Published in final edited form as:
Prev Med. 2011 October ; 53(Suppl 1): S36–S41. doi:10.1016/j.ypmed.2011.08.002.

Genital HPV infection and related lesions in men

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Abstract

Human papillomavirus (HPV) is highly prevalent in men and there is an interest in further understanding the relationship between HPV infection and disease in men, including the development of genital warts, penile intraepithelial neoplasia and invasive penile carcinomas. Genital warts are caused by HPV 6/11 and are the most common clinical manifestation of HPV in men. Though they are benign and not associated with mortality, they are a source of psychosocial distress and physical discomfort. HPV infection can also develop into invasive penile carcinoma which is associated with morbidity and mortality. Approximately 40% of invasive penile carcinomas are attributable to HPV with HPV 16, 18, and 6/11 being the genotypes most commonly detected in penile tumors. Penile carcinomas of the basaloid and warty histologic subtypes are most likely to test positive for HPV. In addition to HPV infection, the risk factors most strongly associated with penile cancer are lack of neonatal circumcision, phimosis (the inability of uncircumcised men to fully retract the foreskin), and anogenital warts. Male vaccination with the quadrivalent HPV vaccine that protects against HPV 6/11/16/18 has been shown to significantly reduce HPV-associated anogenital infection and disease in men. If the quadrivalent vaccine is successfully disseminated to large segments of the young male population, there is the potential for substantial reduction in genital HPV infection and related lesions in men.

Keywords

Human papillomavirus; Male; Genital wart; Penile cancer; Penile intraepithelial neoplasia

Human papillomavirus (HPV) is the most common sexually transmitted infection in men and women in the United States (US), with an estimated 6.2 million new cases each year (Cates, 1999). HPV is an established cause of cervical cancer, and there has been immense progress in understanding the natural history of HPV infection to disease in women. Recently there has been an interest in further understanding the relationship between HPV infection and disease in men, including the development of genital warts, penile intraepithelial neoplasia and invasive penile carcinomas.

Genital HPV infection in men

The reported prevalence of genital HPV DNA in men has ranged from 1.3% to 72.9% (with most studies reporting ≥20%) (Dunne et al., 2006). Variation in reported prevalence is likely due to differences in sampling techniques, the populations studied, genital sites sampled

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Conflict of Interest
None to report.

(e.g., scrotum, shaft, glans, etc.), and HPV DNA detection methods used. The use of a more sensitive sampling technique (i.e., a pre-wetted Dacron swab rather than a cytobrush or collecting a urine sample (Weaver et al., 2004)) can result in a higher HPV prevalence estimate. Similarly, HPV prevalence is higher when samples are collected from a greater number of anatomic sites (Nielson et al., 2007a). A multinational study recently reported that 50.5% of men tested positive for at least one known HPV genotype and an additional 14.7% of men were positive for an unknown HPV type (Giuliano et al., 2008a). There was also a high rate of men testing positive for multiple HPV genotypes (25.7%). Among men with HPV infections in that study, 12.0% had oncogenic types only, 20.7% had non-oncogenic types only, 17.8% had both oncogenic and non-oncogenic types, and 14.7% had unclassified types only (i.e., tested positive for HPV DNA using a generic probe, but negative for all of the 37 HPV genotypes tested for). Similar results were seen in a cross-sectional study of men in the US that sampled for HPV from six anogenital sites (penile shaft, glans/corona, scrotum, urethra, perianal area and anal canal) (Nielson et al., 2007a). HPV was most commonly detected in samples taken from the shaft (49.9%), glans (35.8%), and scrotum (34.2%), and less frequently in samples from the perianal area (20.0%), anal canal (17.6%), urethra (10.1%), and semen (5.3%) (Nielson et al., 2007a). HPV 16 and 6 are consistently among the most common types detected in men across studies regardless of the anatomic site sampled (as reviewed in Dunne et al., 2006). The factors independently associated with HPV detection at the shaft, glans, or scrotum in men include not being circumcised (Giuliano et al., 2009; Gray et al., 2010; Hernandez et al., 2008a; Lajous et al., 2005; Lu et al., 2009; Vaccarella et al., 2006), lack of condom use (Baldwin et al., 2003; Nielson et al., 2009a,b), a history of having ever smoked (Vaccarella et al., 2006; Nielson et al., 2009b; Nielson et al., 2007b), and a high lifetime number of sexual partners (Baldwin et al., 2003; Giuliano et al., 2009; Lu et al., 2009; Nielson et al., 2009a,b).

There does not appear to be an association between age and HPV prevalence in men. This is in contrast to the pattern observed in women, where HPV prevalence is highest among women ages 18–24 and then decreases until middle age, after which it remains steady for the remainder of the lifespan (Burchell et al., 2006). The consistently higher prevalence of HPV in men suggests that women have a stronger immune response. This is supported by serologic studies that find a higher prevalence of HPV antibodies in women than men across all ages (Kreimer et al., 2004; Markowitz et al., 2009; Svare et al., 1997). In a study of participants in the National Health and Examination Survey, the prevalence of antibodies for one or more of the HPV vaccine types (6, 11, 16, and 18) was significantly higher among women (32.5%) than men (12.2%) (Markowitz et al., 2009). A possible explanation for this difference is that when keratinized epithelium is infected with HPV it is less likely to induce an immune response than mucosal epithelium (the tissue type most commonly infected in women).

Only a few cohort studies have examined the incidence and duration of HPV infection in men (Giuliano et al., 2008b, 2011a; Kjaer et al., 2005; Lajous et al., 2005; Partridge et al., 2007; Van Doornum et al., 1994; Wikstrom et al., 2000). It is estimated that the probability of detecting a new HPV infection in men over a 12-month period is between 29% and 39% and does not significantly change across the lifespan (Giuliano et al., 2011a; Lu et al., 2009). The majority of HPV infections clear in less than 12 months; one study of men in the US reported a median time to clearance of 5.9 months (Lu et al., 2009), while a multinational study observed a median time to clearance of 7.5 months (Giuliano et al., 2011a). HPV 16 infections tend to have a longer duration and are estimated to clear at an average of 12.2 months (Giuliano et al., 2011a). Age and lifetime number of female sexual partners influence duration of infection, with increasing age and fewer number of female partners being associated with a greater probability of clearing an oncogenic infection (Giuliano et al., 2011a).

Genital warts

The majority of HPV infections are asymptomatic with an estimated 70% of incident infections clearing within 1 year (Dunne et al., 2006). If an infection does not clear however it can progress to disease. Anogenital warts are the most common clinical manifestation of HPV infection (Scheurer et al., 2005). Though they are benign and not associated with mortality, they are a source of psychosocial distress (Jeynes et al., 2009) and can cause physical discomfort including pain, bleeding and itching (Wiley et al., 2002). Genital warts are highly infectious and approximately 65% of people whose sexual partner has genital warts will develop warts themselves (Lacey, 2005). The estimated incubation period from HPV infection to genital wart development is 2 weeks to 8 months, with the majority of genital warts appearing 2–3 months after an HPV infection (Oriel, 1971). Approximately 20–30% of genital warts will spontaneously regress (Wiley et al., 2002), however, recurrence of warts is common, resulting in high medical costs for repeated treatment. An estimated $200 million is spent annually in the US for direct medical costs of genital wart treatment (Insinga et al., 2005).

In the US, 5.6% of sexually active men and women ages 18–59 years have self-reported ever being diagnosed with genital warts (Dinh et al., 2008) and 1% of US adults ages 18–45 years are estimated to have genital warts at any given time (Koutsky, 1997). Studies utilizing private health insurance claims in the US reported genital wart incidence rates ranging from 1.10 to 1.70 per 1000 person–years (Hoy et al., 2009;Insinga et al., 2003; Koshiol et al., 2004;). These data may underestimate incidence since they exclude individuals who do not seek treatment or are not privately insured. A community sample of men ages 18–70 years observed a slightly higher incidence rate for genital warts of 2.35 per 1000 person–years (Anic et al., in press). Though age is not associated with detection of HPV in men (Giuliano et al., 2011a), the incidence of genital warts is highest among men younger than age 30 years and significantly decreases with age (Hoy et al., 2009; Insinga et al., 2003; Koshiol et al., 2004). The association with age remains significant even after adjusting for sexual behavior (Hughes et al., 2000; Jin et al., 2007; Van Den Eeden et al., 1998; Wen et al., 1999).

Testing positive for HPV types 6 and 11 is the strongest predictor of developing genital warts. In the placebo arm of an HPV vaccine trial, the women who tested positive for HPV 6/11 at baseline were 29 times more likely to develop condyloma in the first year of follow-up compared to women negative for HPV 6/11 (Garland et al., 2009). In a prospective study, men who tested positive for HPV at baseline had almost 12 times the risk of developing genital warts (Anic et al., submitted). While HPV 6 and 11 are the types most commonly found in genital warts, infections with multiple types are common including co-infection with oncogenic types. Oncogenic HPV 16 has been reported as the third most common HPV type detected after 6 and 11 in several studies examining the distribution of HPV types in male genital warts (Anic et al., in press; Aubin et al., 2008; Brown et al., 1999; Chan et al., 2009; Vandepapeliere et al., 2005).

Certain sexual behaviors are also associated with an increased risk for genital warts. A high lifetime number of female sexual partners significantly increases the risk of genital warts (Anic et al., submitted; Dinh et al., 2008; Van Den Eeden et al., 1998; Wen et al., 1999), likely by increasing a man’s chance of being exposed to HPV. Frequent condom use was protective against developing genital warts in some (Anic et al., submitted; Wen et al., 1999), but not all (Van Den Eeden et al., 1998) studies. Similarly, there have been inconsistent findings on the protective effect of condom use against HPV infection in men (Giuliano et al., 2008c). Condoms provide a protective barrier against the transmission of

HPV by skin to skin contact; however, men can be infected with HPV on areas not protected by a condom.

Penile intraepithelial neoplasia

Penile intraepithelial neoplasia (PIN) is a heterogeneous condition that currently does not have standard clinical protocols for diagnosis. Because of the similarities in histologic characteristics, the classifications for PIN I, II and III have been "borrowed" from those assigned to CIN. Benign clinical conditions such as lichen sclerosus or psoriasis may appear similar to PIN on visual inspection alone; therefore, misclassification of PIN is possible without histological confirmation from a biopsy sample. High-grade PIN is considered penile carcinoma in situ and includes the clinical conditions Bowen's disease (often found on keratinized skin) and Erythroplasia of Qeyrat (EQ) (found on the mucosal surface of the glans and foreskin) (Bleeker et al., 2009). Development of high-grade PIN is rare and the risk factors for this condition are not known. The likelihood that these lesions progress to invasive cancer is also unknown as there are currently no natural history studies that examine the proportion of PIN that progress to cancer (Fig. 1).

Studies have estimated that approximately 60–100% of PIN lesions are positive for HPV DNA (Aynaud et al., 1994; Barrasso, 1997; Cupp et al., 1995; Krustrup et al., 2009; Rubin et al., 2001; Wieland et al., 2000). One of the larger case series to date tested for the presence of 25 HPV genotypes in 30 histologically confirmed PIN lesions (Rubin et al., 2001). HPV was detected in 90% of PIN and the majority of lesions were positive for single oncogenic HPV types (59.3%). Among HPV positive samples, HPV 16 was the most common type detected (40.7%), followed by HPV 6 (22.2%,) HPV 52 (14.8%), and HPV 11 (3.7%). HPV 18 was not detected in any lesions. Results were similar in a smaller case series of 12 PIN lesions from men in the US which detected HPV in 92% of lesions (Cupp et al., 1995). HPV 16 was the most common type detected and no lesions were positive for HPV 18. Similar results were observed in a Danish study of 29 penile in-situ carcinomas that detected HPV in 90% of lesions (Krustrup et al., 2009). Most studies to date have only tested for mucosal HPV types, but there is evidence to suggest that oncogenic cutaneous HPV may also be present in PIN. Wieland et al. (2000) detected cutaneous HPV types 5 and 8 in a series of eight EQ lesions. HPV 8 DNA was detected in all lesions and co-infection with HPV 16 was observed in 88% of lesions.

Incidence and prevalence of penile cancer

Invasive penile cancer is rare and accounts for less than 0.5% of all cancers in men worldwide (Parkin & Bray, 2006). Between 1998 and 2003, the annual age-adjusted incidence rate of penile cancer in the US was 0.81 per 100,000 men and accounted for only 0.1% of male invasive cancers (Hernandez et al., 2008b). The disease most commonly affects men ages 50–70 years (Bleeker et al., 2009). Incidence of penile cancer in the US is highest among Hispanics and men who live in the Southern US or areas with high levels of poverty (Barnholtz-Sloan et al., 2007; Hernandez et al., 2008b). Worldwide, areas with a high incidence of cervical cancer also tend to have a high incidence of penile cancer (Bosch & Cardis, 1990). For example, in Brazil, reported incidence rates of penile cancer range from 2.9 to 6.8 per 100,000 men (Favorito et al., 2008). Incidence is also higher in less developed countries, where penile cancer accounts for up to 10% of all male cancers in some parts of Africa, South America and Asia (Bleeker et al., 2009) (Fig. 2).

HPV prevalence in penile cancer

Though the etiology of penile cancer is still unknown, approximately 40% of all penile tumors are thought to be attributable to HPV infection (Human papillomaviruses, 2007).

HPV DNA has been detected in 14%–100% of invasive penile carcinomas (Bezerra et al., 2001a; Chan et al., 1994; Cupp et al., 1995; Ferreux et al., 2003; Gregoire et al., 1995; Heideman et al., 2007; Humbey et al., 2003; Iwasawa et al., 1993; Krustrup et al., 2009; Levi et al., 1998; Lont et al., 2006; Maden et al., 1993; McCance et al., 1986; Nasca et al., 1999; Pascual et al., 2007; Picconi et al., 2000; Rubin et al., 2001; Salazar et al., 2005; Sarkar et al., 1992), with higher prevalence estimates among case series with small sample sizes. Differences in methods used for DNA detection and tumor tissue storage (fresh vs. paraffin embedded) and the inclusion of tumors with different histologic subtypes may contribute to the variation in HPV prevalence across studies. A quantitative review of studies that used PCR methods for HPV DNA detection found HPV present in 45.4% of invasive penile tumors after adjusting for PCR primer, histology sub-type, and year and geographical location of the study (Backes et al., 2009). Another review of 31 studies examining the prevalence of HPV in invasive penile tumors found that among those with HPV, HPV 16 was the most common type detected (60.2%), followed by HPV 18 (13.3%) and HPV types 6/11 (8.13%) (Miralles-Guri et al., 2009). Unclassified infections have been observed in penile tumors even in studies that use assays that test for many genotypes. Rubin et al. (2001) tested for 25 mucosal HPV types and observed unclassified infections in 12% of the HPV positive tumors. Given that the majority of studies only test for mucosal types, it is possible that cutaneous HPV types account for some unclassified infections. In two small case series, oncogenic cutaneous HPV types 5 and 8 were detected in 6% (Humbey et al., 2003) and 11% (Heideman et al., 2007) of penile tumors, respectively.

The difference in the rate of HPV detection is highly dependent on the histologic type of penile cancer, similar to vulvar cancers. Approximately 95% of invasive penile cancers are squamous cell carcinomas (SCC) (Bleeker et al., 2009) and the most common penile SCC histologic sub-types are keratinizing (49%), mixed warty-basaloid (17%), verrucous (8%), warty (6%), and basaloid (4%) (Bleeker et al., 2009). HPV is most commonly detected in basaloid and warty tumors (Bezerra et al., 2001a; Ferreux et al., 2003; Gregoire et al., 1995; Rubin et al., 2001). One of the larger case series to stratify by histologic subtype found HPV present in 100% of warty and 80% of basaloid tumors, but only about one-third of keratinizing and verrucous tumors (Rubin et al., 2001). The same study found HPV 16 to be the most common type, detected in 100% of warty and 83% of basaloid tumors (Fig. 3).

In serologic studies there is a high prevalence of HPV 16 antibodies among penile cancer cases. A study from the Netherlands found men with invasive penile cancer had a significantly higher seroprevalence of HPV 16 (38%) compared to controls with gastric cancer (18%) and hospital-based controls with no cancer (18%) (Van Doornum et al., 2003). Another study also observed a significantly higher seroprevalence of HPV 16 in penile cancer cases (28%) compared to population-based controls (13%) (Carter et al., 2001). This study also tested for HPV 18 antibodies, but did not observe any penile cancer cases seropositive for HPV 18. Only HPV 16 and 18 have been examined in serologic studies of penile cancer thus far and no studies to date have assessed the seroprevalence of HPV by histologic sub-type.

Risk factors for penile cancer

The risk factors most strongly associated with penile cancer are lack of neonatal circumcision (Brinton et al., 1991; Daling et al., 2005; Maden et al., 1993), phimosis (the inability of uncircumcised men to fully retract the foreskin) (Brinton et al., 1991; Daling et al., 2005; Hellberg et al., 1987; Maden et al., 1993; Madsen et al., 2008; Tsen et al., 2001), anogenital warts (Aynaud et al., 1994; Daling et al., 2005; Maden et al., 1993; Madsen et al., 2008), and HPV infection (Brinton et al., 1991; Maden et al., 1993). A very low incidence of penile cancer has been observed among Jewish populations that commonly practice neonatal

circumcision (0.04 per 100,000) (Parkin & Bray, 2006). Circumcision most likely protects against penile cancer by reducing the risk of HPV acquisition (Gray et al., 2010), however, the timing of circumcision may infiuence the protective effect. Men circumcised after the neonatal period have a higher risk of penile cancer compared men who were circumcised at birth (Brinton et al., 1991; Daling et al., 2005). Delayed circumcision may not be protective because men who are circumcised later in life often undergo the procedure as treatment for phimosis or an existing chronic inflammatory condition. Other risk factors for penile cancer include current smoking (Daling et al., 2005; Hellberg et al., 1987; Maden et al., 1993; Tsen et al., 2001), early age at first sexual intercourse (Madsen et al., 2008), high lifetime number of female sexual partners (Daling et al., 2005; Maden et al., 1993; Madsen et al., 2008), lack of condom use (Madsen et al., 2008), chronic inflammatory conditions including balantitis and lichen sclerosus (Daling et al., 2005; Nasca et al., 1999), and treatment with ultraviolet photochemotherapy for psoriasis (Stern, 1990).

The role of HPV as a prognostic factor for penile cancer is not clear. In a study of 82 penile cancer cases, the rate of metastasis was lower among men with penile tumor tissue positive for HPV DNA compared to men with HPV negative tumors, but the difference was not statistically significant, likely due to limited power (Bezerra et al., 2001b; Lopes et al., 2002). The association between HPV status of penile tumors and survival is inconsistent, with one study reporting significantly higher survival rates among men with HPV positive tumors (Lont et al., 2006), but another study found survival rates did not differ between groups (Lopes et al., 2002). The biologic effect of why the presence of HPV DNA in penile tumors may be associated with better prognosis is not known and warrants further research.

Prevention of genital HPV infection and genital warts through vaccination

Several reports have demonstrated the efficacy of the quadrivalent HPV vaccine (HPV4) in preventing genital disease caused by HPV 6/11/16/18 in females including the precancerous lesions CIN 2 and 3 (FUTURE II Study Group, 2007; Brown et al., 2009; Garland et al., 2007; Wheeler et al., 2009). Male vaccination with the quadrivalent HPV vaccine has also been shown to significantly reduce HPV-associated anogenital infection and disease in men. In a recently completed international Phase III trial of the quadrivalent HPV vaccine Gardasil, prophylactic administration of HPV4 vaccine was efficacious in preventing HPV 6/11/16/18-related external genital lesions (EGL) in men aged 16–26 years (Giuliano et al., 2011b). Vaccine efficacy against HPV 6/11/16/18 related EGL in the intent-to-treat population was high (65.5% [95% CI: 45.8%, 78.6%]), as was efficacy against development of any EGL regardless of HPV type (60.2% [95% CI: 40.8%, 73.8%]). In the per protocol efficacy (PPE) population, the HPV4 vaccine reduced the incidence of HPV 6/11/16/18-related EGLs by 90.4% (95% CI: 69.2%, 98.1%). Efficacy against genital warts in the PPE population was 89.4% (95% CI: 65.5%, 97.9%). In addition, the HPV4 vaccine was efficacious against HPV 6/11/16/18-related persistent infection and any-time DNA detection. On the basis of these data the US FDA licensed Gardasil for use in males ages 9–26 for the prevention of genital warts in November 2009. The HPV4 vaccine was also recently approved for use in the prevention of anal cancer in men and women and the efficacy of the vaccine against oropharyngeal cancer is being evaluated. Altogether these results are encouraging and hold promise for an ultimate reduction in genital HPV infection and related lesions in men if the HPV4 vaccine is successfully disseminated to large segments of the young male population.

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Fig. 1.
Penile intraepithelial neoplasm.

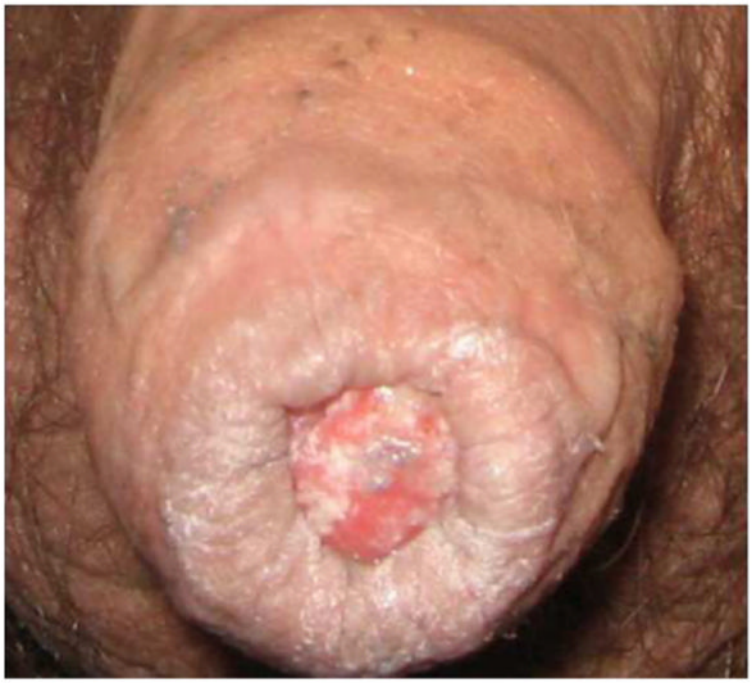

Fig. 2.
Penile cancer.

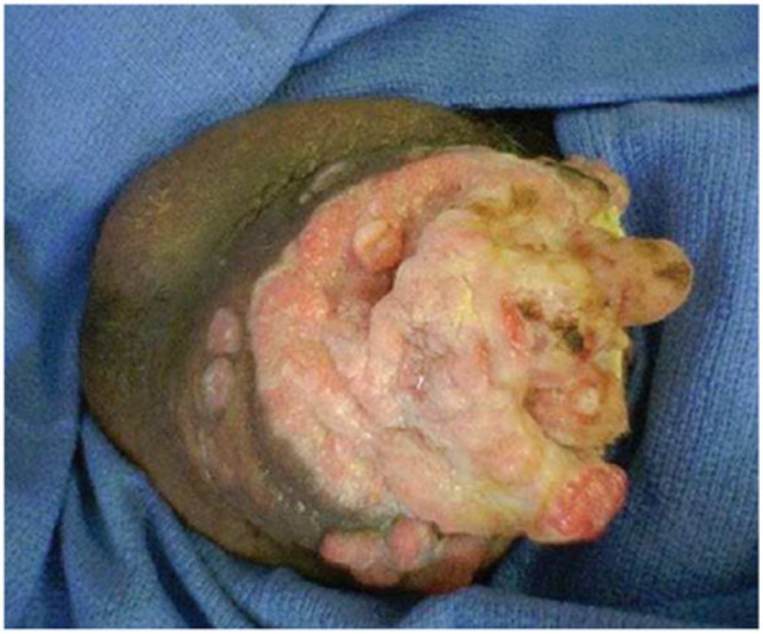

Fig. 3.
Penile cancer affecting the glans.