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HPV in men: an update

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Introduction

HPV 6 and 11 cause greater than 90% of genital warts in males and females. Data show that approximately 3–4 million cases of genital warts in men occur each year with a peak rate of 500 per 100,000 in the 25–29 year old group. (1) The majority of these genital warts are diagnosed in men under the age of 30 years. In addition to genital warts, men are at risk for several HPV-related morbidities including penile, anal and oral cancers.

Penile, oral and anal cancers

As in women, HPV is associated with anogenital cancers in men, specifically of the anus and penis. Approximately 90% of anal cancers are associated with HPV and of those with HPV, 90% are due to HPV 16 and 18. (2) This is higher than seen for cervical cancers, of which ~ 70% are due to HPV 16 and 18. Although women have higher rates of anal cancer than men in the general population, HIV-infected men who have sex with men (MSM) are at greatest risk. (3–5) The age-adjusted incidence rate of anal cancer in women in the U.S. is ~1.4 per 100,000 and in men is ~ 1.0 per 100,000. The estimated annual incidence for HIV infected MSM is between 25 and 100 per 100,000. (6–8) In comparison, age adjustable rates of cervical cancer is 8.1 per 100,000. The incidence of anal cancer is also rising in both men and women in the general population, with an estimated 1,600 new cases of anal cancer occurring each year in women and 900 cases in men. (9) The reasons for this change are unknown. The association with HIV and other HPV-associated cancers underscores the importance of the immune response in controlling HPV.

As with vulvar cancer, the association between penile cancers and HPV varies considerably by histology. Almost 100% of basaloid and warty penile cancers are associated with oncogenic HPV types, whereas only 30–40% of verrucous and keratinizing squamous cell cancers are associated with HPV. (10) HPV 16 is the predominant type found in HPV-associated tumors. Penile cancers are relatively rare in the U.S. with an annual incidence of approximately 1 per 100,000. Hispanics have the highest incidence with 1.3 per 100,000 and Asian Pacific Islanders have the lowest with .4 per 100,000. Penile cancers represent only 0.4–0.6% of all male cancers in the U.S. and Europe. The incidence is almost 20-fold in South American, African and Asian men. In Brazil, the incidence is 3 per 100,000. In Uganda, 1% of men will develop penile cancer. Although the exact reasons for the variation in incidence are not elucidated, circumcision is protective against penile cancer and likely plays a large role. (11) Other risks for penile cancer include smoking, high risk sexual activity and phimosis. These risks may vary by histology, but few studies have examined risk by subtypes. (14) One study found that a reported history of priapism was also

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associated with penile cancer. (12, 13) Like cervical cancer, penile cancer under the age of 20 is extremely rare with a mean age of 63–67 years. (13) In addition, to anogenital cancers, HPV is associated with oropharyngeal cancers in both men and women. (15) Overall, HPV is associated with approximately 25% of head and neck cancers. The tonsil and the base of the tongue are the most common sites of HPV-associated cancers in the oral cavity with approximately 50% being associated with HPV. Among whites and blacks, 5.1 and 6.8, men per 100,000, respectively, were diagnosed with HPV-associated head and neck cancers between 1998 and 2003 (www.cdc.org). In contrast, 1.7 per 100,000 Asian/Pacific Islander men were diagnosed. Sexual behaviors in both men and women are associated with increased risk of these cancers including multiple sexual partners and reporting oral sex. Among men, having sex with other men is a risk factor. (16)

HPV infections

As in the cervix, HPV can be found frequently in samples obtained from the anus and male genitals. Approximately 20% of men (range 1.3 – 72.9%) have HPV DNA detected in the anogenital (including coronal, shaft, scrotum and anal) area. (17) This wide range is due in part to the difficulty in obtaining adequate samples from the genitals of men and the variability in collection techniques. In men who have sex with men (MSM), the prevalence of anal HPV is much higher. (18) The highest prevalence can be found in HIV-infected MSM with a prevalence of over 90% in the anus. (18, 19) Anal HPV infections are also common in adolescent and adult women with rates ranging from 13% to 50%. (20, 21) As in men, the highest prevalence of anal HPV in women is found in those who are HIV-infected. (4)

The most common risk associated with detection of HPV in the anogenital area in heterosexual men is the number of lifetime sexual partners. (18, 22) However, unlike women, older men are as likely as younger men to be HPV-infected. (10, 18) This is true whether the men are heterosexual or MSM. The reasons for this difference may be that men do not develop adequate immune responses to maintain protection. Studies have shown that at all ages antibody levels are lower for men than for women. (23) Alternatively, men may be having more new sex partners than women. In comparison, rates of HPV DNA detection in the oropharynx are much lower than reported for anogenital infections. Most studies have published prevalence rates of HPV in the oropharynx around 4–5%. (24) These figures are likely underestimates since most studies sampled the buccal mucosa or tongue whereas HPV likely resides deep in tonsillar crypts or at the base of the tongue.

Natural history studies of HPV in men show that HPV clears quite rapidly. One study found that over a one-year period, 94% of men cleared penile/scrotal HPV. (25) HPV infections of the anus also appear to clear faster than cervical infections in men and in women. (18, 26) On the other hand, HIV-infected men and women are unlikely to clear their anal infections —this is true for cervical infections in HIV-infected women as well. (27)

To date there have not been any prospective cohort studies in which high-grade anal intra-epithelial neoplasia (HGAIN) has been allowed to progress to cancer. Therefore the frequency and time frame during which HGAIN progresses to invasive cancer are not known in different risk groups. Several observational studies have demonstrated the precancerous potential of HGAIN. (28) Although anal cytology screening in MSM is performed in many centers, screening for HGAIN in men and women remains controversial since the progression rate of HGAIN to invasive cancer is not known. If cytology is performed, it is recommended that a diagnosis of atypical cells of undetermined significance or greater be the indication for evaluation using high resolution anoscopy. Clearly studies

are needed to better assess the utility of screening in these groups. (29) This is true for oropharyngeal and penile cancers as well. No screening guidelines exist for either cancer.

HPV vaccination

The cost-effectiveness to vaccinate boys and men remain controversial. Although there is a clear medical benefit in preventing anogenital and oropharyngeal cancers in men, these cancers remain comparatively rare in the US, and in some models vaccinating men to prevent these cancers demonstrate an unacceptably low cost-effectiveness. (30, 31) Adding protection against genital wart and respiratory papillomas as well as assuming some degree of preventing transmission to women improves the cost-effectiveness in other models. Typically the cost-effectiveness varies inversely with the proportion of eligible women in the general population who are vaccinated. (32) If the uptake is 50% or more among females, cost-effective studies have shown that vaccinating males would not likely benefit females in any substantial manner. However, if the uptake is lower, the value of vaccinating males by improving herd immunity may be greater. Recent data found that only one-third of 13–17 year old females received at least one dose and only 11% received all three doses. (33)

The US Food and Drug Administration (FDA) recently approved the HPV-6, 11, 16 and 18 (quadrivalent) vaccine from Merck (Whitehouse Station, NJ) (Gardasil) for use in males aged 9 to 26 years to prevent genital warts (condyloma acuminata). In the randomized placebo controlled trial in 3,463 males aged 16 to 23 years, the vaccine was found to be 89% effective in preventing genital warts among those who were adherent to the protocol (the per protocol group). Males were excluded if they had a history of external genital warts, genital lesions thought to be associated with HPV and greater than 5 lifetime sexual partners. They must have received all 3 vaccines and were naïve to HPV 6, 11, 16 and 18 at baseline. In addition, the study found that it reduced persistent HPV 6, and 11 anogenital infections (34) as defined by DNA detection from genital samples. The study also showed that the vaccine was 79% effective at reducing of the incidence of persistent HPV 16 infections and 96% of HPV 18 infections. In the full cohort, which included men who received at least one vaccination and included all subjects regardless of baseline HPV status, the efficacy to prevent external genital warts was 67%. Recently data were released on the quadrivalent HPV vaccine trial in MSM. The study enrolled 602 MSM aged 16 to 26 years of age and found an efficacy rate of 77.5% in preventing HPV 6/11/16/18-associated AIN in the per protocol group. The bivalent vaccine, Cervarix, is not approved for use in men.

These findings support the premise that the quadrivalent vaccine can reduce HPV disease and carriage in men. Given these data, American Committee for Immunization Practices (ACIP) gave a permissive recommendation for boys aged 11–12 years with a catch up of 13–26 years of age. Permissive recommendation allows for the use of the vaccine but stops short of placing it on the routine vaccination schedule. However, in the case of the quadrivalent vaccine, the ACIP also recommended that the cost of the vaccine be covered for boys eligible for the Vaccines for Children program.

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