COMMENTARY

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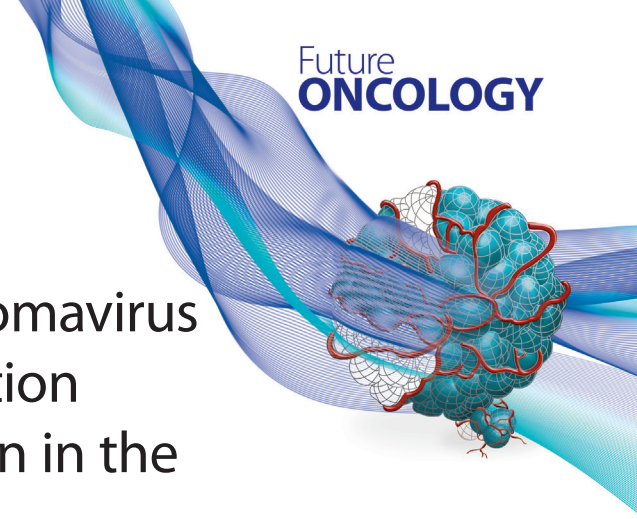

Variation in genital human papillomavirus infection prevalence and vaccination coverage among men and women in the USA

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Human papillomavirus (HPV) is the most common sexually transmitted infection that causes majority of anogenital and oropharyngeal cancers. Prophylactic HPV vaccine is available for the primary prevention of cancer and HPV transmission. Here, we are going to discuss the variation of HPV prevalence, HPV vaccination coverage and potential risk factors of men and women, retrieved from the cross-sectional study of the National Health Nutrition Examination Survey, a representative sample of noninstitutionalized, civilian residents in the USA. The overall penile HPV prevalence in men was 45.2% and the high risk oncogenic HPV prevalence defined by DNA testing was 25.1% that appeared to be widespread among all the age groups, which contrasts the vaginal HPV prevalence of 26.8% in women.

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KEYWORDS
• genital human papillomavirus • human papillomavirus • human papillomavirus vaccine • prevalence

Plain language summary

Human papillomavirus (HPV) is the most common sexually transmitted infection that causes anal, genital, mouth and throat cancers. We report a higher genital HPV infection prevalence rate in US men (45.2%) which appears to be widespread among all the age groups compared with women, with a low vaccination coverage of 10.7%.

HPV, the most common sexually transmitted infection, is the major cause of anogenital and oropharyngeal cancers in both men and women [1–4]. HPV infections can be classified into two categories: low risk (LR) HPV or high risk (HR) HPV. LR-HPV infection can lead to cutaneous warts whereas persistent HR-HPV infection in a susceptible host can lead to cancer.

Prophylactic vaccines to prevent HPV-associated cancers have been available since 2006. The Advisory Committee on Immunization Practices of Centers for Disease Control and Prevention has recommended HPV vaccination for adolescent girls at the age of 11 years to the age of 26 [5]. However, vaccination in men was not approved by the US FDA until 2009 and Advisory Committee on Immunization Practices provided guidance on HPV vaccination for genital warts prevention only. This guidance was further expanded in 2011, similar to women to the age of 26, to decrease HPV transmission and HPV-associated cancers [6]. The age cutoff in men mimicked women vaccination program, but this was determined without reliable epidemiological data on the genital HPV infection prevalence among men of all the age groups. Previously, a quadrivalent HPV (4vHPV) vaccine against types 6, 11, 16 and 18 was available. Subsequently, a 9-valent HPV (9vHPV) vaccine has been FDA-approved for HPV-related cancers that include additional HR HPV types 31,

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33, 45, 52 and 58, which would cover 90% of the HPV types responsible for cervical cancer [7]. Recent epidemiological data has led the Centers for Disease Control and Prevention to issue guidelines that only two doses of HPV vaccine are recommended for young adolescents aged to 14 years, instead of the traditional three shot series [8].

We recently showed that adult men in the USA have a high burden of overall penile HPV infection at 45.2% [9], which contrasts the prevalence of vaginal HPV among women at 26.8% [10]. The distribution of genital HPV infection in US men appeared to be widespread among all the age groups that followed a bimodal pattern with a peak among men of age 28–32 years (50.8%) and a second higher peak among men of age 58–59 years (59.6%). In contrast, HPV infection prevalence in women was higher in the younger age group and decreased as women aged. The HPV vaccination coverage in men, who were eligible for vaccine, was only 10.7% [9]. Over 25 million eligible US men did not receive HPV vaccination. Although the HPV infection prevalence was higher in men, the vaccination rate was lower as compared with women (31.5%) [10].

Estimates suggest 79 million persons are infected with HPV in which half of the new infections occur before the age of 24 [1]. In addition, over 11,000 cases of HPV-related cancers occur in men annually and are responsible for 63% of penile cancer, 89% of anal cancer and 72% of oropharyngeal cancer. It is important to emphasize the indirect causal factor for cervical cancer via men serving as reservoirs for HPV transmission [11]. LR HPV infection is not without consequence. HPV-6 and -11 are responsible for 90% of genital warts affecting 160,000 men annually [12]. HPV may also lead to recurrent respiratory papillomatosis [13].

The prevalence of oral HPV is relatively low as compared with genital infection, occurring in 10.1% of the men and 3.6% of the women, but the distribution pattern of oral HR-HPV infection associated with oropharyngeal cancer was similar to penile HPV infection with a bimodal pattern. Although the oral HPV prevalence is lower than genital HPV infection, the HPV-associated oropharyngeal cancers have significantly increased over time [14]. With this continued trend, the annual incidence of HPV-related oropharyngeal cancers surpassed the annual number of cervical cancers in 2015, despite the availability of a highly efficacious prophylactic vaccine against HPV [11].

A recent study from our group using The National Health and Nutrition Examination Survey, which represents a national sample of 76.9 million US men, revealed that the genital oncogenic HR-HPV infection prevalence for men of age 18–59 years defined by the DNA HPV test was 25.1%, which was widespread among all the age groups. In contrast, the prevalence of vaginal HPV infection was higher among women younger than 20 years, and then decreased with increasing age. The HPV prevalence with at least one of the 4vHPV types in adults of age 18–59 years was 8.5%, representing over 6.5 million US men. The overall prevalence of infection with at least one of the 9vHPV types was 15.1%. Prevalence of 9vHPV types was similarly elevated in vaccine noneligible group (14.6%), questioning the rationale behind the current age cut-off of HPV vaccination in men. Similarly, overall HPV-16 and -18 infection prevalence was 4.3 and 1.7%, respectively, without showing the difference between vaccine eligible and vaccine noneligible men. Prevalence of overall HPV infection was lowest in males of age 18–22 years at 28.9%, which may reflect the current practice of providing HPV vaccination to younger age group in men [9].

Demographic characteristics associated with genital HPV infection included age, race/ethnicity, marital status, education and age at first sex. The genital HPV prevalence was highest among nonhispanic black men (65.0%) and lowest among nonhispanic Asian men (24.4%). Similarly, nonhispanic black women had the highest prevalence at 39.2% [15]. Men who reported never having been married, living with a partner and separated from a spouse were twice as likely to have overall genital HPV infections as compared with married men. In HR HPV group, this prevalence increased to 2.8-times if separated from spouse [9]. These factors associated with HPV infections were similar in women. Nonhispanic black women had the highest HPV prevalence at 39.2% and married women living with spouse had the lowest HPV infection [15]. In addition, current tobacco use was not associated with male genital HPV infection, contrast to a known risk factor for female genital and oropharyngeal infections [9].

The overall HPV prevalence in men is similar to the recent research from Denmark (41.8%),

with the same HR HPV type 51, being the most prevalent type [16]. In females, the most prevalent HPV type was 53, and type 51 was the fourth most common type [15]. Furthermore, the most prevalent HPV subtype may not reflect putative potency of carcinogenesis. This inconsistency of the most prevalent HR HPV subtype in infection and in cancer may reflect different aggressiveness of HPV subtype, because common HPV subtypes in cancer are HPV 16 and 18, which is responsible for 70% of all anogenital cancer. This overall HPV prevalence in US men (45.2%) was found to be lower than the multinational population study (65.2%) [17]. The prevalence difference may also be due to the types of test that were used, the location of the male genital area swabbed and/or the study population. Nevertheless, the other study populations were heavily concentrated in the younger age groups with under representation of men above age 40 years [16,17]. Perhaps, the cumulative high prevalence of chronic, persistent infections would be expected to increase as it was shown in the oral HPV infection secondary to decreased immune response to natural infection in aging men [18].

Clearance of genital HPV infection in men has been reported to be between 6 and 18 months, which is comparable with women [19]. However, men have lower circulating HPV antibodies than women despite higher HPV infection prevalence [20]. This phenomenon may explain the difference in the HPV immune responses between genders. Multinational cohort study reported that the number of partners and new partners in the last 3 months was similar for all the age groups, hence potentially providing continued exposure to HPV throughout life in men [17]. Therefore, if men generate a lower and weaker HPV immune response in the setting of remaining at high risk of acquiring new HPV infections throughout their lives, then vaccination programs for older men might be warranted.

Any sexually active person is at risk for HPV infection given the high prevalence of this infection. Traditionally, sexually transmitted infections have a disproportionate burden among adolescents and young adults [1]. However, HPV is unique in that prevalence in men is high and widespread among all the age groups. In addition, most of these HPV infections are silent, asymptomatic and do not cause disease until later years with persistent infection that presents as cancers. Higher HPV prevalence among men suggests that there is a greater opportunity for increased vaccine effectiveness as a society as the vaccine coverage increases with the benefit of herd immunity. HPV vaccination may have a profound impact in the prevention of HPV-related cancers in both men and women as one serves as a silent host for the other, in addition to being a direct cause of anogenital and oropharyngeal cancers. Furthermore, widespread HPV infection in all the age groups of men questions the rationale regarding the current vaccination age cutoff, which warrants further evaluation. Only when vaccination coverage is significantly increased, progress will be made in eradicating most HPV-associated cancers in the USA.

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