

Human papillomavirus (HPV) infection: a Mozambique overview

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Abstract Human Papillomavirus is agent of the most common sexually transmitted disease which is able to infect mucosal and cutaneous membranes of the anogenital region, upper aerodigestive tract, and other head and neck mucosal regions. Although mainly HPV infection can be asymptomatic and transient, it may persist and give rise to various lesions such as warts, condyloma dysplasia and cancers depending on low or high risk type of HPV infection. Moreover, growing recent evidence suggests a role of this virus in male and female fertility. To date no effective prevention, test, treatment and control strategies are provided for people in developing countries despite the reported high incidence of HPV both in women and men. This paper reviews the more recent literature about HPV infection highlighting epidemiology, related pathologies and possible fertility effects of HPV in male and female with particular attention to the Mozambique context.

Keywords HPV · Infectious disease · Genital warts · HPV and cancer · HPV and fertility

Introduction

Human papillomaviruses (HPVs) are agents of the most common sexually transmitted diseases [80, 18] that can infect both females and males. HPVs commonly infect mucosal genital epithelia, upper aerodigestive tract, and other head and neck mucosal regions, with an estimated 75 % of humans being affected during life [51, 26, 46]. HPV infection is very common among men and women across all geographical, racial and socio-economic subgroup worldwide. More than 150 types of HPV have been completely sequenced and classified into low-risk, which are associated with anogenital warts and mild dysplasia, and high-risk types, which are associated with high-grade dysplasia and anogenital cancers, such as cervical and anal carcinoma [51, 26, 46, 49]. Considering both males and females, the overall prevalence of HPV infection is about 40 % of general population, with variations based on the HPV type and the anatomical site of infection [8]. Transmission of the infection may be horizontal (by genital–genital, manual-genital, or oral-genital contact) or vertical (from mother to fetus). The risk factors that aid the establishment of this infection are sexual intercourse at a young age, multiple sexual partners, prolonged use of oral contraceptives, high degree of parity, lack of circumcision, smoking, immunosuppression, coinfection with HIV and other sexually transmitted agents, and of course, lack of condom use [63, 60]. This infection has been largely investigated in women and it is estimated that about 10 % of women worldwide with normal cytological screening, tested positive for HPV at cervical level [10]. Moreover, oncogenic HPV type infection represents a well-known cause of invasive cervical cancer, which is the third most common cancer among women worldwide [25]. Only recently HPV has been partially taken into account for men's health and it has been well documented not only in the anal

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region, perineal area, scrotum, glans, penile shaft, and urethra, but also in the reproductive system (testis, epididymis, and ductus deferens) [38, 59, 76, 53, 31]. Moreover, several reports documented the presence of HPV in the semen and its association with an impairment of sperm motility and presence of anti-sperm antibodies [68, 37, 35]. These findings suggest a role for HPV on infertile couples and human reproduction and reinforce the concept of considering this infection not only in women but as a couple's problem [37]. Furthermore, new evidence brings out a high percentage of oral HPV infection among both men and women, also due to increasing unprotected oral sex [75]. Also at this site, the presence of the virus may be completely asymptomatic or associated with ulcerative precancerous lesions, warts and even cancers [28, 3]. Recently, increasing interest has been shown towards HPV and viremia and several studies conducted in female patients with cervical cancers, have shown that HPV DNA can be found in peripheral blood, mononuclear cells, sera, plasma and arterial cord blood [7, 69]. Also in infected males HPV markers were found in peripheral blood, although it is unclear whether it represents the result of cell-mediated immunity or involvement in virus spreading [32].

Researches about HPV infection in sub-Saharan Africa show a high prevalence both in female and male [21, 73, 6]. Considering, in this region, the high rate of immunosuppression due to high incidence of HIV infection and malnutrition, it is mandatory improve and increase studies to better understand and to try to defeat, or at least reduce, HPV infection. The aim of this review is to contextualize and to understand the state of the scientific literature on HPV infection in Mozambique to evaluate the starting point of future investigation.

HPV in female

Epidemiology

The prevalence of HPV in female has been clearly estimated. It ranges between 1.7 % in Western Asia and more than 30 % in Caribbean and Eastern Africa. In Europe, the prevalence of HPV infection is estimated around 8.8 %. Data dealing the clearance of HR-HPV are also available in women, and more than 50 % of patients show no more evidence of infection at 6 months. This rate achieves more than 90 % at 3 years [8]. The Pap test, which is usually reported following Bethesda System 2001 is the most important screening instrument that allowed a large decline in cervical cancer incidence and mortality in high-income countries [77]. However, it is estimated that about 10 % of women worldwide with normal cytological screening, tested positive for HPV at cervical level [10].

HPV related pathologies

Most of HPVs are very rarely associated with malignancies and are then classified as low-risk (LR). LR-HPV mostly cause subclinical infections or benign papillomas, which can persist for months or years, until they are generally solved by the host's immune system [26]. However, HPV related genital warts represent the most common anogenital viral sexually transmitted disease found in the general population [30]. The treatment destroys mainly the visible lesions, without certainty in clearing the virus and it represents a significant health and cost burden [71]. On the other hand, cervical cancer represents the third most common cancer among women and they reported that among the estimated 12.7 million new cancers occurring in women in 2008 world-wide, 700,000 occurred at an HPV-associated cancer site, and 610,000 of these were attributable to HPV [8]. Moreover, this cancer is considered a leading cause of mortality worldwide, with 265,653 deaths estimated in 2012 [79]. Eighty-three percent of cases occur in the developing world, where cervical cancer accounts for 15 % of female cancers, as compared to just 3.6 % in developed countries [61]. The large decline in cervical cancer incidence and mortality in high-income countries is largely credited to effective screening programs and the Pap test [77]. Therefore, it is crucial to create a basis for effective, low cost and easy screening, in countries in the developing world, to try to significantly reduce the incidence of mortality related to this disease.

HPV and fertility

Growing insights on human reproduction suggested a role for HPV on human infertility. Some authors demonstrated that artificially HPV infected sperm are able to enter the oocyte, deliver HPV genome, and that viral genes are then actively transcribed by the penetrated oocyte [34]. Again, a stage-specific maturation arrest in HPV artificially infected embryos has been previously reported [41] and infected couples undergoing assisted reproduction techniques (ART) cycles experienced an increased risk of pregnancy loss compared to non-infected ones [65]. Although this topic is not of vital importance, it must be taken into consideration in developing countries, especially when it is associated with other widespread conditions such as STD or immunodeficiencies.

What is known in Mozambique?

Limited data are available on the impact of HPV and its associated diseases in Mozambique, and most of the concerns are on females and cervical cancers. Those concerning prevalence and risk factors, attest a high

prevalence ranging from 40 to 96 % depending on the considered population, and listed the most common and known risk factors, such as multiple sexual partners, reproductive age and other STD, including HIV [1, 54, 58]. Studies characterizing HPV infection, confirmed the presence of high-risk genotypes in patients with cervical cancer and showed no association between HPV and P53 and/or Ki-67 that are instead associated with invasive cervix carcinomas, mainly of the squamous keratinizing histotype [12, 57, 13, 17]. Too little is being done to prevent transmission of HPV and only few studies have been conducted regarding vaccination, effectiveness and cost/benefit analysis [47, 11, 16]. Finally, only one study considered both, male and female and regards the incidence of HPV infection in squamous cell carcinoma of the conjunctiva, suggesting a strong association between virus presence and carcinoma development [14].

HPV in male

Only recently HPV has been partially taken into account for men's health and it has been found not only along the whole male genital tract but even in semen and bound to sperm cells [59]. The systematic review of Dunne showed that the overall prevalence of HPV ranges from 1.3 to 72.9 %. In particular, it ranges from 7–15 to 35–45 % among healthy sexual active males while it is higher (50–70 %) in partners of women with precancerous lesions. Again, the age range reported by the studies is very broad and ranges from 20 years to 60 [27]. Another review conducted by Partridge on heterosexual males, showed a variability in the prevalence of HPV infection from 3.5 to 45 %, reporting the largest peak between 30 and 40 years [64]. Again, recent paper showed that even 86 % of asymptomatic men with HPV infected partners, had positive HPV DNA detection by PCR [24]. Diagnosis of HPV infection is often difficult because in most patients the infection is transient and asymptomatic. Specimen for HPV detection in men come mainly from three genital sites (penile brushing, urethral brushing, and semen) and INNO-LiPA system and PCR assay are the most used methods [37, 35].

It remains still much to study and, in particular, the natural history of the disease, the incidence and prevalence in different cohorts and the viral clearance.

Related pathologies

HPV infection is in most cases asymptomatic but it can manifest with mucosal and skin lesions or with more complex diseases caused by oncogenic HR genotypes.

Warts don't represent a problem in terms of mortality but are associated with clinical symptoms such as bruising, pain and bleeding and are mainly caused by genotypes 6 and 11 [52, 45, 44]. It is estimated that warts represent the result of only a fraction of HPV infections and populations studies showed a prevalence of 0.6–1.5 up to 4–13 % in relation to sexual behavior [48, 56, 15]. Warts can develop in 2–3 months and 20–30 % of them regress spontaneously, but in about one-third of cases can recur [23, 22]. In males as in females, HR HPV infection is involved in the carcinogenic process. In fact, HPV has been recognized as an important risk factor for penile, anal, oropharyngeal, conjunctival, head, and neck tumors [59, 72, 74, 19]. Some authors estimated that HPV-related cancers at penile, anal, and oropharynx sites are rare among men, occurring in about 1–6/100,000 in the general population [39]. It is estimated that penile cancer amounts to 1/100,000 inhabitants in the Western world, while increases in the Latin America area (1.5–3.7/100,000) and East Africa (2.8/100,000) [29, 55]. HPV DNA is found in approximately 40–50 % of all penile cancers of the penis and epidemiological studies confirmed the predominant role of HPV 16 and 18 [5]. The positivity for HPV is higher (75–80 % frequency) in intraepithelial cancer and in basaloid histological types [70, 4]. The majority (65 %) of invasive anal cancer is represented by squamous cell carcinoma which develops from anal intraepithelial neoplasia and that was often linked to HPV infection [43]. In fact, HPV has been shown in more than 80 % of these cancerous lesions and HPV16 was the most frequent type (87 %), while HPV18 was found in about 9 % of cases [78]. In recent years the incidence of anal cancer showed a clear increase and, in particular, there was a greater increase in men than women; the incidence is particularly high in homosexual men and the risk is further increased in the presence of HIV infection [64]. Other risk factors are smoking, anal intercourse and high number of sexual partners [20]. Head and neck cancers are squamous cell carcinomas arising in the upper respiratory and digestive tract: oral cavity, oropharynx, hypopharynx and larynx, while nasopharynx and salivary glands cancers differ histologically [67]. It is estimated that in 2002 there were 405,000 new cases in the world with 211,000 deaths, and two-thirds of these cases occurred in developing country areas [62]. The male/female ratio ranges from 2:1 to 15:1 and in particular, buccal mucosa and tongue cancers predominate in developing areas while in industrialized areas the pharynx cancer represent the most common form [62]. The association with HPV is very common, even if important risk factors are considered also smoking and/or alcohol consumption, and oral sex [50, 2, 66].

HPV and fertility

HPV is frequently detected in semen and can be localized at different levels: in sperm, in exfoliated cells or in both sites [68, 37, 35]. Many authors demonstrated that the presence of HPV in semen is associated with an impairment of sperm parameters, in particular, motility and the presence of sperm antibodies [37]. A possible cause–effect relationship between unexplained male infertility and HPV semen detection is supported by the observation that HPV-related impairment of sperm motility is more frequently reported in idiopathic infertile patients than in healthy fertile controls. In fact, authors reported that several cases of idiopathic asthenozoospermia did not present any known risk factor except for the HPV-DNA sperm detection [35, 36, 81]. Moreover, in vitro evidences show that when HPV is bound to spermatozoa it is potentially transferred to fertilized oocytes, blastocysts, and trophoblast cells [40, 9, 42]. Even if different studies failed to identify a relationship between early miscarriage/ART failure and HPV positivity in women, new evidences reported a possible role of HPV sperm detection in adverse pregnancy outcome and ART failure [65]. To date, the biological mechanisms by which HPV infection affects sperm fertilization ability is not clear but, it is increasingly clear the role of this infection even in male infertility.

What is known in Mozambique?

There are only few studies concerning HPV infection in women in Mozambique. Only one paper dealt with HPV infection in men and considers the HPV infection in squamous cell carcinoma of the conjunctiva showing a strong association [14]. Due to this lack of studies and the evidence of the impact of HPV related pathologies in male, it is mandatory to increase research on this topic.

Conclusions

HPV represent an actual health and economic problem worldwide both for men and women. HPV infection can involve male as much as female and can be easily transmitted between sexual partners and it is associated with a variety of genital and non genital manifestations such as warts and cancers in both genders. Recent evidences highlight that this virus is involved also in fertility. To date there is no effective therapies and vaccination represents the only available weapon. Although, especially in men, cost-effectiveness of the use of HPV vaccine is under investigated, recent evidences demonstrated the efficacy of prophylactic vaccination for genital condyloma and precancerous lesions [33]. In this regard there are no data

available in Mozambique but, after investigating the state of art of HPV related diseases in this country, this approach could be considered as a strategy. In light of this evidence, it is necessary to increase and improve research also in developing areas as sub saharan Africa, especially considering the high rate of HIV infection that represents one of the most important risk factor. This will allow not only to assess the incidence and prevalence of HPV infection, but also to develop programs for primary and secondary prevention, impacting on community benefits and health costs.

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