability value calculated using Fisher's exact test. \*Statistically significant differences ( $P < 0.05$ ).

STDs agents and HPV coinfection in penile cancer progression is unknown.

With respect to the predominant location of the penile lesion, 51.7% of the cases showed more than one affected region, with the glans being identified in 93.1% of the patients. This result supports a study by Wanick [16], where the predominant localization of penile cancer (55.5%) was found to be the glans alone, and, in association with other regions of the penis, comprised 91.1% of the cases.

All patients were diagnosed with squamous cell carcinoma. Ulcerative and warty tumors were prevalent in our study (65%) and were associated with HPV infection. Well differentiated tumors (grade I), according to Broders' classification, were the most prevalent among the tumors that could be classified. In a Brazilian study, Fonseca [21] also identified a greater number of cases classified as well differentiated (grade I). Jackson staging demonstrated an equal prevalence between stage I and II lesion.

Regarding the detection of HPV DNA, the presence of HPV was detected in 72.4% of the patients with penile cancer. The overall prevalence in a study by Calmon [22] on patients from the States of Pará and São Paulo, was 48.9% for some type of HPV. Backes [23] found a 48% prevalence of HPV in 1266 cases from 30 studies of invasive penile cancer. Chaux [8] found HPV DNA in 36% of the analyzed samples. Therefore, a great variation of the incidence of HPV can be observed in studies involving penile cancer, ranging between 15% and 77.5%. This variation can be explained through the methodology used in the detection of HPV, the nature of the studied population, and the conservation of the samples [24]. The PCR technique that we performed, using PGMY 09/11 and GP5+/6+ primers, has been widely used in epidemiological studies of HPV, due to its high specificity and sensitivity [2].

HPV 16 was detected in 55.6% of the patients through automated sequencing, followed with subtypes 6, 33, 45, and 52, with a prevalence of 11.1%. Cubilla [25] found HPV 16 in 72%, followed with subtype 6, in 9% of cases. In a study conducted by Scheiner [26] in Rio de Janeiro, Brazil, subtype 16 was also the most prevalent (52%). Alemany [27] also found a higher incidence of subtype 16. In Brazil, high-risk HPVs account for 25% to 56% of cancer cases. All of the HPV types founded in our study can be preventable by the nonavalent vaccine (GARDASIL®9, Merck) which prevents against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. However, in Brazil, the public health system offers the quadrivalent Gardasil (prevent types 6, 11, 16 and 18). So, to improve prevention against penile, cervical, vulvar, vaginal, and anal cancers, all caused among other things by HPV, the Brazilian authorities should think in the implementation of nonavalent vaccine.

As shown in Table 3 and 4 no statistically significant difference was observed ( $p < 0.05$ ) between the variables evaluated and the presence of HPV. The same was the case in the research by Sousa [9] Scheiner [26], Do [28] and Fonseca [29]. It seems that HPV infections are associated with the development of penile cancer; however, the role of viruses is not associated with the gravity of the disease.

## CONCLUSION

HPV DNA was found in 72.4% of our patients. The high-risk type HPV 16 was observed in 55.6% of the lesions. The average age of the patients in the study was 63.2 years old. According to sociodemographic data, penile cancer patients consisted of a low educated and low socioeconomic status man, illiterate, were brown color and lived in municipalities in the interior of Maranhão. They were not circumcised and had never used condom. Prevalent lesions were in the glans region, in general ulcerated, and with Broder's grade I (well differentiated). The clinical and histopathological variables did not tend to have an association with infection by the HPV virus.

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