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Review

Clinical and Public Health Considerations for HPV Infection in Men: A Narrative Review

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HIGHLIGHTS

- Genital wart is the most common sexually transmitted disease which is a result of infection with human papilloma virus.
- Genital HPV infections in men are less persistent than in women and usually clear up within 12 months.

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ABSTRACT

Genital wart is the most common sexually transmitted disease which is a result of infection with human papillomavirus (HPV), mostly type 6 and 11. Despite its usually benign characteristic, HPV infection can pose considerable psychological, social, and economic burdens on patients and society. Here, we focused the existing data in this regard through searching on PubMed, Google Scholar, and Scopus and tried to provide a comprehensive review of the vast range of presentations and complications of HPV infection in the male population. HPV infection most commonly manifests with benign lesions including skin and genital warts, oral lesions, and laryngeal papillomatosis in men. Genital warts are the most important epidermal manifestations of the epidermotropic HPV. Non-oncogenic HPVs (types 6 and 11) cause the majority of genital warts in men. Interestingly, HPV can decrease sperm motility by binding to the head of the human spermatozoa and reducing sperm's normal morphology rate which can lead to infertility. Moreover, several male-specific malignancies like penile cancers are associated with HPV infection, especially immunocompromised individuals. Despite a relatively benign course of HPV infection in men versus women, its role in anogenital warts, infertility, and malignancies warrants the prompt inclusion of the male population in the vaccination programs, not only to decrease HPV-related disorders, infertility, and deaths in men but also to improve the quality of life of women, considering the main route of virus transmission.

Keywords: Human Papilloma Virus; HPV; Genital Wart; STD; Male Patients



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Introduction

Historically, it has been believed that human papillomaviruses (HPVs) are important causes of genital warts and cervical cancers in the female population. However, recent decades of experience and study have demonstrated the highlighted role of HPVs in anogenital warts and malignancies in men. The burden of HPV-associated diseases in the male population is substantial. Adolescent boys and adult men can acquire genital HPV soon after sexual contact. They are also quite responsible for infection transmission to the female. The high prevalence of HPV infection in females confirms the corresponding high prevalence in males, as this infection is a sexually transmitted disease (STD). However, genital HPV infections persist less commonly in men than in women, and they usually clear within 12 months (1, 2).

On the other hand, a great majority of head/neck, anal and penile malignancies occur as a result of HPV infection. Among the hundreds of HPV serotypes, only some strains have been considered important for humans. Based on the risk of oncogenicity, HPVs are classified as low-risk and high-risk types. The low-risk types of HPV (Types 6 and 11) are the cause of skin warts and benign anogenital warts, also known as condyloma accuminata, while high-risk types (Types 16, 18, 31, and 45) are predisposing agents for anogenital malignancies (3-5).

Anogenital HPVs are one of the most common etiologies of STDs. The main risk factors for transmission of HPV include multi-partner sex affairs, co-infections, and age at the first intercourse (6, 7). Among these, sexual behaviors and circumcision are specific risk factors for HPV infection in the male population. Male circumcision not only decreases the risk of HPV infection in men but also greatly contributes to the reduction of cervical cancer development in women (8, 9). On the other hand, genital HPV infection may be more common among men having sex with women and men (MSWM) than among men having sex with women (MSW) or men having sex with men (MSM) (10). Chronic alcohol abuse can also impair the immune system and subsequently predispose to HPV infection (11).

In general, HPV infection is mainly transmitted through sexual contact. Other routes of transmission include direct manual contact, perinatal transmission from the birth canal, and indirect transmission from fomites. HPV infection can be subclinical in the individuals who acquire it; hence, transmission can occur from an asymptomatic person (12-14). The incubation period of HPV infection varies from weeks to months. Manifestations of HPV infection in men vary from a benign skin wart to anogenital warts. Moreover, HPV infection can cause consequences like infertility and malignancies. Also, HPV can have transformed features in immunocompromised patients including human immunodeficiency virus (HIV) positive individuals (15,

16). Here, we have provided a comprehensive review of the vast range of presentations and complications of HPV infection in the male population.

Benign lesions

HPV infection most commonly manifests with benign lesions in both genders; of those we can mention skin and genital warts, oral lesions, and laryngeal papillomatosis.

Cutaneous lesions

Cutaneous warts are the most prevalent manifestations of HPV infection. They include a wide range of presentations like common warts (*verrucae vulgaris*), plantar warts, deep palmoplantar warts (*myrmecia*), flat warts (*verrucae plana*), butcher's warts and mosaic warts. These lesions are almost always caused by low-risk HPV strains (17, 18).

Nevus sebaceus is one of the benign skin lesions that is most often associated with HPV. This hamartoma consists of abnormal epidermal and dermal components and is demonstrated to be related to epidermodysplasia *verruciformis* (19, 20).

Seborrheic keratosis (SK) is another benign feature of HPVs. It is an epidermal tumor arising on the face or trunk and usually involving middle-aged or older adults. Stucco keratosis is one type of SK. It presents with papular wart-like lesions on the lower extremities of older individuals (21).

Skin tags or fibroepithelial polyps are small benign lesions usually developing on the eyelid, neck, groin, and other friction areas and are demonstrated to be associated with HPVs (22).

Epidermal cysts, especially those that develop in the palmar and plantar skin, are also attributed to HPV infection (23, 24). On the other hand, the association of some HPV serotypes has been demonstrated with lichen sclerosis, plaque psoriasis, and Darier disease (25-27).

Mucosal lesions

Oral HPV infection consists of benign and malignant lesions. Oral warts (*verruca vulgaris*) usually occur in children and are often asymptomatic. These benign lesions develop on the palate and gingiva and can also present as oral papillomas (condyloma). Oral papillomas are small exophytic lesions with a rough or cauliflower-like verrucous surface. They transmit through digital or oral-genital sexual affairs. In addition, lichenoid reaction, epithelial hyperplasia, aphthous ulcers, geographic tongue, and conjunctival papillomas are other mucosal lesions sometimes believed to be of HPV infection origin (28-30).

Focal epithelial hyperplasia (FEH), also known as Heck's disease, is an uncommon mucocutaneous disorder mostly occurring in children and HIV-positive patients. It manifests as multiple dome-shaped nodules in the labial, lingual, and buccal mucosa and is attributed to HPVs (31,

32).

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is an uncommon disorder resulting from the formation of warty lesions on the respiratory tract, most frequently at the larynx, which is known as recurrent laryngeal papillomatosis. This disease is much more common and aggressive in children than adults and is attributed to HPV types 6 and 11 infections. The juvenile-onset form of RRP is usually the result of maternal transmission of HPV to the child during the vaginal delivery. RRP is manifested as hoarseness, stridor, odynophagia, chronic cough, and respiratory distress. The most important challenge is the recurrent formation of lesions which makes surgery a transient therapeutic solution. Respiratory obstruction and malignant transformation are the most important complications of RRP (33-35).

Anogenital lesions

Genital warts are the most important epidermal manifestations of the epidermotropic HPV. Non-oncogenic HPVs (types 6 and 11) cause the majority of genital warts in men and women. Millions of men get involved annually with genital warts, with a peak age of less than 30 years. Despite the benign nature of genital warts, significant concern and shame are brought about for patients (36). The average incubation period of genital warts is 2–3 months after HPV infection. These highly infectious lesions readily transmit to sexual partners. It is important to know that flat penile warts contain the highest number of HPV, responsible for the most considerable increase in sexual transmission (37).

Anogenital warts usually manifest as either smooth keratotic papular warts on dry surfaces or cauliflower-like condylomata accuminata on moist surfaces. They are located on the shaft or base of the penis, glans, coronal sulcus, scrotum, under the prepuce, or at the pubic and rectal area in men (38, 39). Keratotic genital warts are sometimes known as genital seborrheic keratosis (SK). However, the role of HPV infection in genital SK is not certainly determined (40). About one-third of genital warts regress spontaneously but they recur commonly; however, a number of them undergo malignant transformation within years (41).

Infertility

Since HPV infection is an STD, it has been suggested that it may affect sperm parameters and thus lead to male infertility. Studies have demonstrated that HPV can decrease sperm motility by binding to the head of the human spermatozoa. Moreover, it can reduce sperm's normal morphology rate. The viral load of HPV in the semen is significantly associated with decreased sperm quality (42-44). It has been reported that the presence of high-risk HPVs in the male reproductive tract (e.g.

epididymis, vas deferens, external genitalia) of infertile men is more likely than fertile ones (45, 46).

Malignant lesions

HPV has long been notorious for inducing cervical cancer in women; however, it has been lately demonstrated that several male-specific malignancies such as penile cancers are associated with HPV infection. Immunocompromised individuals like malnourished, HIV-infected, dialysis, transplant, and immunorheumatologic patients who are on immunosuppressive therapy are at increased risk of HPV-related malignancies (4, 47). Skin, oropharyngeal, and anogenital cancers comprise most of HPV-related malignancies. However, the association between breast, lung, esophageal, colorectal, and prostate cancers and HPV has also been demonstrated (48-51).

Penile cancer

Penile cancers are among the most common male neoplasms, particularly in South America, Africa, and Asia. Risk factors of penile cancer include lack of circumcision, phimosis, balanitis, penile lichen sclerosus, cigarette smoking, penile trauma, poor hygiene, high-risk sexual activity, a history of priapism, and HIV and HPV infections (52). Approximately 50% of penile cancers are attributed to HPV infection. This type of malignancy is classified as basaloid, warty, verrucous, and keratinizing squamous cell cancers. Almost all basaloid and warty types and up to half of verrucous and keratinizing squamous cell types of penile cancers are associated with oncogenic HPV types (53-55).

Bowenoid papulosis (BP) is another HPV-associated STD in both genders. In men, it is also known as penile intraepithelial neoplasia (PIN). High-risk HPVs are usually involved in the pathogenesis of BP. It is manifested as red-brown to violaceous papules in the anogenital area. BP clinically resembles genital warts but it is histologically similar to squamous cell carcinoma in situ (Bowen's disease). However, they are benign as they regress spontaneously (56, 57).

Buschke-Lowenstein tumor, also known as Gigantski kondilom, is a verrucous carcinoma of the anogenital area. It is a rare type of well-differentiated squamous cell carcinoma and has been linked to low-risk HPV infection (58).

Erythroplasia Queyrat (EQ), which is another HPV-attributed disorder, is an in situ carcinoma of the penile mucosa and is associated with high-risk HPV serotypes. It presents as an asymptomatic bright red, shiny papule(s), plaque(s), or ulcer(s) around the urethra or on the glans of the penis or coronal sulcus. It usually occurs in uncircumcised men of any age. It may take several years to diagnose this condition (59).

Bowen's disease (BD) is a type of intraepidermal (in situ) squamous cell carcinoma (SCC) that can develop

in genital and nongenital areas. This HPV-associated disease has similar histology as erythroplasia of Queyrat and bowenoid papulosis in men. BD manifests as a well-demarcated erythematous plaque with an irregular margin and crusting or scaling surface. BP may be associated with other internal malignancies like leukaemia and lung cancer, hence a thorough evaluation is necessary (60, 61).

Anal cancer

Similar to cervical cancers, anal cancers are also associated with oncogenic HPVs. In men, the majority of anal cancers are attributed to HPV, especially types 16 and 18. In MSM, the anal canal is the anatomical site with the most abundant load of HPV DNA. Hence, anal cancers are the most common HPV-related cancers in the MSM, accounting for 80–85% of anal malignancies (62, 63). Furthermore, the risk of this HPV-associated malignancy is the highest in the MSM who are HIV infected. This confirms the important role of efficient immunity in controlling HPV. Anal cancers can reflect an immune-deficient condition. SCCs comprise most cases of invasive anal carcinoma. Initial manifestations of anal cancers include dermatitis, fissures, haemorrhoids, fistulas, discharges, rectalgia, and fecal incontinence. However, they later develop mass lesions in the anal canal. In addition, abscess formation, inguinal lymphadenopathy, and metastatic lesions in the bones, lungs, and eyes may be detected in the advanced stages (64, 65).

Head& neck cancer

HPV is one of the predisposing factors for head and neck cancers (HNCs) in both genders. In general, HNCs include malignancies that occur in the oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx, and salivary glands (66). Oropharyngeal cancers that are mostly HPV-associated usually involve the palatine tonsils and the base of the tongue. Risk factors in men include high-risk sexual behaviors like homosexuality, having oral sex, and multiple sexual partners (67). HPV-associated head and neck cancers often happen in younger men with high-risk sexual affairs and are usually related to poorly differentiated or basaloid histopathology. Moreover, similar to anogenital cancers, HPV-associated oral cancers are also related to immunosuppression (68, 69). It is postulated that smoking can increase HPV persistence in the oral cavity among men, hence promoting oropharyngeal cancer development (70).

Oral florid papillomatosis (OFP) is another HPV-associated disorder that is the result of verruciform and papillomatous growths that lead to plaque formation. It is manifested as multiple squamous papillary nodules and large verrucae usually on the buccal mucosa, alveolar-gingivae, and paranasal sinuses. HPV serotypes 6, 11, and 16 have been implicated in the pathogenesis of OFP. It is considered a low-grade mucosal verrucous carcinoma

which can progress to SCC (71).

Skin cancer

HPV has been implicated in the development of several skin cancers, either premalignant or malignant ones. Actinic keratosis (AK) is a premalignant cutaneous lesion that most commonly results from ultraviolet (UV) DNA damage. It has been postulated that HPV not only is a risk factor for recurrence in actinic keratosis but also has a carcinogenic role in triggering AK progression to cutaneous squamous cell carcinoma (72).

Keratoacanthomas are distinct benign skin tumors with occasional infiltration and cellular atypia. An etiology of HPV has been suggested for this premalignant cutaneous lesion (73).

Epidermodysplasia verruciformis (EV) is a genetic cutaneous disorder manifested as flat warty lesions on the hands, limbs, face, and neck. This rare autosomal recessive disorder usually presents in childhood and may lead to malignant transformation in adulthood, especially in sun-exposed areas. It is manifested as disseminated, persistent, flat warts and macular lesions with irregular margins. The association of HPV and cutaneous malignancies had initially been demonstrated in epidermodysplasia verruciformis (EV) (74, 75). Later, the contribution of HPV to other skin cancers became evident.

Cutaneous squamous cell skin carcinoma has been attributed to HPV infection both in immunocompromised and immunocompetent individuals. Other nonmelanoma skin cancers (NMSC) like basal cell carcinoma (BCC) and Bowen's disease have also been linked to HPV infection. However, this association is stronger in SCC than in BCC, especially in immunocompromised individuals (76). In addition, high-risk HPVs have been demonstrated in dysplastic melanocytic naevi and primary melanoma (77, 78).

HPV and HIV coinfection

HIV and HPV interact in various ways. HIV-infected individuals, particularly MSM, are at increased risk of other STDs like *Neisseria meningitidis*, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, and HPV infections. HPV infection is present in more than 90% of HIV-positive individuals. HIV-associated immunosuppression might increase the risk of acquiring HPV infection (79, 80). HIV patients can carry multiple HPV serotypes at the same time, which might lead to increased risk of persistence, reactivation, and progression to abnormalities like anal intraepithelial neoplasia (AIN) (80). Furthermore, HPV-related malignancies like anal and oral cancers are increasing, particularly in immunosuppressed individuals including HIV-infected patients. It is important to know that this increased risk of HPV-related cancers may not be affected by the reconstitution of the immune system with antiretroviral therapies (ART) (81). Oropharyngeal cancers are much more common in HIV and HPV

coinfection than either infection alone (82). Anal cancer is among the non-AIDS-defining cancers (NADCs). This type of malignancy is more common in HIV-infected individuals who are MSM even those on highly active antiretroviral therapy (HAART) (83). All of these issues acknowledge the essential need to get vaccinated against HPV in HIV-infected patients.

Vaccine

Vaccination is one of the most effective means of preventing infectious diseases. Accordingly, HPV infection and its associated disorders can be readily prevented through scheduled vaccination. Although HPV vaccination can prevent infection and disease in both genders, vaccine programs have primarily targeted the female to be vaccinated against HPV. However, despite the limited data, men have been the main victims of HPV-associated diseases and infections (84). The US Food and Drug Administration (FDA) approved HPV vaccination for the male population in 2009. The quadrivalent HPV vaccine (HPV4) can decrease HPV carriage and disease in men. Hence, the American Committee for Immunization Practices (ACIP) has recommended this vaccine for boys aged 11–12 years with a catch-up of 13–26 years of age. This recommendation is stronger for MSM and those who have high-risk sexual behaviors, for whom HPV4 is advised to be administered (2). The inclusion of the male population in the vaccination program has significantly decreased HPV-related disorders and deaths and improved the quality of life in men. However, HPV vaccine acceptability has always been lower among men than women (85). The HPV vaccination in men can protect against genital warts and respiratory papillomas. In addition, it leads to decreased HPV infection and its associated disorders in women through lowering the transmission and consequently prevention of HPV-related cancers in both men and women (86–88). HPV vaccines are not only effective in preventing cervical cancers but also reduce anal and oral cancers. Moreover, it can prevent anal epithelial neoplasias (AINs) which are precursors of anal cancers (89).

Conclusions

HPV in men has been less discussed in the literature, probably because of its benign course in most cases. Genital HPV infections in men are less persistent than in women and usually clear up within 12 months. However, recent studies have shown a prominent role of HPV in anogenital warts and malignancies in men. Moreover, positive HPV diagnoses are frequent among patients receiving assisted reproductive services and recent studies suggest that HPV can decrease sperm motility through binding to the head of the human spermatozoa, and the viral load of HPV in the semen is significantly associated with reduced sperm quality

which means the role of HPV infection in male infertility. Hence, the prompt inclusion of the male population in the vaccination program will not only reduce HPV-related disorders, infertility, and mortality in men but also improve the quality of life of women, considering the main route of virus transmission.

Authors' contributions

All authors contributed to the preparation of data and finalization of this article.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Data availability

Data will be provided on request.

Abbreviations

ACIP	American Committee for Immunization Practices
AIN	Anal intraepithelial neoplasia
ART	Antiretroviral therapies
BD	Bowen's disease
EQ	Erythroplasia Queyrat
EV	Epidermodysplasia verruciformis
FDA	Food and Drug Administration
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HNCs	Head and neck cancers
HPV	Human papilloma virus
NADCs	Non-AIDS-defining cancers
OPF	Oral florid papillomatosis
PIN	Penile intraepithelial neoplasia
PIN	Penile intraepithelial neoplasia
STD	Sexually transmitted disease
UV	Ultraviolet

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