Chapter 7

Diagnosis and Prevalence of High-Risk Human Papillomavirus Infection in Heterosexual Men

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Additional information is available at the end of the chapter

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Abstract

A better understanding of human papillomavirus (HPV) infection in men is an essential component of prevention programs aimed to reduce cervical cancer and other HPV-related diseases. A screening test capable of detecting asymptomatic/subclinical genital HPV infection in men at a reasonable price and causing minimal discomfort to the patient would be very valuable. The following chapter focuses on acetowhite test usefulness in the detection of asymptomatic/subclinical genital high-risk (HR) HPV infection in high-risk men populations, HR-HPV prevalence in sexually active healthy male partners of women diagnosed of high-grade cervical intraepithelial neoplasia and genotype-specific concordance between partners, addressing the preventive strategies that would reduce HPV infection in men. We present data from 125 men, sexual partners of women with preneoplastic cervical lesions. Prevalence of HR-HPV infection in male was high (50, 24% HPV16) and genotype concordance within the 60 infected couples was remarkable (62% shared at least one genotype). Acetowhite (AW) test was positive in 27% patients, showing low sensitivity for the identification of HR-HPV infection but allowed the diagnosis of subclinical HPV-related lesions in more than 10%. Current smoking and genital warts were associated with an increased risk of HR-HPV infection in men (OR: 2.4 and 5.6, respectively).

Keywords: human papillomavirus DNA test, prevention, prevalence, cervical intraepithelial neoplasia, male, mass screening, genital warts, diagnosis

1. Introduction

Human papillomavirus (HPV) infections are one of the most common sexually transmitted infections worldwide [1], representing a significant health problem due to their high preva-

lence and transmissibility. HPVs are a very large family of double-stranded DNA viruses (dsDNA), very resistant that can survive in the environment without a host and is able to infect humans. These viruses are not classified as serotypes, but as genotypes on the basis of DNA sequence. Currently, over 120 genotypes have been identified and about 40 genotypes (the alpha genus) can be transmitted through sexual contact and infect the anogenital region. HPV genotypes have been classified into low-risk genotypes, associated with anogenital warts, low-grade cervical lesions and recurrent respiratory papillomatosis, and high-risk genotypes (HR-HPV) [1] (**Table 1**), which eventually can lead to malignant transformation. HR-HPV are strongly associated with cancer and high-grade neoplasia of the anogenital tract, including the anus (AIN), penis (PeIN), uterine cervix (CIN), and vulva (VIN), and also a proportion of oropharyngeal cancer [2]. Although these infections are typically transient and asymptomatic, some of them will result in anogenital warts, and dysplastic and/or neoplastic lesions, which cause a substantial disease burden in both sexes and generate a considerable economic distress within society [3].

IARC classification	HPV genotypes
HR-HPV	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
pHR-HPV	26, 34, 53, 66, 67, 68, 69, 70, 73, 82

Classification of oncogenic HPV genotypes detected in this work.
IARC, International Agency for Research on Cancer; HR-HPV, high-risk HPV genotypes; pHR, probable/possible high-risk genotypes.

Table 1. Oncogenic HPV genotypes.

The virus may remain inactive for a long time and produce asymptomatic infection of the skin. It can be transmitted from one individual to another directly (by sexual contact) or indirectly. The dynamics of heterosexual transmission of HPV are still being investigated [4].

About one-third to one-quarter of invasive penile cancers (Alemany et al.) and nearly 99.7% of cervical cancer worldwide and in 96.8% of cervical preneoplastic and neoplastic lesions in our community (Perez et al.) may be related to HPV according to the retrospective studies. Although rare, penile cancer is associated with a high morbidity and mortality. The carcinogenesis of penile cancer is thought to involve two pathways: one related to inflammation and other dermatological conditions of the penis, and other related to HPV infection (López-Romero et al.). HPV DNA prevalence in invasive penile cancer varied geographically, with the highest prevalence in Oceania (55.6%), North America (48.7), Africa (36.8%), South America (39.7%), and Europe (45.9%), being the most common HR-HPV types: HPV16 (30.8%) and HPV18 (6.6%) [5]. So that, it is important to be cautious and not to consider overall prevalence as universal because the role of HPV in penile cancer etiology could be strongly influenced by histologic distribution and geographic region as it is also true for other HPV malignancies such as vulvar and head and neck cancers [6].

Genital warts (GWs) represent a significant public health problem associated with clinical symptoms (burning, bleeding, and pain) and psychosocial problems (embarrassment, anxiety,

and decreased self-esteem). Several studies have suggested that the occurrence of genital warts has been increasing over time [7]. Approximately 65% of people who have sex with an infected partner will develop warts themselves [8].

There has been immense progress in understanding the natural history of HPV infection in women disease. HPV is the primary cause of cervical cancers. Recently, there has been an interest in understanding the relationship between HPV infection and disease in men [9]. The male sexual partner`s role and in his partner's genital warts or high-grade cervical intraepithelial neoplasia (CIN II, CIN III-Ca in situ) lesions is also undefined. The diagnosis of most cutaneous and external genital wart (GW) can be made on clinical examination or with AW test and biopsy. In case of genital intraepithelial neoplasia, determining the extent of diseases is essential.

2. HR-HPV transmission among sexual partners

Epidemiological studies show that the HR-HPV infection is necessarily the sexual transmitted cause of invasive cervical cancer in women and its precursor lesion, cervical intraepithelial neoplasia (CIN) [10].

Direct genital mucosa contact during sexual intercourse is the principal route of HPV transmission [11]. About 80% of newly sexual couples will develop HPV-related lesions within 3 years after commencing sexual activity, most of whom will spontaneously regress within 1–2 years or until the age of 30–35 years [12]. The biology and dynamics of HPV transmission among sexual partners is still a cause for debate and has not already been completely established. Models have shown that HPV transmissibility is substantially higher than that of other viral sexually transmitted pathogens [13], but data on the natural history of HPV transmission between heterosexual partners are limited. Many studies [14–17] analyzed the prevalence and genotypes of high-risk infections of the foreskin before first sexual intercourse found asymptomatic infection in 12–83.3% [14, 16], speculating that non-sexual routes play significant roles in HPV transmission. In this regard, HPV transmission may occur upon contact with infected towels or other objects. In contrast to these findings, Pilatz et al. [15] did not find HPV in the foreskin of boys.

Despite the recommendation of the guidelines on sexually transmitted diseases, investigation of the presence of HPV in men who are sexual partners of infected woman has not been agreed. Previous studies suggested that the cancer of the penis and cervix may share the same etiological factor(s), because significant numbers of invasive cervical cancer were detected in partners of patients with penile cancer [18, 19]. It was assessed the contribution of the males' genital HPV DNA status to the risk of development of cervical neoplasia in their sexual partners, confirming that men could be vectors of HPV types typically observed in cervical cancer [20]. However, another studies did not confirm the findings of these investigators [21]. As the process of HPV infection can take more than 15 years, the current partner could not be necessarily the source of infection.

3. HR-HPV prevalence in heterosexual men populations

HPV infection causes substantial morbidity and its incidence is similar in both genders. The ongoing HPV in men study (HIM) provides the most current data on HPV infection and lesion development in men [9, 22–24]. Assessing HPV prevalence in men and investigating the sources of variation are essential for understanding the epidemiology of HPV infection.

The pooled HPV in the general population is significantly higher (20.4–36.3%) [25, 26] in studies published after 2000 (8.8%) [27]. The lower pooled prevalence in earlier publications might therefore be due to the detection method used and potentially not to a change in HPV prevalence over time. Age-specific prevalence curves among men are flatter [19, 28, 29] in contrast to the pattern observed in women [30]. The prevalence of genital infection in men does not differ significantly among age groups as it does in females [30]. In general population, HPV infection has a consistently higher prevalence within the penile epithelium of asymptomatic men than within the cervix of women with normal cytological testing [29].

Several factors have been suggested to influence HPV prevalence, varying substantially between sampling sites, techniques [31, 32], and different populations [33]. HPV prevalence is higher when samples are collected from a greater number of anatomic sites [29]. Hebnes et al. [27] in meta-analysis of studies examining HPV prevalence among men found a wide heterogeneity between general and high-risk populations. HIV-positive men, men with sexually transmitted infection and male sexual partners of women with HPV, CIN, CIS, or invasive cervical cancer are considered a high-risk population [34, 35]. Number of types tested for varies between articles. In studies reporting prevalence estimates for more than one HPV type, the commonest detected types were HPV16 [20, 24, 26, 27, 36, 37] and HPV18 [27].

From a socio-epidemiological standpoint, it is important to note that HPV-infected men play a key role in the transmission of the HPV virus to their female sexual partners. The range reported in other studies for sexual partners of women with CIN was 30–68% [19, 24, 26, 36, 38]. Geographical region, anatomical sampling site, or HPV detection methods have not explained the wide heterogeneity of results [27]. In contrast, Franceschi et al. [39] showed the strongest variation by countries, with a higher prevalence of HPV infection among Brazilian sexual partners of woman with CIN compared with those detected in other countries (Colombia, Mexico, Spain).

The natural course of disease in men by establishing rates of acquisition and time to clearance of HPV infection has not been investigated properly. Although fewer data of infection duration have been reported in men, findings suggest that HPV infection clear more quickly for men than for women and that men have similar duration of infection for oncogenic and non-oncogenic types [7, 28]. Mean clearance time, defined as time to elimination of 50% of all infections, was estimated to be 5.9 months (patridge JM). HPV infections in women tend to have a longer duration and are estimated to clear at average of 12.2 months [40].

4. Concordance between sexual partners

Positive concordance is defined as both partners having the HPV outcome of interest. HPV concordance in heterosexual couples has important clinical and public health implications. In terms of HR-HPV detection, the percentage of couples harboring HR-HPV was 32–65% [28, 36, 37, 41]. In couples where both members were HPV positive, more than 60% were infected with one or more of the same HPV types. This level of concordance was observed independently of HPV prevalence and is consistent with the high transmissibility of HPV [25, 28, 36, 38, 41]. Studies over the past 20 years evaluating HPV infection concordance among heterosexual partners have shown many inconsistencies, reporting concordances of type-specific infection between 2 and 87% [20, 42–44]. Such heterogeneous findings may be due to diverse laboratory DNA detection techniques, methods for study population selection and different anatomical sites sampling, among other factors [25].

Positive concordance was usually higher for female partners of men with HPV infection than for male partners of women with HPV infection. Men with HPV-positive female partners had one or more of the same HPV types more often in studies that recruited men with HPV-related diseases compared with studies without this inclusion criterion for men (65.8 vs. 27.2%) [28]. These findings suggest that the epithelial cells of the penile skin are more resistant to HPV infection than the cervical epithelium and the duration of HPV infection is shorter in men than in women [28, 38].

5. Acetowhite test versus molecular detection of HR-HPV infection

Infection with one or more of the 40 HPV detected at the genitals is common among men aged 18–70 years. Only 5% of these HPV infections progressed to an external genital lesions during follow-up. There were observed substantially higher rates of progression for certain HPV types [45].

Most genital infections in men are asymptomatic, detectable only by viral DNA testing and become undetectable over time. Subclinical lesions, including those related with HR-HPV types, are more than 10 times common than clinical (apparent) infection and are identified on examination after application of acetic acid solution, a procedure known as acetowhite test (AW test, peniscopy). Since the American Society for Colposcopy and Cervical Pathology recommended the use of HPV DNA testing for the triage and management of women with atypical squamous cells of undetermined significance result of Pap test, an increasing number of female patients are requesting HPV DNA testing for their partners. Although the current gold standard for HPV genotyping is a genetic sequencing targeting the product of gene amplification (Heidegger), a screening test capable of detecting asymptomatic and subclinical genital HPV infection in men at a reasonable price and causing minimal discomfort to the patient would be very valuable.

To date, economic data have primarily focused on the more common HPV-related cervical cancer and its precursor lesions, as well as the benign, very common condition of genital warts.

Nevertheless, available data indicate that HPV-related disease is associated with a significant economic burden in males. Specifically, in men, the total direct cost of HPV infection acquired through the age of 24 years was estimated at 62 million dollars per year, the comparable figure for women being 2.8 billion [46].

Studies of the psychosocial effects of HPV-related disease in males are lacking. However, there is a significant psychosocial burden reported in women being screened for, or diagnosed, with HPV-related disease [47].

The currently available methods for evaluating HPV infection in male are HPV DNA test and AW test [12]. This is full description of our study procedures: The entire penis and scrotum of the patient were examined under magnification, and the presence of genital warts was recorded. After this examination, we sprayed them with 5% acetic acid solution. After 5 min, we enhanced the visualization of the skin by a colposcope under fourfold and sevenfold magnification, respectively. AW lesions were classified as typical for the presence of well-demarcated lesions with a slightly elevated border and the occurrence centrally of punctuated capillaries with or without an associated epithelial depression (Groove) and non-typical for the presence of lesions exhibiting a ragged border and lacking punctuated capillaries. Regardless of AW test result, the specimen for HPV DNA detection was obtained. Samples were taken with three cytobrushes from the preputial cavity (the inner part of the foreskin, the glans and the sulcus coronarius, scrotum, and urethral meatus) rotated 360 grades and suspended together into one single vial containing TE buffer pH 8.0 Molecular Biology grade (AppliChem GmbH, Darmstadt, Germany). Samples were maintained at 2–8°C and processed within 24–72 h after collection. The brushings were collected without spraying the genital region with saline solution. DNA was isolated using QIAamp MinElute Media Kit (Qiagen, Hilden, Germany). Extracted nucleic acids were stored at −20°C. An aliquot of the original sample was also stored at −20°C. Amplification and detection were carried out using the Linear Array HPV Genotyping Test (Linear Array. Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. We described the distribution of 22 HPV genotypes classified as HR (HR-HPV, IARC Group 1 carcinogens) or probable/possible HR (pHR-HPV, IARC Group 2A/B carcinogens) by the International Agency for Research on Cancer Monograph Working Group (**Table 1**). This test also detects human beta-globin in order to test the adequate sample cellularity and absence of inhibitors. Linear Array does not have individual probe for HPV52 but uses a probe that simultaneously detects HPV52, HPV33, HPV35 and HPV58. Additional specific PCR was performed in case of HPV33, HPV35 and/or HPV58 infection in order to properly detect confections of these three genotypes with HPV52 [48].

In our study, around 30% of positive AW results were not related with HR-HPV infection [49–51]. False-positive results may be due to low-risk HPV infection or inflammatory conditions, common in patients with sexually transmitted diseases [52]. Nevertheless, the need for detecting subclinical genital HPV infection, associated with detectable AW lesions [53], has been emphasized and these population would need follow-up or biopsy. Afonso et al. [37] found that 50% of sexual partners of women with CIN harbored HPV in lesions and these were predominantly subclinical. The diagnosis and treatment of acetowhite lesions in men do not seem to alter or improve the progress of the squamous intraepithelial lesions in their female

partners [54]. Nevertheless, these acetowhite lesions on male genitalia are in fact squamous intraepithelial alterations and should not be left due to the risk of their further development [37] as Sudenga et al. [45]. have presented the first estimates of genital HPV infection progression to PeIN. They are the first authors that follow these HPV infections and their progress to lesion in men. We encourage the importance of the clinical follow-up of this men and perhaps of taking a biopsy afterwards, in case of HPV infection persistence.

Problems associated with screening techniques in men include inadequate collection of cells for the detection of HPV DNA by use of swabs and brushes, poor specificity, and patient discomfort during peniscopy. When lesions are not visible, sampling at multiple penile sites could increase the sensitivity of the HPV [41, 55]. In addition, the use of acetic acid and a colposcope requires specific training, clinical experience, and significant costs associated with the procedure and training. Polymerase chain reaction (PCR) has emerged as the most sensitive available method for the detection of latent HPV infection. The infectious diseases literature supports the lack of the US Food and Drug Administration (FDA) approval of HPV tests for HPV detection in men and the absence of adequate therapy for established HPV infection in this population.

6. Our results of HPV prevalence in a high-risk population of heterosexual men and concordance between heterosexual partners

A cross-sectional study was conducted by the Urology Department of the University Hospital of Vigo, Spain, from January 2013 to June 2015 (López Díez et al., Enf Infecc Microbiol Clin, 2016 *in press*). We recruited 125 asymptomatic men, aged 18 years, whose SP (sexual partner, regular sexual intercourse for more than 1 year) had presented high-grade squamous cervical lesions (CIN grade 2 or CIN grade 3-carcinoma in situ) in the previous 6 months. Prevalence of HR-HPV infection in men was 50.4% (63/125). Multiple HR-HPV infections were detected in 30.4% (38/125) of this population. Data of HPV genotype were available in 120 women. HPV16 was the most frequent genotype, detected in 47.6% (30/63) of infected men and 67.5% (81/120) women (**Table 2**). HR-HPV infection was detected in both partners in 50% (60/120). Among these infected couples, 62% (37/60) harbored at least one genotype in common. The HPV16-specific concordance was as follows: 41.7% (25/60) couples were concordantly HPV16 positive and 18.3% (11/60) were concordantly HPV16 negative (Kappa value: 0.21).

The proportion of women with the same genotype as their male partner was 58.7% (37/63). The proportion of men sharing the same genotype as their female partner was 30.8% (37/120), $p < 0.0001$.

AW procedure was positive in 34/125 (27.2%) patients. AW procedure showed 25.4% (95% CI 13.8–36.9) sensitivity, 71.0% (95% CI 58.9–83.1) specificity, 47.1% (95% CI 28.8–65.3) positive predictive value and 48.3% (95% CI 37.5–59.2) negative predictive value for the identification of HR-HPV infection (**Table 3**). AW lesions and HR-HPV were detected at the same time in 16/125 (12.8%) males.

IARC classification	Genotype	Infected men (n)	Global prevalence (N = 125) %	Prevalence in HPV-positive men (N = 63) %
HR-HPV	HPV16	30	24.0	47.6
	HPV18	4	3.2	6.3
	HPV31	9	7.2	14.3
	HPV33	2	1.6	3.2
	HPV39	6	4.8	9.5
	HPV45	5	4.0	7.9
	HPV51	11	8.8	17.5
	HPV52	12	9.6	19.0
	HPV56	8	6.4	12.7
	HPV58	3	2.4	4.8
	HPV59	6	4.8	9.5
pHR-HPV	HPV53	13	10.4	20.6
	HPV66	10	8.0	15.9
	HPV67	1	0.8	1.6
	HPV68	2	1.6	3.2
	HPV69	1	0.8	1.6
	HPV70	4	3.2	6.3
	HPV73	3	2.4	4.8

HR-HPV, high-risk HPV genotypes; pHR, probable/possible high-risk genotypes; IARC, International Agency for Research on Cancer.
Crude HPV prevalence calculated in 63 HPV-positive patients: 25 single and 38 multiple infections (López Díez et al., Enf Infecc Microbiol Clin, 2016 *in press*).

Table 2. Type-specific HPV prevalence in men.

		HR-HPV DNA detection			
				Yes	No
		n (%)	n (%)	*p*	OR (95% CI)
AW lesion	Yes	16 (25.4)	18 (29.0)	0.648	0.83 (0.38–1.83)
	No	47 (74.6)	44 (71.0)	–	–

Genital lesions detected by peniscopy in asymptomatic sexual partners of women with high-grade cervical lesions, according to the presence of HR-HPV.
HR-HPV DNA, high-risk HPV; AW, acetowhite test; OR, odd ratio; 95% CI, confidence interval.
Statistically significant, $p < 0.05$ (chi-square test).

Table 3. Acetowhite lesions according to HR-HPV DNA detection.

Genital warts were present in 17/125 (13.6%) patients. AW procedure showed sensitivity 82.3 (95% CI 55.8–95.3), specificity 81.4% (95% CI 72.6–88.6), positive predictive value 41.1% (95% CI 25.1–59.1) and negative predictive value 96.7% (95% CI 89.9–99.1) for genital warts' detection (**Table 4**).

		Genital warts			
		Yes	**No**		
		n (%)	**n (%)**	***p***	**OR (95% CI)**
AW lesion	Yes	14 (82.3)	20 (18.5)	<0.0001	20.53 (5.39–78.27)
	No	3 (17.6)	88 (81.5)	–	–

AW: Acetowhite test, OR: odd ratio, 95% CI: confidence interval.
Statistically significant, *$p < 0.05$ (chi-square test).

Table 4. Acetowhite lesions according to genital warts' detection.

HR-HPV prevalence was 6/15 (40.0%) in circumcised men and 57/110 (51.8%) in not circumcised men ($p > 0.05$).

7. Risk factors for HR-HPV prevalence in men

Coexistence of non-oncogenic and oncogenic HPV-types is frequent [56, 57], which may itself predispose to cancer. A Danish study of 50,000 people with GW found an elevated risk of HPV-associated cancers in people with GW compared with the general population [56]. Although test for the presence of HPV are not recommended for the diagnosis of GW [58] in our study, the AW test was sensitive and specific for genital warts' detection, showing a high negative predictive value. This procedure could avoid missing small clinical lesions. They are generally regarded as a benign condition not associated with mortality, but they can be difficult to treat and recurrence is often observed. Visible warts represent only the tip of the iceberg, and low- and high-risk HPV infections contribute to the genital lesion burden in men [24]. Healthcare providers should have a higher suspicion for HPV-associated cancers in immunocompromised patients with GW. AW test can be helpful in the diagnosis of GW. In particular, soaking acetic acid into suspicious lesions can enhance the degree of suspicion in lesions without classic features. Taking a biopsy might also be indicated if diagnosis is uncertain, the lesions do not respond to standard therapy or the disease worsens during therapy [58].

Limited data exist on the association between HPV infection and smoking in men. In this study, current smoking could increase 2.3-fold the risk of HPV-prevalent infection in males, as found in the HIM study. At present, it is unclear how smoking may influence HPV infection in men, but many possible mechanisms exist. Smoking could potentially increase viral load by weakening the cellular immune response [59].

Sexual behavior has been strongly associated with HPV infection and seropositivity in men [60]. Features previously associated with HR-HPV were as follows: young age at first sexual intercourse (FSI), a higher number of lifetime sexual partners (LSP) and a higher number of recent SP. Contradictory results about the influence of lifetime number of SP were reported [26, 41, 55, 61, 62]. This data could be attributable not only to the range of birth year of men but also to geographical characteristics [27, 33]. In Western population, the numbers of lifetime sexual partners in men and women are both relatively high, and little gender difference could be observed. Burchell et al. reported that the proportion of ≥5 lifetime sexual partners was 64.4% for men, in line with our results (55.2% in men).

The risk of having one or more SP in the preceding year was has been poorly evaluated. The risk of HPV re-infection between a monogamous couple is still a matter of debate [63]. In contrast, Rombaldi et al. [64] and Parada [25] found a high association between both variables.

In the National Questionnaire of Sexual Health, published by Spanish Government in 2009, it was found that the mean age of FSI was 17–18 years (29.3%) for Spanish men. In our study, younger age at FSI was not a risk factor for HPV infection as other authors have previously reported [27, 64]. There are contradictory data that could be attributable not only to the range of birth year of men but also to geographical characteristics [55, 60].

Similar to other studies [55, 65], we did not find the expected protective effect of circumcision on HPV acquisition. Circumcision seems to be associated with reduced persistence in men [66] even though the mechanism of protection is unclear. Removal of the foreskin could minimize the chance of acquisition of new infections or could result in an increased clearance of preexisting infections [28, 67]. Our different results could be due to the fact that circumcision is not very common in our geographical area and that analysis could not assess specific associations in the glans penis, the area expected to be most likely protected by removal of the foreskin [68].

8. HR-HPV risk factors found in our study

Epidemiological characteristics of the studied high-risk population are shown in **Table 5**. Current smoking status was associated with an increased risk of HR-HPV infection in men: 38.2% (21/55) versus 60% (42/70), OR 2.3 (95% CI 1.1–4.7), $p = 0.016$.

Variable	HPV detection (n = 125)		*p*-value	
	Positive	Negative	Bivariate analysis	Multivariate analysis
Age at FSI	16.9 ± 2.7	17.4 ± 2.4	0.382	
Lifetime SP				
1–5 SP	10 (34.5%)	19 (65.5%)	0.050	
>5 SP	53 (55.2%)	43 (44.8%)		

Variable	HPV detection (n = 125)		*p*-value	
	Positive	Negative	Bivariate analysis	Multivariate analysis
Recent SP				
1 SP	51 (49.0%)	53 (51.0%)	0.498	
>1 SP	12 (57.1%)	9 (42.9%)		
Current smoking				
Yes	42 (60.0%)	28 (40.0%)	0.015*	0.016* (OR 2.3, 95% CI 1.1–4.7)
No	21 (38.2%)	34 (61.8%)		
CIN grade in partner				
CIN 2	30 (54.5%)	25 (45.5%)	0.411	
CIN 3-CIS	33 (47.1%)	37 (52.9%)		

FSI, first sexual intercourse;, SP, sexual partners; CIN, cervical intraepithelial neoplasia; CIS: carcinoma *in situ*.
Age was expressed as mean ± standard deviation.
* $p < 0.05$, statistically significant.

Table 5. HPV detection in men according to epidemiological characteristics.

Prevalence of HR-HPV infection was 14/17 (82.4%) in patients with genital warts versus 49/108 (45.4%) in patients without genital warts (OR 5.6, 95% CI 1.5–20.7, $p = 0.008$) (**Figure 1**).

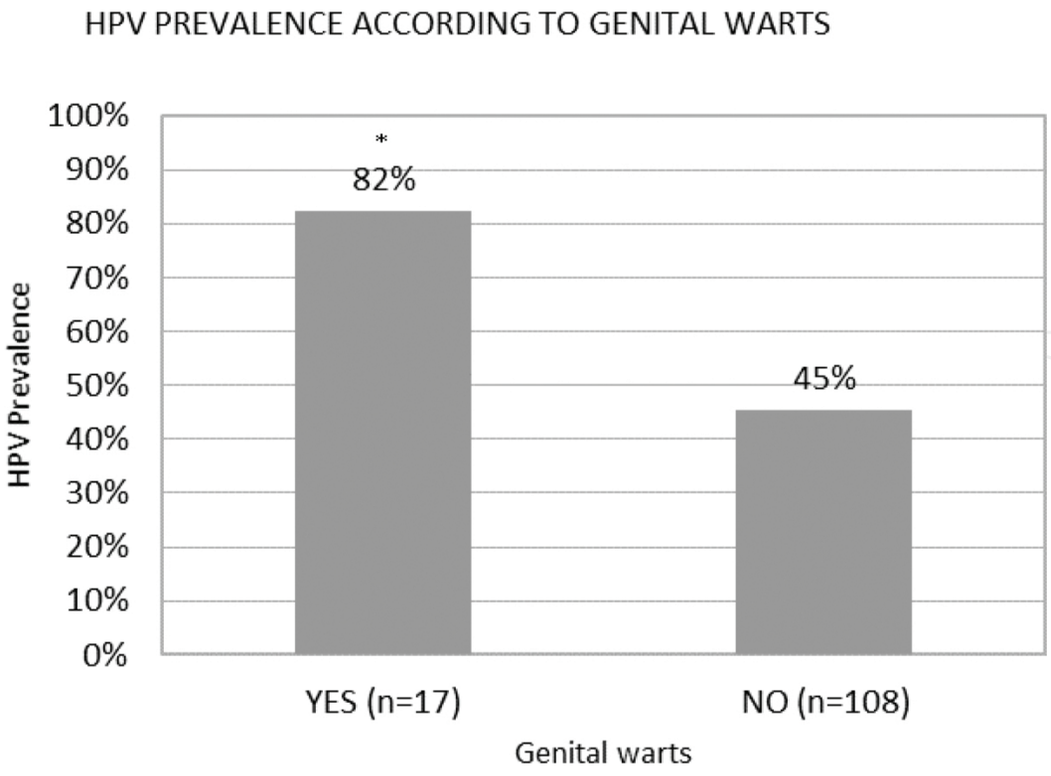

Figure 1. Statistically significant, *$p < 0.05$ (chi-square test).

9. Prevention of HPV infection in men

Until recently, no highly effective primary prevention strategy to reduce the risk of HPV acquisition existed. However, research has demonstrated that nonavalent, quadrivalent and bivalent HPV vaccines stimulate immunogenicity in males and females [69]. On October 16, 2009, the FDA approved the use of quadrivalent vaccine in males aged 9–26 years for the prevention of genital warts. Subsequently, the Advisory Committee on immunization Practices (ACID) declined to recommend the quadrivalent vaccine for routine immunization in men [70], providing a permissive recommendation in this age range for HPV vaccination. Most European countries offer HPV vaccination for girls, but vaccine recommendations for boys are warranted. HPV vaccination of girls will in theory also benefit the male population through herd immunity.

Uninfected sexual partners may be an important target population for HPV vaccination [71]. Potential interventions such as a therapeutic HPV vaccine may avert new HPV infections. Moreover, vaccinating boys would reduce HPV-related diseases in both sexes to a greater extent than herd immunity, which depends on high vaccination rates among females.

The benefits of vaccination to individuals seronegative to HPV types included in the vaccine are clear, and emerging studies suggest that HPV vaccine may also help people who previously had and cleared an infection [72] although additional researches in this population are needed. While prophylactic HPV vaccine does not have substantial impact on established infection, it may have cross-protection against non-vaccine genotypes [73]. However, if these vaccines could also be successful in lowering the HPV load, they may also assist in lowering transmission [13].

There is no direct evidence for protection by HPV vaccines against penile cancer because penile cancer is so rare that there could never be a clinical trial large enough to measure the effect [74]. HPV vaccines have not been around long enough to measure the population impact on penile cancer. However, the observed HPV type distribution reinforces the potential benefit of current and new vaccines in reduction in HPV-related penile neoplasia lesions [6].

Future trials of HPV vaccines in men should take into account not only the presence of penile HPV infection but also the presence of penile subclinical lesions as an outcome measure for the efficacy of a vaccine. More complex study designs would also allow researchers to better understand first transmission, reinfection and back and forth passage within couples, concordance in couples in which one partner has received HPV vaccine and concordance after treatment for HPV-related lesions is an essential component of prevention programs aimed to reduce cervical cancer and other HPV-related diseases in men and women.

10. Final considerations

HPV causes cancer in both men and women. The HPV-related cancer burden remains higher in women than men, even in countries that have effective cervical cancer screening programs.

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It is clear that males have poor knowledge of HPV infection, morbidity, transmission, and prevention. Moreover, several issues are controversial and should be addressed by adopting a multidisciplinary and multiprofessional approach. Regardless of vaccination strategies adopted, efforts should be made to educate males about HPV and its health implications.

Currently, there is no licensed test for HPV detection in men and there are no recommendations for male screening. Although routine HPV testing is not necessary for men in general population, findings from emerging research in high-risk population suggest that HPV infection is pervasive and persistent in these groups, warranting the adoption of additional screening and prevention policies. Our findings suggest the need for greater attention to sexual partners of HPV-infected individuals. Male sexual partners of female with high-grade lesions should be referred for evaluation and combined peniscopy, and HPV DNA test will ensure accurate detection of HPV status among males. Female partners of men with HPV-related diseases should be encouraged to get screened for HPV-related disease given that they have a high likelihood of concomitant infection and that most infection in couples are of the same viral type. Screening may also benefit male partners of HPV-infected women. Interventions that study the true prevalence of HPV infection in asymptomatic men and try to reduce HPV-associated penile lesions could be important to both men and women.

Further prospective and controlled studies in different populations are needed to provide adequate counseling to men that demand to know whether they are infected by HR-HPV. Long-term follow-up will contribute to the knowledge about the influence of persistent HPV infection in male and the potential recurrence of his sexual partner after treatment. We assume that the faster way to achieve greatest protection for cervical cancer and its precursors is to vaccinate males as well as female because both genders contribute to the transmission of HPV infection.

The prevention, diagnosis, and treatment of HPV-associated diseases in men will reduce the disease burden not only in males, but also in females, and help destigmatize the focus of the HPV-related disease on women.

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