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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 into 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 into 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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References

- [1] Palefsky JM. Human papillomavirus-related disease in men: Not just a women's issue. *Journal of Adolescent Health*. 2010;**46**(4 Suppl):S12-S19
- [2] Veldhuijzen NJ, Snijders PJ, Reiss P, Meijer CJ, van de Wijgert JH. Factors affecting transmission of mucosal human papillomavirus. *The Lancet Infectious Diseases*. 2010;**10**(12):862-874
- [3] Münger K. Papillomaviruses. In: *Encyclopedia of Cancer*. Vol. 3. USA: Elsevier Science; 2002. pp. 393-401
- [4] Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers—United States, 1999-2015. *Morbidity and Mortality Weekly Report*. 2018;**67**(33): 918-924
- [5] Chikandiwa A, Pisa PT, Sengayi M, Singh E, Delany-Moretlwe S. Patterns and trends of HPV-related cancers other than cervix in South Africa from 1994-2013. *Cancer Epidemiology*. 2018;**58**:121-129
- [6] Lenzi A et al. Rome consensus conference-statement; human papilloma virus diseases in males. *BMC Public Health*. 2013;**13**:117
- [7] Forster AS, Gilson R. Challenges to optimising uptake and delivery of a HPV vaccination programme for men who have sex with men. *Human Vaccines & Immunotherapeutics*. Article in press; published online 30th January 2019
- [8] Pollock KG, Wallace LA, Wigglesworth S, McMaster D, Steedman N. HPV vaccine uptake in men who have sex with men in Scotland. *Vaccine*. Article in press; available online 10th December 2018
- [9] Grandahl M, Nevéus T, Dalianis T, Larsson M, Tydén T, Stenhammar C. 'I also want to be vaccinated!'—adolescent boys' awareness and thoughts, perceived benefits, information sources, and intention to be vaccinated against human papillomavirus (HPV). *Human Vaccines & Immunotherapeutics*. Article in press; published online 20th December 2018
- [10] Gottvall M, Stenhammar C, Grandahl M. Parents' views of including young boys in the Swedish national school-based HPV vaccination programme: A qualitative study. *BMJ Open*. 2017;**7**(2):e014255
- [11] Holman DM, Benard V, Roland KB, Watson M, Liddon N, Stokley S. Barriers to human papillomavirus vaccination among US adolescents. *JAMA Pediatrics*. 2014;**168**(1):76-82
- [12] Sherman SM, Nailer E. Attitudes towards and knowledge about human papillomavirus (HPV) and the HPV vaccination in parents of teenage boys in the UK. *PLoS One*. 2018;**13**(4):e0195801
- [13] Faneye AO, Adeiga AA, Awoderu OB, Fayemiwo AS. Human papilloma virus vaccine awareness and vaccination history in patients attending STI clinics in Lagos and Ibadan, Nigeria. *Archives of Basic and Applied Medicine*. 2018;**6**(1):95-98
- [14] Bisi-Onyemaechi AI, Chikani UN, Nduagubam O. Reducing incidence of cervical cancer: Knowledge and attitudes of caregivers in Nigerian city to human papilloma virus vaccination. *Infectious Agents and Cancer*. 2018;**13**:1-6
- [15] Muhwezi WW, Banura C, Turiho AK, Mirembe F. Parents' knowledge, risk perception and willingness to allow young males to receive human

papillomavirus (HPV) vaccines in Uganda. PLoS One. 2014;**9**(9):e106686

- [16] Tjalma WAA, Van Waes TR, Van den Eeden LEM, Bogers JJPM. Role of human papillomavirus in the carcinogenesis of squamous cell carcinoma and adenocarcinoma of the cervix. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2005;**19**(4):469-483
- [17] McLaughlin-Drubin ME, Munger K. Viruses associated with human cancer. Biochimica et Biophysica Acta. 2008;**1782**(3):127-150
- [18] McBride AA. Oncogenic human papillomaviruses. Philosophical Transactions of the Royal Society B: Biological Sciences. 2017;**372**(1732):20160273
- [19] Stanley M. Immunobiology of HPV and HPV vaccines. Gynecologic Oncology. 2008;**109**(2 Suppl):S15-S21
- [20] Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. The Lancet. 2007;**370**(9590):890-907
- [21] Mariani L, Venuti A. HPV vaccine: An overview of immune response, clinical protection, and new approaches for the future. Journal of Translational Medicine. 2010;**8**:105
- [22] Seaman WT et al. Detection and quantitation of HPV in genital and oral tissues and fluids by real time PCR. Virology Journal. 2010;**7**(1):194
- [23] Zandi K et al. Prevalence of various human papillomavirus (HPV) genotypes among women who subjected to routine Pap smear test in Bushehr city (South west of Iran) 2008-2009. Virology Journal. 2010;**7**(1):65
- [24] Faridi R, Zahra A, Khan K, Idrees M. Oncogenic potential of human

papillomavirus (HPV) and its relation with cervical cancer. Virology Journal. 2011;**8**(1):269

- [25] Cheng W. Human papilloma virus vaccine for cervical cancer: Where are we now? Taiwanese Journal of Obstetrics & Gynecology. 2005;**44**(3):232-241
- [26] McLaughlin-Drubin ME, Munger K. Oncogenic activities of human papillomaviruses. Virus Research. 2009;**143**(2):195-208
- [27] Margaret S. HPV vaccines. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(2):279-293
- [28] Sánchez-Anguiano LF, Alvarado-Esquivel C, Reyes-Romero MA, Carrera-Rodríguez M. Human papillomavirus infections in women seeking cervical Papanicolaou cytology of Durango, Mexico: Prevalence and genotypes. BMC Infectious Diseases. 2006;**6**(1):27
- [29] Mariani L et al. Human papilloma virus prevalence and type-specific relative contribution in invasive cervical cancer specimens from Italy. BMC Cancer. 2010;**10**(1):259
- [30] Burd EM. Human papillomavirus detection and utility of testing. Clinical Microbiology Newsletter. 2007;**29**(21):159-167
- [31] Dadar M et al. Advances in designing and developing vaccines, drugs and therapeutic approaches to counter human papilloma virus. Frontiers in Immunology. 2018;**9**:2478
- [32] Barzon L, Giorgi C, Buonaguro FM, Palù G, Italian Society for Virology. Guidelines of the Italian society for virology on HPV testing and vaccination for cervical cancer prevention. Infectious Agents and Cancer. 2008;**3**(1):14

- [33] Anorlu RI. Cervical cancer: The sub-Saharan African perspective. *Reproductive Health Matters*. 2008;**16**(32):41-49
- [34] Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of human papillomavirus (HPV) disease: A critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infectious Diseases*. 2009;**9**(1):119
- [35] Smith EM, Parker MA, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Evidence for vertical transmission of HPV from mothers to infants. *Infectious Diseases in Obstetrics and Gynecology*. 2010;**2010**:326369
- [36] Castellsagué X et al. Human papillomavirus (HPV) infection in pregnant women and mother-to-child transmission of genital HPV genotypes: A prospective study in Spain. *BMC Infectious Diseases*. 2009;**9**(1):74
- [37] Nielson CM et al. Risk factors for anogenital human papillomavirus infection in men. *The Journal of Infectious Diseases*. 2007;**196**(8):1137-1145
- [38] Rodríguez-Álvarez MI, Gómez-Urquiza JL, Husein-El Ahmed H, Albendín-García L, Gómez-Salgado J, Cañadas-De la Fuente GA. Prevalence and risk factors of human papillomavirus in male patients: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*. 2018;**15**(10):2210
- [39] Tsikis S et al. Risk factors, prevalence, and site concordance of human papillomavirus in high-risk Greek men. *European Journal of Cancer Prevention*. 2018;**27**(5):514-520
- [40] Pan L-J, Ma J-H, Zhang F-L, Pan F, Zhao D, Zhang X-Y. HPV infection of the external genitalia in men whose female partners have cervical HPV infection. *Zhonghua Nan Ke Xue*. 2018;**24**(6):516-519
- [41] Huang L-L et al. Circumcision reduces the incidence of human papillomavirus infection in men. *Zhonghua Nan Ke Xue*. 2018;**24**(4):327-330
- [42] Hebnes JB, Olesen TB, Duun-Henriksen AK, Munk C, Norrild B, Kjaer SK. Prevalence of genital human papillomavirus among men in Europe: Systematic review and meta-analysis. *The Journal of Sexual Medicine*. 2014;**11**(11):2630-2644
- [43] Moscicki A-B, Palefsky JM. HPV in men: An update. *Journal of Lower Genital Tract Disease*. 2011;**15**(3):231-234
- [44] Ong JJ et al. Incidence, clearance and persistence of anal HPV in men who have sex with men living with HIV: Implications for HPV vaccination. *Sexually Transmitted Diseases*. 2018. Published online 30th November 2018 (epub ahead of print)
- [45] Lin C-C et al. Human papillomavirus prevalence and behavioral risk factors among HIV-infected and HIV-uninfected men who have sex with men in Taiwan. *Medicine (Baltimore)*. 2018;**97**(45):e13201
- [46] Videla S et al. Natural history of human papillomavirus infections involving anal, penile, and oral sites among HIV-positive men. *Sexually Transmitted Diseases*. 2013;**40**(1):3-10
- [47] Alemany L et al. Role of human papillomavirus in penile carcinomas worldwide. *European Urology*. 2016;**69**(5):953-961
- [48] Castellsagué X et al. HPV involvement in head and neck cancers: Comprehensive assessment of

biomarkers in 3680 patients. *Journal of the National Cancer Institute*. 2016;**108**(6):403

[49] Mboumba Bouassa R-S et al. Unusual and unique distribution of anal high-risk human papillomavirus (HR-HPV) among men who have sex with men living in the Central African Republic. *PLoS One*. 2018;**13**(5):e0197845

[50] Nowak RG et al. Prevalence of anal high-risk human papillomavirus infections among HIV-positive and HIV-negative men who have sex with men (MSM) in Nigeria. *Sexually Transmitted Diseases*. 2016;**43**(4):243-248

[51] Müller EE, Rebe K, Chirwa TF, Struthers H, McIntyre J, Lewis DA. The prevalence of human papillomavirus infections and associated risk factors in men-who-have-sex-with-men in Cape Town, South Africa. *BMC Infectious Diseases*. 2016;**16**(1):440

[52] Medel-Flores O et al. Association between HPV infection and prostate cancer in a Mexican population. *Genetics and Molecular Biology*. 2018;**41**(4):781-789

[53] Aydin M et al. Lack of evidence of HPV etiology of prostate cancer following radical surgery and higher frequency of the Arg/Pro genotype in turkish men with prostate cancer. *International Brazilian Journal of Urology*. 2017;**43**(1):36-46

[54] Adamane SA, Mittal N, Teni T, Pawar S, Waghole R, Bal M. Human papillomavirus-related multiphenotypic sinonasal carcinoma with unique HPV type 52 association: A case report with review of literature. *Head and Neck Pathology*. 2018;**12**(48):1-8

[55] Shah AA, Lamarre ED, Bishop JA. Human papillomavirus-related multiphenotypic sinonasal carcinoma: A case report documenting the potential

for very late tumor recurrence. *Head and Neck Pathology*. 2018;**12**(4): 623-628

[56] Bishop JA, Westra WH. Human papillomavirus-related multiphenotypic sinonasal carcinoma: An emerging tumor type with a unique microscopic appearance and a paradoxical clinical behaviour. *Oral Oncology*. 2018;**87**: 17-20

[57] Bishop JA et al. HPV-related multiphenotypic sinonasal carcinoma: An expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features. *The American Journal of Surgical Pathology*. 2017;**41**(12):1690-1701

[58] Gavioli CFB, Festa Neto C, Tying SK, Silva LL d C, de Oliveira WRP. High-risk mucosal HPV types associated with squamous cell carcinoma on the nose tip in an immunocompetent young man. *Anais Brasileiros de Dermatologia*. 2018;**93**(5):716-718

[59] Corbalán-Vélez R, Ruiz-Maciá JA, Brufau C, Carapeto FJ. Cutaneous squamous cell carcinoma and human papillomavirus. *Actas Dermo-Sifiliográficas*. 2007;**98**(9):583-593

[60] Masini C et al. Evidence for the association of human papillomavirus infection and cutaneous squamous cell carcinoma in immunocompetent individuals. *Archives of Dermatology*. 2003;**139**(7):890-894

[61] McLaughlin-Drubin ME. Human papillomaviruses and non-melanoma skin cancer. *Seminars in Oncology*. 2015;**42**(2):284-290

[62] Turowski CB, Ross AS, Cusack CA. Human papillomavirus-associated squamous cell carcinoma of the nail bed in African-American patients. *International Journal of Dermatology*. 2009;**48**(2):117-120

- [63] Javanmard B, Barghi MR, Amani D, Fallah Karkan M, Mazloomfard MM. Human papilloma virus DNA in tumor tissue and urine in different stage of bladder cancer. *Urology Journal*. 2018; ePub ahead of print 8th December 2018
- [64] Llewellyn MA et al. Defining the frequency of human papillomavirus and polyomavirus infection in urothelial bladder tumours. *Scientific Reports*. 2018;**8**:11290
- [65] Abdollahzadeh P, Madani SH, Khazaei S, Sajadimajd S, Izadi B, Najafi F. Association between human papillomavirus and transitional cell carcinoma of the bladder. *Urology Journal*. 2017;**14**(6):5047-5050
- [66] Loran OB et al. High oncogenic risk human papillomavirus and urinary bladder cancer. *Urologia*. 2017;**(3)**:60-66
- [67] Kosova IV. The role of viruses in the etiology of bladder cancer. *Urologia*. 2016;**1999**(3):100-103
- [68] Jørgensen KR, Høyer S, Sørensen MM, Jensen JB. Human papillomavirus types 44, 52, 66 and 67 detected in a woman with squamous cell carcinoma of the urinary bladder. *Scandinavian Journal of Urology*. 2017;**51**(1):85-86
- [69] Golovina DA et al. Loss of cell differentiation in HPV-associated bladder cancer. *Bulletin of Experimental Biology and Medicine*. 2016;**161**(1):96-98
- [70] Villa L, Denny L. Methods for detection of HPV infection and its clinical utility. *International Journal of Gynecology & Obstetrics*. 2006;**94**(Suppl 1):71-80
- [71] Meites E. Use of a 2-dose schedule for human papillomavirus vaccination—Updated recommendations of the advisory committee on immunization practices. *MMWR. Morbidity and Mortality Weekly Report*. 2016;**65**(49):1405-1408
- [72] Markowitz LE, Gee J, Chesson H, Stokley S. Ten years of human papillomavirus vaccination in the United States. *Academic Pediatrics*. 2018;**18**(2S):S3-S10
- [73] Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database of Systematic Reviews*. 2018;**5**:CD009069
- [74] Harder T, Wichmann O, Klug SJ, van der Sande MAB, Wiese-Posselt M. Efficacy, effectiveness and safety of vaccination against human papillomavirus in males: A systematic review. *BMC Medicine*. 2018;**16**:110
- [75] Mupandawana ET, Cross R. Attitudes towards human papillomavirus vaccination among African parents in a city in the north of England: A qualitative study. *Reproductive Health*. 2016;**13**(1):97
- [76] Oz M et al. Awareness and knowledge levels of Turkish college students about human papilloma virus infection and vaccine acceptance. *Journal of Cancer Education*. 2018;**33**(2):260-268
- [77] Schnaith AM et al. An innovative medical school curriculum to address human papillomavirus vaccine hesitancy. *Vaccine*. 2018;**36**(26):3830-3835
- [78] Mendes Lobão W et al. Low coverage of HPV vaccination in the national immunization programme in Brazil: Parental vaccine refusal or barriers in health-service based vaccine delivery? *PLoS One*. 2018;**13**(11):e0206726
- [79] Alcalá HE, Maxwell GL, Lindsay B, Keim-Malpass J, Mitchell EM,

Balkrishnan R. Examining HPV vaccination practices and differences among providers in virginia. *Journal of Cancer Education*. 2018;33(6): 1543-0154

[80] Annual Cancer Focus Northern Ireland (NI) Men's Health Conference. Urgent action on HPV vaccine needed to protect boys. *BDJ*. 2018;225:911

[81] Koplas PA, Braswell J, Saray Smalls T. Uptake of HPV vaccine in traditional-age undergraduate students: Knowledge, behaviors, and barriers. *Journal of American College Health*. 2018:1-10. Published online 5 November 2018

[82] Cates JR et al. Developing a serious videogame for preteens to motivate HPV vaccination decision making: Land of secret gardens. *Games for Health Journal*. 2018;7(1):51-66

[83] Schneede P. One decade of HPV vaccination in Germany. *Urologe A*. 2017;56(6):728-733

[84] Lai D et al. Diverse families' experiences with HPV vaccine information sources: A community-based participatory approach. *Journal of Community Health*. 2017;42(2):400-412

[85] Patel C et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: What additional disease burden will a nonavalent vaccine prevent? *Eurosurveillance*. 2018;23(41):1700737