Chapter

Human Papillomavirus (HPV) Infection in Males: A Need for More Awareness

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Abstract

Globally, human papillomavirus (HPV) is the most common viral sexually transmitted pathogen, which is significantly associated with high morbidity and mortality in both sexes. Except those vaccinated, virtually all sexually active individuals will be infected with HPV in their lifetime. Although most HPV infections are transient, association with anogenital warts, cervical, penile, and other malignancies have been reported. HPV can be transmitted from one person to another through contact especially during sexual contact including anal, vaginal, or oral. Although HPV infection affects both males and females, its causal association with cervical cancer has made most literature to be mainly on females. In view of its sexual transmissibility and the increasing prevalence of HPV-related malignancies among males worldwide, there is need for more awareness on the infection in males. Most developed countries offer HPV vaccination for girls, but vaccine recommendations for boys are still relatively uncommon especially in developing countries where the burden of HPV-related malignancies is still very high. The current discourse highlights the need for increased awareness on HPV vaccination among this neglected gender group.

Keywords: human papillomavirus, males, awareness, anogenital, malignancies

1. Introduction

The concern on male HPV infection stems from both the disease burden and the potential risk of its transmission from males to females [1]. To date, prevalence and incidence of HPV infection in males is much less established compared to females [2]. In males, infection with high-risk HPVs is associated with penile intraepithelial neoplasia (PIN) in addition to others such as anal and oropharyngeal cancers [3, 4]. The incidence of HPV-related anal and oral cancers is generally on the increase but especially among individuals who are immunocompromised [1, 5]. In some developed nations, the prevalence of oropharyngeal/anal squamous cell carcinoma (SCC) among both men and women was reported to be on the increase [4]. The range of HPV prevalence among males is between 1.3 and 72.9% and is minimally affected by age as against the observed trend in females. Females tend to have a higher probability of acquiring high-risk genotypes compared to males whose risk for acquiring both high- and low-risk types appear to be similar [6].

Based on successes recorded in females, HPV vaccination among males was introduced and had shown much promises so far [6]. However, acceptability/uptake and awareness of HPV vaccines among different male populations have continued to face challenges even in some developed countries despite the successes in female programs [7–12]. This is worst in developing nations where even female immunization programs are almost nonexistent [13–15].

2. Historical background

Over a century ago, an increased risk for the development of cervical cancer was observed among prostitutes as against nuns. Subsequently in the early 1980s, the suspected linkage between sexual behavior and the development of cervical neoplasia was confirmed to be due to genital infection with HPV [16]. In 1983 and 1984, HPV 16 and 18 were isolated from cervical cancer specimens [17].

Currently, there are more than 300 human and animal papillomaviruses which constitute the *Papillomaviridae* family out of which over 200 have been described and organized into 5 phylogenetic genera named alpha, beta, gamma, mu, and nu [17, 18]. However, even as at 1970, it was assumed that there was only one HPV which was thought to be the cause of various warty lesions that infected different tissue sites in humans. Initial perceptions about HPV were mainly as the etiology of transient and trivial/unsightly excrescences. This assertion was changed with the advent of recombinant DNA technology which revealed the presence and effect of multiple HPV types with tropism for different mucosal/cutaneous squamous surfaces and associated development of warts. It further became obvious that some of the HPV genotypes infecting the anogenital tract were oncogenic and causally associated with cancer of the uterine cervix [19].

Evolution of papillomaviruses have been closely linked with their relevant animal hosts over millions of years. The life cycle of HPV genotypes also reflects the differentiation of its respective epithelial target including different parts of the skin and oropharyngeal mucosa [20]. In view of the assertion that humans evolved from nonhuman primates in Africa, origin of HPV types was also linked to Africa phylogenetically. Additionally, the phylogeny of HPV variants (three lineages: European, Asian American, and African) reflects the migration patterns of *Homo sapiens*. The spectrum of diseases associated with HPV infections (anogenital malignancies and warty lesions) have also accompanied humans throughout evolution [21].

3. HPV structure and morphology

HPVs belongs to *Papillomaviridae* family which comprises a diverse family of non-enveloped, small circular double-stranded DNA viruses of about 55 nm in size and consists of about 72 capsomeres [22–24]. The HPV genome is made up of 8000 base pairs. They are relatively stable and could maintain infectivity over a long period in moist environment [25].

It has three functional coding regions: E, a gene coding early viral function; L, a gene coding late viral function; and LCR, a long control region (also referred to as noncoding regulatory region "NCR" or "upstream regulatory region" (URR)) which lies between E and L [24, 26]. Genes are designated as "early" or "late" on the basis of their functional action timing [16].

The genome is organized into eight open reading frames: a long local control region, six early proteins (E1, E2, and E4–E7) and two late proteins (L1 and L2). E1, E2, E5, E6, and E7 are expressed early in the differentiation, E4 is expressed

throughout, and L1 and L2 are expressed during the final stages of differentiation [20]. The early genes are involved in DNA replication, transcriptional regulation, and cellular transformation, whereas late genes encode the viral capsid proteins (the capsomeres) which accounts for 80% of the viral particle [3, 16, 25, 27].

Two of the viral proteins, E6 and E7, are consistently expressed in HPV-positive cervical cancers. The high-risk HPV E6/E7 expression is rate limiting for cervical cancer development. These oncoproteins contribute to tumor initiation and also play important roles in malignant progression through the induction of genomic instability and other mechanisms [26]. E1 and E2 play direct roles in viral replication [3]. The viral gene expression also correlates with the differentiation stages of the epithelium [16]. The viral genome is maintained at the basal layer of the epithelium, where HPV infection is established [20]. The virally infected cells differentiate as they move upward from the basal layer toward the surface of the epithelium with associated induction of high-level viral replication and gene expression followed by virion assembly/release [18].

The phylogeny of HPV variants revealed three lineages: European, Asian American, and African. The evolutionary process stemmed from greater adaptability of certain intra-type HPV variants to specific human population groups. They remained stable viruses over time and have neither changed host species nor reorganized themselves. HPVs have maintained their basic genomic organization for a period exceeding 100-million-year period [21].

4. HPV genotypes

More than 200 types of HPV have been identified by DNA sequence data, and 85 HPV genotypes have been well characterized to date [25]. Classified under the *Alpha papillomavirus* genus are about 40 HPV genotypes that commonly infect the genital tract and are subdivided in to low- and high-risk types [28]. The high-risk types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Others which include HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89, and CP6108 are the low-risk group and are frequently detected in benign lesions such as condylomata acuminata [22, 23, 29]. HPV types 26, 53, 66, 68, 73, and 82 are considered as probably carcinogenic [29, 30]. However, HPV types 68, 73, and 82 were occasionally grouped under the high-risk types, while HPVs 34, 57, and 83 are of undetermined risk [30]. Another approach to classification of HPVs on the basis of different oncogenic potentials grouped them in to high-risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), intermediate-risk (HPV 26, 53, and 66) and low-risk (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81) types [31].

The distinction between high- and low-risk HPV genotypes is constantly being revised as greater details about the virus become clearer. It therefore follows that classification based on oncogenicity of some HPV types could change over time, with consequent implications on diagnosis and management of HPV-related infections [32].

5. Pathogenesis of HPV infection

Oncogenic human viruses generally infect, but without killing their host cells. They have the tendency to establish long-term persistent infections. Malignant progression of hrHPV-associated lesions usually occurs in the presence of other risk factors, such as decreased immune function and/or after a long latency period after other genomic alterations in the host cell DNA has occurred [17].

In biological evolution, HPVs are successful infectious agents which induce persistent infections without frequent and serious complications for the host and shed virions for transmission to other naive individuals. They avoid the host's defense systems through several processes which include lack of viral-induced cytolysis or necrosis and absence of inflammation, lack of blood-borne or viremic phase, poor access to vascular and lymphatic channels and to lymph nodes where immune responses are initiated, and having mechanisms for inhibiting interferon synthesis and receptor signaling [21].

5.1 Cell cycle and HPV-induced carcinogenesis

Series of phases including the G0, G1, S, G2, and M constitute normal cell cycle which are modulated by cell cycle regulatory genes. These phases are under strict control during transition and are also well coordinated during progression with different cell signals. Cyclin-dependent kinases (CDKs), CDK inhibitors, p53, p27, and p21, and the retinoblastoma gene product (Rb) are the main regulators of cell progression with p53 and Rb as the two most important tumor suppressor genes in the human body. Minor mutations could alter the concentration of p53 with resultant arrest of mitosis and failure of DNA repair, while major damage is associated with apoptosis [16].

The life cycle of HPV follows the differentiation of keratinocytes and begins with expression of E6 and E7 oncoproteins by the virus in the affected epithelium. In the acute phase, viral DNA which is usually present as an episome within the affected host cell is cleared by IFN-β. However, cells with integrated HPV DNA are resistant to this antiviral effect, and the virus completes its life cycle and produces new infectious viral particles, using the host's DNA and RNA polymerase [16, 19]. This mechanism of viral reproduction which is tightly controlled by E2 and regulated by E6 and E7 does not cause cancer [16]. But in high-risk HPVs, T-cell responses to E2 and E6 are lost or reduced, and E7 proteins bind to pRB more efficiently than in low-risk HPV. The E2 oncoprotein usually functions as a transcriptional repressor of the promoter that drives expression of both the E6 and E7 genes. With abrogation of E2 expression, there is dysregulation in E6/E7 expression due to loss of the transcriptional control and resultant suppression of the killer defense response and loss of p53-induced apoptosis increasing chromosomal instability and cancer development [3, 19, 26].

6. Epidemiology of HPV infection

HPVs remain a serious global public health problem due to their association with anogenital/oral cancers and warts [22]. Approximately 630 million individuals are infected with HPV worldwide, while 30 million genital HPV infections are diagnosed each year. It is estimated that in the United States alone, there are 20 million people infected with HPV, and 6.2 million individuals become newly infected each year. Over half of sexually active men and women are infected at some point during their lives [26, 30]. The overall HPV transmission rate was estimated to be 58.8 per 100 person-years from penis-to-cervix and 208.8 per 100 person-years from cervix-to-penis [2]. The estimated total cost for the clinical management of HPV-related diseases in the United States is greater than $3 billion per year; the majority of this sum is spent on the management and treatment of premalignant lesions [26].

The widespread presence and acceptability of many risk factors (including early/polygamous marriages, high parity, and poverty) have made HPV infection to

be endemic in Africa. This is due to both increase in acquisition and promotion of the oncogenic effect of the virus [33].

About 15 HPV types have been classified as oncogenic. Among the oncogenic viruses, HPV 16 and HPV 18 are the most prevalent [20]. HPV types tend to be transmitted together, resulting in a high proportion (20–30%) of concurrent infections with different types [20]. HPV 16 is the most prevalent type worldwide. HPV 18, 45, 31, and 33 are the next most prevalent types [23].

HPVs have both pronounced tropism for certain epithelial cells in addition to being specie specific and have been detected in a wide range of animal species [3]. The hrHPVs are causally related to anogenital cancers including cervix, vulva, and anus in women and penis and anus in men [19, 34]. Low-risk HPV types 6 and 11 are most commonly detected in genital and anal warts, representing 90% of these cases [22].

Although the predominant mode of viral transmission occurs through sexual contact, HPV also has been found in individuals prior to first coitus suggesting the possibility of vertical transmission from mother to child [35]. However, the viral mode transmission in children is still being elucidated [36].

6.1 Risk factors for HPV infection in males

Several studies [37–41] have reported different factors significantly associated with HPV infections which include current and past sexual behavior (including lifetime number of female sex partners (FSPs)), MSM, female partner with positive cervical HPV infection, early sexual debut, absence of circumcision, lack of condom use, immunosuppression, history of other sexually transmitted infections, race/ethnicity, educational level, and smoking cigarettes.

6.2 Prevalence of HPV in males

Different studies have reported varying prevalence rates from different countries. In the United States, prevalence was found to be 65.4% for any HPV, 29.2% for oncogenic HPV, and 36.3% for non-oncogenic HPV among males [37]. Another study revealed a prevalence of 49% of any type of HPV and 35% of hrHPV [38]. Overall prevalence in Europe was found to be 12.4–28.5% in general population and 30.9% in high-risk population [42]. Approximately 90% of anal cancers are associated with HPVs out of which 90% are due to types 16 and 18. This is in contrast to cervical cancers in which about 70% are due to these predominant high-risk genotypes [43]. Although women have higher rates of anal cancer than men in the general population, the greatest risk is seen among HIV-infected men who have sex with men (MSM) who also have higher prevalence of anal HPV [43–45].

Variation in prevalence has also been observed based on differences in the infected sites. In a Greek population, it was highest at anal sites (33%) compared with 23% at penile sites and 4% at oral sites [39]. In another study, the prevalence of HPV infection was 73% at anal site, 26% at penile site, and 16% at oral site [46]. MSM had higher prevalence (84 vs. 42%) at anal site and a lower clearance rate than heterosexuals [46]. Globally, HPV DNA was detected in 33.1% of penile cancers [47]. Prevalence of HPV-related malignancies have been found to be 22.4, 4.4, and 3.5% for oropharynx, oral cavity, and laryngeal cancers, respectively [48].

In Africa, the prevalence of anal HPV was 69.1% in Central Africa and 40.6% in Nigeria [49, 50]. Up to 82.7% of hrHPV was reported in Central Africa out of which 52.0% were multiple infections and more prevalent among HIV-positive MSM [49]. The prevalence of anal hrHPV among HIV-positive MSM was 91.1% in Nigeria [50].

In South Africa, HPV genotypes were detected in 72.8, 11.5, and 15.3% of anal, oropharyngeal, and urine specimens, respectively [51].

7. HPV-associated diseases in men

Neoplasias associated with HPV in men include genital warts, penile, anal, and oropharyngeal and other head and neck cancers [43]. Although there were studies suggesting possible association between HPV and prostate cancer in males, none have reached universal acceptability [52, 53]. Recently, a causal association between hrHPV and HPV-related multiphenotypic sinonasal carcinoma (HMSC) has been described [54–57]. Other malignancies associated with HPV include SCC of the skin/nose tip and skin appendages [58–62]. Association between HPV and bladder cancer even though without uniform conclusions has also been reported in several studies [63–69].

8. Diagnosis of HPV infection

Specimens for detecting HPV in males could be collected from any or all of the following parts of the genital tract, glans, coronal, penile shaft, scrotum, and anal region [43]. Other specimens could be based on the part of the body affected.

The diagnosis of human papillomavirus (HPV) can be inferred from morphologic, serologic, and clinical findings. HPVs cannot be cultured, and the detection of virus relies on a variety of techniques used in immunology, serology, and molecular biology [70].

9. Immunity against HPV

Men do not develop adequate immune responses to maintain protection. Studies have shown that at all ages, antibody levels are lower in men than women [43]. Natural history studies of HPV in men show that HPV clears quite rapidly compared to females [43].

9.1 Natural immunity against HPV

Despite HPV's ability to evade the host's immune system and to downregulate innate immunity, a primary HPV infection is cleared naturally in approximately 90% of cases within 2 years mainly because of cell-mediated immune responses directed against the early HPV proteins particularly E2 and E6. Seroconversion only occurs in about 60% of women, and men are much less likely to have HPV antibodies detected. CD4+ T-helper cells are crucial in avoiding persistent HPV infection, as well as inducing wart regression [2, 19, 21].

The host's immune response to HPV infection (humoral immunity, mainly IgG) is usually slow, weak, wane over time, and varied considerably with many women not seroconverting [17, 19]. Generally, close to half of the individuals seroconvert to L1 protein of HPV 16, 18, or 6 within 18 months. Other HPV antigens [E1, E2, E6, and L2] do not evoke any antibody responses in patients with acute or persistent HPV infection [21]. Natural infection-elicited antibodies may not provide complete protection to HPV over time. A recent WHO position paper stated that host antibodies, mostly directed against the viral L1 protein, do not necessarily protect against subsequent infection by the same HPV genotype [21].

9.2 Immune response to HPV vaccine

The evidence from animal papillomavirus infections, including some of the earliest published works, showed very clearly that neutralizing antibodies were protective. The experiments showed that if rabbits were infected systemically with the cottontail rabbit papillomavirus (CRPV) by direct injection of virus; papillomas did not arise on the skin of the challenged animals, and neutralizing antibodies were generated. The animals were completely resistant to subsequent viral challenge by abrasion of the epithelium [19]. Immunization also facilitates the regression of existing lesions [25].

Technological advancement leading to production of virus-like particles (VLPs) is the prelude to development of effective HPV vaccine. Highly immunogenic VLPs capable of mimicking natural infection and eliciting high titers of long-lasting virus-neutralizing antibodies (significantly more than natural infection) could be generated using recombinant DNA. This is because the antigenic dose in VLPs is much higher than what obtains in natural infection as the capsids are directly exposed to systemic immune responses. This leads to better quality and the quantity of the immune response generated by vaccines compared to natural infection. The intramuscular administration of HPV vaccines leads to rapid access to the local lymph nodes with subsequent evasion of immune avoidance strategies of the virus [19, 21].

A rapid, potent, and sustained immunologic response due to the administration of both quadrivalent vaccine (targeting HPV 6, 11, 16, and 18) and a bivalent vaccine (targeting HPV 16 and 18) has been reported. These vaccines can elicit an immunological response against the two most common oncogenic types (16 and 18) but not against all the high-risk types except for cross-neutralizing antibodies in some individuals [19, 21]. The duration of protection afforded by the vaccines revealed greater than 98% protection over a 5- to 6.4-year period against HPV 16, 18, 6, and 11 [19].

9.3 The HPV vaccines

Strategies for the control and treatment of genital HPV infections are a matter of high priority typically because of their relationship with anogenital and other malignancies. Traditionally, vaccines have remained a cost-effective means of preventing many viral diseases including HPV in recent times [19]. Sexually naïve adolescents are routinely being vaccinated in many countries as recommended by the World Health Organization (WHO). The effectiveness of these vaccines is most pronounced in unexposed as against previously infected individuals [24]. This is because the current vaccines are not therapeutic against existing infections or lesions, and cross-protection against other HPV types is partial or nonexistent. Therefore, the greatest public health benefit of the current HPV vaccines is when given at an age before sexual debut [20].

Recommendation for routine vaccination of adolescents at ages 11 or 12 years has been in place.

Since 2006 for females and since 2011 for males [71]. The United States was the first country to adopt a gender-neutral routine HPV immunization policy in the year 2011 for both males and females [72]. The time of commencement of vaccine administration determines the minimum number of doses recommended based on the age of recipient. Two doses are recommended for those who initiate between ages 9 and 14 years, while three doses are for those initiating at ages 15 through 26 years and for immunocompromised individuals [71]. A three-dose regimen could be for all the three vaccines at time intervals of 0, 1, or 2 and 6 months [71].

The effect of all vaccine types is higher for HPV 16-/18-associated lesions than for others. It is also greater in those who are high-risk HPV negative at initiation compared to those with unknown HPV status [73]. The effect of HPV vaccination in males is also moderate against persistent anogenital infection and high-grade anal intraepithelial lesions if given to HPV infected males as against those without the infection. This supports a recommendation for vaccination of boys also before sexual debut so as to ensure maximum protection [74].

10. Conclusion

Although global attention has been more toward HPV infection in females, it is equally important in males due to increasing prevalence especially among the high-risk populations. Many developed countries have commenced routine immunization of males for HPV but virtually no low-income country followed the same pathway. There is need for more awareness especially in developing countries where the burden of HPV is highest.

11. Future perspectives on HPV in males

The current trend suggests a relatively low level of awareness on HPV-associated diseases in males and acceptability of vaccination against the virus in most countries but worst in developing nations [75–79]. There are efforts from varying perspectives by different groups to improve the current situation based on findings from some studies [80, 81]. Technological advancements will see the use of various means such as mobile computer applications to influence the knowledge about HPV and acceptability/uptake of the vaccines [82]. There might be a need for changes in policies even in developed countries to accommodate more challenges as they unfold [83]. Culture and beliefs may be explored to further strengthen the level of awareness and acceptability of HPV vaccines in different populations [84]. Design and development of more potent and user-friendly vaccines for both preventive and therapeutic purposes will continue with resultant wider acceptability/improved safety [31]. With the successes observed in countries who have implemented structured programs for HPV vaccination, more nations may embrace similar/improved approaches for better outcomes [85].

Abbreviations

CIN	cervical intraepithelial neoplasia
CDKs	cyclin-dependent kinases
CRPV	cottontail rabbit papillomavirus
DNA	deoxyribonucleic acid
FSPs	female sex partners
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	high risk
LCR	long control region
LR	low risk
MSM	men having sex with men
NCR	noncoding regulatory region
PIN	penile intraepithelial neoplasia

SCC	squamous cell carcinoma
STIs	sexually transmitted infections
URR	upstream regulatory region
VLPs	virus-like particles
WHO	World Health Organization

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