# Update in the Human Papillomavirus Infection Prevalence Rates and Risk Factors Associated with Penile Cancer Cases

## *Atualização no Conhecimento acerca da Prevalência das Infecções Causadas pelos Papilomavírus Humanos e Fatores de Risco Associados aos Casos de Câncer de Pênis*

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**ABSTRACT**

Penile carcinoma is an uncommon and potentially mutilating disease with a still unknown etiology. Human papillomavirus (HPV) infection seems to play an important role in the development of a subset of these carcinomas and its presence is thought to be related to the histological type of the lesion. HPV prevalence in penile tumors is reported to be associated to a variety of morphological changes. In recent years, increased insight has been gained into the pathogenesis of penile cancer, the risk factors associated with penile cancer development and the clinical and histological precursor lesions related to this disease. Although penile carcinoma is recognized to be a multi-step process showing a polyclonal profile, a proportion of penile carcinoma is attributable to high risk HPV infection, while in the remaining penile cancers molecular mechanisms independent of HPV are likely to represent the more common underlying events. However, research on the mechanisms behind penile carcinogenesis is warranted.

**Keywords**: HPV, penile cancer, prevalence, circumcision, STD

**RESUMO**

O carcinoma de pênis é uma doença rara e potencialmente mutilante, com etiologia ainda pouco conhecida. A infecção pelo papilomavírus humano (HPV) parece ter um papel importante no desenvolvimento de um subgrupo desses carcinomas e a sua presença parece estar relacionada com determinados tipos histológicos. A prevalência do HPV em tumores de pênis é descrita como sendo associada a uma variedade de alterações morfológicas. Recentemente, houve um aumento de conhecimento acerca da patogênese do câncer de pênis, dos fatores de risco associados ao desenvolvimento das lesões precursoras relacionadas com essa doença. Embora o carcinoma de pênis seja reconhecido como um processo que ocorre em várias etapas, demonstrando um perfil policlonal, uma parte dos carcinomas de pênis é atribuída à infecção pelo HPV de alto risco, enquanto nos outros carcinomas de pênis, mecanismos moleculares independentes do HPV podem apresentar papel subjacente relevante. Entretanto, mais pesquisas sobre os mecanismos por trás da carcinogênese são necessárias.

**Palavras-chave:** HPV, câncer de pênis, prevalência, circuncisão, DST

Penile cancer is a disease with a high mortality rate. Although its occurrence is relatively rare worldwide, it can be high in some developing countries. The incidence rates of penile cancer vary enormously among different populations, being highest in some poor countries. The disease can constitute up to 10% of malignant disease in men in some African, Asian, and South American countries, with incidence rates of 4.2 and 4.4 per 100,000 in Paraguay and Uganda, respectively[1,2]. In Western Europe and the United States, age-standardized incidence rates range from 0.3 to 1.0 per 100,000, accounting for 0.4–0.6% of all malignancies in this part of the world[3,4]. In Brazil, incidence rates reach 2.0 per 100,000, placing our country as a highly prevalent area (INCA, 2010). The mean age at diagnosis of patients with penile cancer is 60 years with an age-related incidence rising constantly to reach its highest level at 70 years but the disease may occasionally present in young men. The substantial worldwide variation in penile cancer incidences is likely linked to differences in socio-economic and religious conditions[5]. Of note, penile cancer is predominantly seen in men who have not been circumcised shortly after birth, and is very rare in populations who routinely practice circumcision during the neonatal or childhood period[6,7]. Even in developing countries with high incidence of penile cancer, such as Nigeria and India, the disease is rare in subpopulations that ritually practice circumcision after[7].

Insight into its precursor lesions, pathogenesis and risk factors offers options to prevent this potentially mutilating disease. Consistently, poor penile hygiene, smegma retention and phimosis (or an unretractable foreskin), are described as risk factors for penile cancer[6-8]. In addition, a number of penile conditions, including penile rash, tear, urethral stricture, and inflammation have been reported to be associated with penile cancer[8]. Inflammation may represent a critical component of tumour development or progression as many penile cancers arise at sites of infection, chronic irritation or injury. Complete circumcision prevents most of these pathologic conditions. Phimosis leads invariably to retention of the normally desquamated epidermal cells and urinary products (smegma) resulting in conditions of chronic irritation with or without bacterial inflammation of the prepuce and the glans. The frequency of phimosis in men with penile carcinoma is high, ranging from 44% to 85%[7]. Tumour development has been attributed to chronic inflammation due to the irritating effects of smegma although no harm evidence indicates that smegma per se acts as a carcinogen[8]. Other risk factors for penile cancer include number of sex partners and history of genital warts or other sexually transmitted diseases[9].

It is well established that part of the penile cases is related to infection with human papillomavirus (HPV). Several studies have shown that an infection with mucosal high-risk (hr) HPV, mainly type 16, is involved in the pathogenesis of a subset of penile

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carcinoma[1,10,11]. The prevalence of penile carcinomas carrying hrHPV DNA ranges from 30 to 100%, depending on methods of HPV detection, population studied and histological subtype[1,6,10]. In a systematic review of the literature, Parkin et al (2006) that 40% of penile cancers were HPV-associated, with HPV16 being the dominating causal virus type (found in 63% of the cases)[12]. A more recent systematic review described 45% of penile cancers to be HPV-associated[7], corroborating the data from Backes et al.[10]. In terms of annual number of penile cancers globally, it represents a total cancer burden of about 26,000 cases, of which about 8,000 cases would be expected to be prevented by eradication of HPV16/18[10,12]. The association of HPV16 infection with penile cancer has been consistently supported by many epidemiological studies[7], including prospective studies[13]. Seropositivity to HPV16 is strongly associated with penile cancer as it is with cervical cancer and the association has been remarkably consistent in many case-control studies over the years[7,11,14]. Association of a small subset of penile cancers with low-risk HPV types has also been suggested[15]. However, whether mucosal low risk or cutaneous HPV types are etiologically involved in the pathogenesis of penile cancer is not clear[11]. Recently, a study involving 776 biopsies from 43 countries worlwide described HPV 6 as the second type of HPV, after HPV 16, more frequent in cases of penile cancer[16].

The use of tobacco in any form, as a risk factor for penile carcinoma has been described in several studies[6,9,17]. In these studies, cigarette smoking was found to be strongly associated with risk of penile cancer. Maden et al.[6] found an elevated risk for penile cancer in current cigarette smokers with an increase in risk with the number of pack-years. Although an association with smoking has been repeatedly observed for penile cancer, the exact role that smoking plays in the development of this disease is not yet known. Tobacco might act through its metabolites or directly after systemic absorption[18].

In Brazil, information regarding penile HPV infection is primarily derived from studies that examined husbands of female cervical cancer cases, cross-sectional studies of selected populations such as individuals attended at sexually transmitted diseases Clinics, as well as from small prospective studies. HPV infection has been detected in up to 73% of healthy individuals[19]. Data are summarized in **Table 1**.

Increased insight has also been gained into the pathogenesis of penile cancer and the clinical and histological precursor lesions related to this disease. Careful monitoring of men with lichen sclerosis, genital Bowen's disease, erythroplasia of Queyrat and bowenoid papulosis seems useful, thereby offering early recognition of penile cancer and, subsequently, conservative therapeutic options. Special attention is given to flat penile lesions, which contain high numbers of HPV. Their role in HPV transmission to sexual partners is highlighted, but their potential to transform as a precursor lesion into penile cancer has been unsatisfactorily explored[7].

As described by the IARC group[19], nearly 95% of penile cancers from Brazil comprises squamous cell carcinoma (SCC) and both warty and keratinizing types are the most common histological types (45 and 49%, respectively). Penile cancers are thought to arise from precursor lesions and can be subdivided into HPV positive and HPV negative cases. Similar to vulvar and head and neck carcinomas, squamous cell carcinoma of the keratinizing and the warty types display the strongest association with hrHPV (ranging from 70 to 100%) and their etiological relationship with hrHPV infection is most plausible[1,21,22]. The remaining penile squamous cell carcinomas demonstrate about 30% positivity for hrHPV DNA[15].

In Brazil, few studies have been conducted regarding the histological grade of the lesion. In the study by Scheiner et al.[20] HPV DNA was detected in 75% of patients with invasive carcinomas and in 50% of patients with verrucous carcinomas. High risk HPV were detected in 15 of 54 (27.8%) patients with HPV positive invasive tumors and in 1 of 4 (25%) patients with HPV positive verrucous tumors. HPV 16 was the most frequent type observed. No correlation was observed among histopathological subtypes of invasive squamous cell penile carcinomas and HPV infection, although the majority of HPV DNA positive cases were observed among the moderately and poorly differentiated carcinomas. The overall survival was related only to the presence of lymph node metastases. In the HPV positive cases, HPV 16 is the predominant type found in Brazil[23-26] as well as world wide[1,6,10,11,23,27] (**Tables 2** and **3**).

Despite the similarities between penile and vulvar cancer including their presence of HPV (mainly HPV 16) and their precursor lesions, the clear bimodal age distribution that is found for vulvar cancer is not clearly seen for penile cancer[28]. Cubilla et al.[22] observed a lower age of patients with basaloid or warty types (i. e., average 55 years) of cancer compared to other types of penile squamous cell carcinomas. However, in another study, including large series of penile cancer cases, no age difference was found between HPVpositive and negative cases (i. e., average 64 years)[29].

Low-risk HPV (lrHPV) associated condylomata acuminate do not have a malignant potential although in some cases, long-lasting giant condylomata acuminata (Buschke-Löwenstein tumour) might become malignant, showing invasion in more than 50% of the cases[30]. Although in the literature these tumours are sometimes classified as verrucous carcinomas, it seems best to consider this type of carcinoma as a separate entity, which is supported by distinct clinicopathological characteristics like the pre-

**Table 1 –** Studies on HPV prevalence among male population from Brazil.

| Study | HPV detection method | Population | HPV prevalence | |
|---|---|---|---|---|
| | | | Men tested | % |
| Giuliano, 2008 | PCR-PGMY09/11 | General population | 382 | 72.3 |
| Nicolau, 2005 | Hybrid Capture II | Partners of women with HPV | 50 | 56 |
| Franceschi, 2002 | PCR GP5+/6+ | Partners of women with cervical cancer | 53 | 35.8 |
| Carestiato, 2006 | Hybrid Capture II | General population | 1481 | 26.2 |
| Cavalcanti, 2008 | PCR-PGMY09/11 | Partners of women with HPV | 88 | 40 |

**Table 2 –** Studies on high risk HPV prevalence among male population from Brazil.

| Study | HPV types tested | Population | HPV prevalence | |
|---|---|---|---|---|
| | | | Sample | % |
| Giuliano,2008 | PCR and probing for 16,18,31,33,35,39,45,51,52,56,58,59,66 | General population | 382 | 36.1 |
| Nicolau, 2005 | Hybrid capture hr-cocktail 16,18,31,33,35,39,45,51,52,56,58,59,66 | Partners of women with HPV | 50 | 56 |
| Franceschi, 2002 | 16,18,31 and 33 | Partners of women with cervical cancer | 53 | 28.3 |
| Carestiato, 2006 | Hybrid capture hr-cocktail 16,18,31,33,35,39,45,51,52,56,58,59,66 | General population | 1.063 | 17.1 |
| Cavalcanti, 2008 | Specific PCR for 6,11, 16,18,31,33,35,45,58 | Partners of women with CIN | 88 | 40 |

**Table 3 –** Studies on HPV prevalence among penile cancers from Brazil.

| Study | HPV types tested | HPV prevalence | | |
|---|---|---|---|---|
| | | Sample | % | HPV 16 |
| Bezerra, 2001 | gp5/6 and Type-specific PCR for 16,18,31,33,35,39,45 | 82 | 30.5 | 15.9 |
| Levi, 1988 | MY and probing for 6,11,16,18,31,33,35 | 50 | 56 | 32 |
| McCance, 1986 | Southern blot analysis for HPV 16,18 | 72 | 49 | 45 |
| Scheiner*, 2008 | MY09/11 + restriction length polymorphisms(RFLP) | 80 | 44% | 54.2 |

*HPV DNA was detected in 44% (35 of 80) of patients using the MY9/11 first round PCR. The overall detection of HPV DNA increased to 72.5% (58 of 80) using the nested GP5+/6+ PCR.

sence of lrHPV (i. e., HPV 6 and 11), its relative young age at presentation and their condylomatous appearance (both clinically and histopathologically)[30,31]. Yet, the role of lrHPV types in penile carcinogenesis merits further investigation, particularly the clinical behavior of lrHPV positive penile carcinomas (i. e., its potential to metastasing disease).

Although benign lesions of the penis are the most common manifestations related to HPV infection, penile neoplasias (PIN) are also described and may represent the true precursor lesions to penile cancer. HPV-DNA has been found in 70-100% of PINs and in 29-81% of invasive penile cancers (depending on the histological type), with HPV16 being the most prevalent type[1,27,32]. HPV-associated PIN is considered a precursor of some forms of penile SCC. In immune competent patients, only 5-30% of PIN cases will progress to invasive SCC and even high-grade PIN lesions may regress spontaneously[33]. HIV infected men who have sex with men (HIV+MSM) have a strongly increased risk for development of AIN and anal cancer[15,34]. Highly active antiretroviral therapy is not associated with reduction of AIN[34]. Although up to 29% of younger men bear HR-HPV-DNA on the penis, PIN/penile cancer is a relatively rare disease in immunocompetent patients in Europe and North America and mostly elderly men are affected[32,35]. Compared with HIV-negative men, those HIV-positive patients have a somewhat higher penile HPV prevalence[36].

## Molecular pathogenesis

Although the etiology of penile cancers is not yet fully understood, penile carcinoma is recognized to be a multi-step process showing a polyclonal profile. A proportion of penile carcinoma is attributable to hrHPV infection, while in the remaining penile cancers molecular mechanisms independent of HPV are likely to represent the more common underlying events[1]. It is established that HPV-mediated penile carcinogenesis hrHPV-associated penile cancers are developed from precursor lesions caused by an hrHPV infection. The penile carcinogenic pathway is thought to be equivalent to cervical carcinogenesis: a persistent infection with hrHPV is the initiating causative event, and subsequent (epi)genetic alterations are necessary for an hrHPV-infected cell to become fully malignant. HrHPVs exert their oncogenic effect by expressing the oncoproteins E6 and E7, which bind to and inactivate the p53 and Rb tumour suppressor gene products, respectively[37].

The E6 and E7 gene products of the oncogenic HPV types are required for induction and maintenance of the transformed phenotype of the infected cells. By disturbance of the ubiquitin pathways, oncogenic HPV types interfere with control of the cell division cycle and apoptosis. Subsequent host-cell (epi)genetic events involved in hrHPV-induced penile carcinogenesis are not well studied, but may include those identified for hrHPV-mediated cervical carcinogenesis, for example promoter methylation of CADM-1, an immunoglobulin (Ig)-like cell surface protein involved in cell-cell adhesion[27], and a change in the composition of the AP-1 complex, a transcription factor consisting of different proteins[37]. Whether the same (epi)genetic alterations are involved in hrHPV-mediated penile carcinogenesis as in cervical carcinogenesis warrants further research. It should be realized that despite a common causative event, differences exist between hrHPV associated cervical and penile carcinoma, which are reflected by different incidence rates (26,300 penile cancer cases vs. 492,800 cervical cancer cases) worldwide in 2002[12] and time-span of development. While penile hrHPV infections are equally common as those of the cervix[37,38], the incidence of HPV-associated penile carcinoma is very rare as compared to cervical cancer. This may infer that penile epithelium represents a less favorable environment for virus-induced transformation compared to the epithelium of the cervical transformation zone, in which cervical cancers arise. Furthermore, the peak incidence of cervical cancer is around the age of 35-45 years while the peak incidence of hrHPV-associated penile cancer is, as indicated above, about 64 years[29], similar to non-HPV associated penile can-

cer. These findings suggest that there exist tissue and/or hormonal specific variables that influence the course of the hrHPV-mediated carcinogenic process that should gain further attention.

### Targets for preventive strategies

Several preventive strategies for penile cancer can be considered. Among them, circumcision has been described as an important and protective measure, not only for HPV and cancer development but for different sexually transmitted infections (STIs). Neonatal circumcision has been well established as an effective prophylactic measure for penile cancer. The protective effect of circumcision is mainly explained by the fact that certain conditions like phimosis with retention of smegma and lichen sclerosus (LS) are less prevalent in neonatal circumcised men[39]. The prophylactic efficacy of circumcision at older age requires further research but male circumcision is associated with a reduced risk of penile HPV infection[40], which proved to be a significant risk factor for penile cancer. In male partners of women with cervical neoplasia, a lower rate of penile neoplasia was found in neonatal circumcised when compared to uncircumcised men[41].

In Brazil, prevalent religious and cultural practices do not recommend circumcision and its occurrence is often related to phimosis. Its application as a medical procedure ranges from 7% to 18% of the studied populations[19].

Regarding other primary prophylactic measures, eradication of the etiological agent mediated by vaccination has proven to be a successful goal for other human viral infections. To date, two prophylactic HPV vaccines, that is a bivalent HPV16/18 vaccine Cervarix® (GlaxoSmithKline.) and a quadrivalent HPV16/18/6/11 vaccine Gardasil® (Merck), have been registered by the European Medicines and Evaluation Agency (EMEA) and the Federal Drug Administration (FDA) and are commercially available in a great number of countries worldwide, including Brazil. High prophylactic efficacy of these vaccines for persistent HPV infection and incident high grade cervical lesions has been observed in HPV negative women in preliminary large multicentric trials[42-44]. Similar effects might be expected in the prevention of HPV associated penile lesions. Preliminary results from Australian trial on vaccinated young women showed that male sexual partner protection was observed, leading to the decrease of condylomata cases in both sexes, in a period of two years after vaccination program was established, reinforcing the role of vaccines in HPV infection prevention[45].

Another important tool for HPV infection and subsequent cancer development is the adoption of safe sex behavior. Although there is no 100% protection, condom use is effective in the prevention of sexually transmitted infections (STI), including HPV[46]. To study whether viral shedding among sex partners might have consequences for viral persistence and the natural history of genital lesions, a randomized clinical trial has been performed. In this study, sex partners were randomized for condom use and it was shown that healing of HPV associated genital lesions was considerably shortened in condom using couples[47]. The healing time of hrHPV associated FPL was 7.4 months in male partners of the condom group compared to 13.9 months in the non-condom group.

Other behavioral factors such as smoking, once proven to be associated with penile cancer would contribute to preventive campaigns regarding smoking cessation. Although the precise role of tobacco use in penile carcinogenesis is undefined, a strong association between tobacco use and penile cancer has been found, alike for other (HPV associated) anogenital cancers. Smoking is most important in cases who are current smokers at time of diagnoses as compared to former or never smokers[6,9]. Consequently, it seems advisory to put efforts in smoking cessation programmes.

## CONCLUSION

Further research are necessary, mainly in our country and should not only focus on HPV mediated pathogenic pathways but also on related molecular and genetic factors that play a role in penile cancer development. Options for prevention of penile cancer include circumcision, limitation of penile HPV infections (either by prophylactic vaccination or condom use), prevention of phimosis, treatment of chronic inflammatory conditions associated to hygienic measures and smoking cessation.

### Conflict of interest

No conflict of interests to be declared.

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