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Epidemiology and pathology of HPV disease in males

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Abstract

It is currently recognized that besides the significant impact of human papillomavirus (HPV) infection in females, HPV causes substantial disease in men as well. Genital warts are a common manifestation of male infection with HPV. Genital warts are highly infectious and approximately 65% of people who have sex with an infected partner will develop warts themselves. More than 90% of genital warts are caused by non-oncogenic HPV types 6 and 11. In addition, recurrent respiratory papillomatosis is a rare disease most often associated with HPV types 6 and 11. Several cancers of the anogenital tract and upper aero-digestive tract, and their precursor lesions in men are now understood to be caused by infection with sexually transmitted HPV. For example, there is increasing incidence of anal cancer in western countries; however, there are limited data on its primary cause, anal canal HPV infection. Genital HPV infection is very common in men with an ongoing international study estimating a prevalence of 65.2% in asymptomatic males aged 18–70 years. Lifetime number of sexual partners was the most significant risk factor for the acquisition of HPV infection ($P<0.05$), and circumcision has been associated with reduced detection of HPV infection in men. HPV infections may be less likely to persist in men than in women. In men, the median time to clearance of any HPV infection was 5.9 months, with 75% of infections clearing within 12 months. More data are needed to better understand the natural history of HPV infection. Although the quadrivalent HPV vaccine has been shown to be effective and safe in men, low awareness of HPV in males may be a barrier to its use for the prevention of HPV infection.

Keywords

Male; HPV infection; Genital warts; Recurrent respiratory papillomatosis; Head and neck cancer; Penile cancer; Anal cancer; Transmission dynamics; Natural history

Introduction

There is increasing interest in understanding the burden of human papillomavirus (HPV) infection and disease among men. In earlier work, much of this interest focused on the role of men in the transmission of HPV to women, and its contribution to the burden of cervical cancer [1–3]. Over the past several years research findings have led to the recognition that

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HPV causes substantial disease in men [4]. Several cancers of the anogenital tract and upper aero-digestive tract, and their precursor lesions in men are now known to be caused by infection with sexually transmitted HPV [5]. In addition, there is now evidence that the currently licensed HPV vaccine for females confers protection against HPV 6, 11, 16, and 18 infection and HPV-related genital lesions in males aged 16–26 years [6,7].

Pathology of HPV infection in men

Benign conditions

Genital warts—Genital warts are a common sexually transmitted disease in the US with an estimated 1 million new cases each year [8]. The prevalence of genital warts is highest among men aged 25–29 years and decreases with age [9]. In the 1999–2004 National Health and Nutrition Examination Survey, 4.0% of sexually active males aged 18–59 years reported having ever been diagnosed with genital warts [10]. Though genital warts are benign and not associated with mortality, they are a source of psychosocial distress such as shame and embarrassment [11]. The incubation period is 3 weeks to 8 months, with most warts developing 2–3 months after infection with HPV [12]. Genital warts are highly infectious and approximately 65% of people who have sex with an infected partner will develop warts themselves [12]. About 20–30% of genital warts will spontaneously regress; however, recurrence of warts is common [13].

More than 90% of genital warts are caused by non-oncogenic HPV types 6 and 11 [14]; however, approximately one-third of genital warts have multiple HPV types including coinfection with oncogenic types [15]. Data available for the HPV type distribution of genital warts in men are sparse. One case series of 135 men from Hong Kong detected HPV DNA in 96% of genital warts [15]. Among warts that tested positive for HPV, 75.4% had nononcogenic types only, 3.8% had oncogenic types only, and 20.8% had both oncogenic and nononcogenic types. There was a high rate of multiple infections (33.8%), often including coinfection with oncogenic types. HPV 6 was the most common type detected (54.6%), followed by HPV 11 (40.8%) and HPV 16 (6.2%).

Recurrent respiratory papillomatosis—Recurrent respiratory papillomatosis (RRP) is a rare disease characterized by the formation of wart-like lesions on the respiratory tract, most frequently at the larynx. RRP is most often associated with HPV types 6 and 11. There is a bimodal age distribution with peaks among infants and young children and again in adulthood between ages 20 and 30 years [5]. Incidence of RRP is estimated to be 4.3 per 100,000 in children and 1.8 per 100,000 in adults [16], and occurs equally between genders among children and more frequently among males in adults. Juvenile-onset RRP may develop as the result of vertical HPV transmission from mother to child during birth [17]. The disease is more aggressive among children, characterized by a high rate of recurrence that often requires multiple surgeries to remove lesions to keep the airway unobstructed.

Cancers associated with HPV infections

Anal cancer—The incidence of anal cancer in men in the US has increased from 0.5 per 100,000 in 1974 to 1.3 per 100,000 in 2004 [18], and was the most commonly diagnosed

anogenital HPV-associated cancer in men in 2007 [19]. Approximately 85% of anal canal cancer cases worldwide are attributable to HPV, although high-risk HPV types are found more often in anal cancers in women than in men [20][21]. Incidence is highest among men having sex with men (MSM) and HIV-infected males [22]. Increasing incidence of anal cancer may be due to increased anal disease occurring in immunocompromised persons and in MSM [23,24]; the risk ratio of observed to expected anal cancers has been reported as 37.9 (95% confidence interval [CI], 33.0–43.4) in males with HIV and 59.5 (95% CI, 51.5–68.4) in MSM with HIV [25]. The majority of invasive anal carcinoma are squamous cell carcinomas (SCCs) (65%) [22].

Factors associated with anal cancer in men include being single/never married [21,26–28], smoking [28–30], a history of anogenital warts [27–30], a history of anal intercourse [28,29,31], and number of sexual partners [27,28].

Penile cancer—Invasive SCC of the penis is rare and accounts for less than 0.5% of all cancers in men worldwide [22]. The annual age-adjusted incidence of penile cancer in the US is 0.81 per 100,000 men [32]. Worldwide, areas with high incidence of cervical cancer also tend to have high incidence of penile cancer [33]. Incidence is highest in developing countries, with rates as high as 4.4 per 100,000 in Uganda [34]. Conversely, incidence is very low among Jewish populations that commonly practice neonatal circumcision (0.04 per 100,000) [22]. Though penile cancer is rare, the disease is associated with high morbidity and mortality.

The factors most strongly associated with penile SCC in case-control studies are phimosis [35–40], lack of neonatal circumcision [36,38,39], anogenital warts [35,36,38], and HPV infection [38,39]. Other identified risk factors for penile SCC are current smoking [36–38,40], early age at first sexual intercourse [35], high lifetime number of female sexual partners [35, 36,38], and lack of condom use [35].

A recent quantitative review reported that HPV DNA was prevalent in 46.9% of penile carcinomas with HPV 16 (60.23%), HPV 18 (13.35%), and HPV 6/11 (8.13%) being the most common types [41]. The prevalence of HPV DNA in penile tumors varies with histological subtype; HPV DNA is present in 80–100% of basaloid and warty types, but only about one-third of verrucous and keratinizing types [42].

Head and neck cancer—HPV-related head and neck cancers include cancers of the oral cavity, oropharynx, hypopharynx, and larynx. In 2002, there were approximately 405,000 new cases of head and neck cancer worldwide [22]. While most head and neck cancers are associated with tobacco and alcohol use, an estimated 33–72% of oropharyngeal cancers and 10% of cancers of the larynx are attributable to HPV infection [5]. The proportion of oral cavity and oropharyngeal cancers related to HPV has increased over the last several decades and is expected to continue to increase [43]. A recent review of the prevalence of HPV in head and neck cancers reported that 25.9% of all head and neck cancers are positive for HPV DNA, with higher HPV prevalence in oropharyngeal cancers (35.6%) than oral (23.5%) or laryngeal (24.0%) cancers [44]. HPV 16 is the type most strongly associated with head and neck cancer. A case-control study found that testing positive for oral HPV 16 is

associated with a 14 times the odds of oropharyngeal cancer [45]. Among HPV-positive head and neck cancers, HPV 16 is found in 90% of oropharyngeal, 69% of laryngeal, and 68% of oral cavity cancers [44].

Natural history of HPV infection in men

In general, genital HPV infection prevalence among healthy men appears to be as high, or higher, than prevalence among women. Based on a systematic review of the literature, the prevalence of genital HPV infection in men ranges from 1.3% to 72.9% [46]. The variation in prevalence is likely due to differences in populations studied, anatomic sites sampled, and HPV DNA detection methods used. In recent reports from an ongoing multinational prospective cohort study, 50.5% of men were positive for at least one known oncogenic or nononcogenic HPV type, and an additional 14.7% were positive for an unclassified HPV infection (tested PCR HPV positive, but negative to 37 mucosal HPV types tested) [47]. HPV 16 was the most common type detected (6.5%). Similar results were observed in a cross-sectional study of US men [48]. Among asymptomatic heterosexual men, the penile shaft, coronal sulcus/glans penis (including prepuce in uncircumcised men), and scrotum are the sites that contribute to more than 95% of genital HPV infection detected [49].

HPV infections may be less likely to persist in men than in women. In a Dutch study, persistent infection (defined as detection of HPV DNA of a specific type at 2 consecutive visits over a period of 1 year) was observed more frequently in women than in men ($p < 0.05$) [50]. Twenty percent of HPV-positive women and 6% of men had a persistent infection, while short-lasting infections with proven regression of HPV was demonstrated in 49% of infected men and 31% of infected women.

In a recently published study, the 12-month cumulative risk of acquiring a new HPV infection among a cohort of US men was 29.2% [51], with a similar estimate reported for young males [52], and females [53]. Unlike what has been observed among women, there is no clear age pattern in rates of HPV acquisition in men [51]. The lack of an association with age suggests that the relatively constant HPV prevalence observed in cross-sectional studies may be due to continued acquisition of new infections through the lifespan. The median time to clearance of an infection has been reported as 5.9 months (95% CI, 5.7–6.1 months), with 75% of infections clearing within 12 months [51]. Reduced risk of persistent infection has been observed among circumcised men [54].

Anal HPV infection in men has been studied less than genital HPV infection, with most research focused on MSM and men with HIV. Like genital HPV prevalence, variations in anal HPV prevalence are likely due to different populations studied, variations in sampling techniques, and differences in diagnostic sensitivity. Prevalence of HPV infection at the anal canal in men ranges from 1.2% [55] to greater than 50% in MSM and men with HIV [56, 57]. In heterosexual men recruited from the general community, anal canal prevalence for any HPV DNA was estimated at 16.6%; when combined with the perianal region, anal HPV prevalence was 24.8% [58].

Transmission dynamics

Several small HPV studies of heterosexual partners have been published [59]. In a study comparing HPV status in the cervix and semen of heterosexual partners, Kyo et al. demonstrated that 75% of women whose male partners were HPV positive had HPV DNA in their cervix, while only 39% of the men whose partners were HPV positive carried HPV DNA in their semen [60]. Campion et al. examined HPV disease in women whose sexual partners had penile condyloma, and found that 76% of the women had genital HPV infections, including 36% with abnormal cervical cytology and 27.7% with cervical HPV DNA detected by hybridization [61].

Risk factors

Although few studies define correlates of genital HPV infections in men, consistently positive associations between HPV detection and measures of sexual history, including lifetime and recent number of sexual partners and sexual frequency, have been observed [46,62]. Conversely, circumcision has been consistently (4 of 6 studies) associated with reduced detection of HPV infection in men [3,46,63,64]. In an international study, HPV prevalence was significantly lower among circumcised men [47]. Less consistently (2 of 6 studies), condom use has been associated with reduced risk of HPV detection in men [46,62]. Most studies found no association between age and genital HPV prevalence in men [46].

Vaccination

Recently, the quadrivalent HPV vaccine was shown to be efficacious in decreasing the incidence of HPV-related external genital lesions in men aged 16–26 years [65]. Among 1,397 vaccinated men and 1,408 placebo controls, efficacy against any HPV 6/11/16/18-related external genital lesions in the per-protocol population was 90.4% (95% CI, 69.2–98.1). Vaccine efficacy against condyloma and penile intraepithelial neoplasia was 89.4% (95% CI, 65.5–97.9) and 100% (95% CI, –141.2–100), respectively. Efficacy against HPV 6-, 11-, 16-, and 18-related external genital lesions was 84.3% (95% CI, 46.5–97.0), 90.9% (95% CI, 37.7–99.8), 100% (95% CI, <0–100), and 100% (95% CI, <0–100), respectively. No vaccine-related serious adverse experiences were observed.

Much of the arguments for male vaccination are related to the direct benefits men can receive from the vaccine as well as the indirect benefits women can receive from male vaccination. Highlighting the potential for herd immunity after only one sex is vaccinated are recent results from Australia that demonstrate a protective effect for males when a majority of females, but no males, are vaccinated [66]. In 2007, the quadrivalent HPV vaccine was administered to females ages 12 to 26, with coverage rates between 65% and 75%. Both heterosexual men and women younger than 28 years showed a significant decrease in the incidence of genital warts in 2008 compared to 2004 to 2007, with prevalence ratios of 0.83 (95% CI, 0.74–0.92) and 0.52 (95% CI, 0.44–0.63), respectively. The decrease in incidence of genital warts was not observed among MSM and women older than 28 years. In countries such as the US, where only 18% of age-eligible females have

received all three doses of vaccine, male vaccination may provide a viable approach to increase protection against HPV in both males and females.

The effectiveness of any vaccination program that incorporates males will be reliant on awareness of HPV infection and disease within the general male population. Population-based data among Danish men (n=23,000) aged 18 to 45 years, suggest there is lower awareness of HPV in men (10%) compared to women (25%) [67,68]; thus, low awareness of HPV in males may be a barrier to the prevention of HPV infection. More data are needed regarding the transmission dynamics of the different HPV types and the effectiveness of male vaccination to reduce HPV-related disease in men and women.

Ongoing studies

To better understand the natural history of HPV infection, its progression to benign and malignant disease in men, and to better inform the development and implementation of vaccination programs, more data are needed regarding the incidence and persistence of HPV at the different anatomical sites it infects, the incidence of external genital lesions, and the diversity of HPV types in these lesions. Furthermore, progression rates, and the role of the immune response in protection against infection and disease progression should be determined [47,54].

In addition to the available modeling studies, more data are needed to reveal the efficacy of male vaccination and its effect on female protection. A number of ongoing studies are currently addressing issues surrounding the natural history and transmission of HPV infection in men in the US, Mexico, Brazil, the Netherlands, and Denmark [32,47,54,69,70].

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Conflict of interest statement

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Key points

- Men have a significant role in the transmission of the human papillomavirus (HPV) to women.
- There is a knowledge gap with regard to the natural history of HPV infection and progression to disease in men.
- In males, HPV infection commonly presents as genital warts, and nearly all cases are caused by low-risk HPV types 6, 11 or 6/11.
- HPV types 6 and 11 are implicated in the majority of cases of a rare condition known as recurrent respiratory papillomatosis.
- HPV has been identified in the majority of anal carcinomas and in approximately 50% of penile cancers.
- A subset of head and neck carcinomas appear to be linked to HPV infection, and there is a strong causal association between these cancers and high-risk HPV types, such as HPV 16.
- In a multinational study, HPV DNA was present in 65.2% of asymptomatic males aged 18–70 years.
- Lifetime number of sexual partners was the most significant risk factor for the acquisition of HPV infection ($P<0.05$).
- Genital HPV infections may be less likely to persist in men than in women; in men, the median time to clearance of any HPV infection was 5.9 months, with 75% of infections clearing within 12 months.
- Preliminary data from Australia show that vaccination of girls leads to a decrease of genital warts in men, demonstrating that herd immunity occurs with HPV vaccination.
- Low awareness of HPV in males may be a barrier to the prevention of HPV infection through vaccination.