Short Communication

Gender Bias in Human Papillomavirus-Associated Anal and Oral Cancers

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Abstract

HPV-associated anal and oral cancers are increasing. The reason is still unclear although sexual behavior changes in the general population are postulated as one of the factors. The incidence is drastically higher in specific risk groups, such as men who have sex with men, and HIV-1 infected individuals. Interestingly, anal cancer is predominant in women while a higher incidence of oral cancer is found in men. This review gives a brief summary of epidemic, risk factors, mechanisms, diagnosis, and treatment of these two HPV-associated cancers.

ABBREVIATIONS

HPV: Human Papillomavirus; MSM: Men who have Sex with Men; AIN: Anal Intraepithelial Neoplasia; OSCC: Oropharyngeal Squamous Cell Carcinomas

INTRODUCTION

Most sexually active individuals will have detectable human papillomavirus (HPV) at least once in their lifetime. Fourteen million people are infected annually, and 79 million people have the prevalent infection. Approximately 5% of the cancers globally are HPV-associated anogenital or oral cancers [1]. HPV is transmitted frequently between partners; more frequent transmission has been reported from females to males than from males to females [2]. The incidence of anal and oral cancers related to HPV is increasing in the general population and is growing even faster among individuals who are immunocompromised because of human immunodeficiency virus (HIV) infection [3,4]. Two prophylactic vaccines (Gardasil and Cervarix) have been approved for a decade. Recently, the nonavalent vaccine including additional high-risk HPV types is promised to provide more coverage against cervical cancers[5]. The HPV vaccine is recommended routinely for 11- or 12-year-olds, as well as for young men through age 21 years and young women through age 26 years who have not previously been vaccinated. HPy vaccine is also recommended for men who have sex with men (MSM), people living with HIV/AIDS, and immunocompromised persons through age 26 years. However, the high-risk HPV types included in the nonavalent vaccine contribute little to anal, oropharyngeal, penile, vulvar and vaginal cancer [5,6].

HPV infection is mostly asymptomatic, but may also have many diverse clinical signs encompassing benign anogenital lesions, and carcinomas [6]. Recently, anal and oral cancers are becoming the focus because the incidence has been greatly increasing in developed countries over the last decades, both in women and men, and the incidence is drastically higher in specific risk groups, such as MSM, and HIV-1 infected individuals [7,8]. A higher incidence of anal cancer as compared to oral cancer has been reported in HIV-infected individuals, which suggests that the anal epithelium may be more susceptible to HPV infection [10]. In this short review, the gender bias of these two HPV-associated cancers in the general population will be discussed.

HPV-ASSOCIATED ANAL CANCER

The HPV-associated anal cancer is a rare malignancy of the distal gastrointestinal tract. Ninety to ninety three percent of anal canal cancers are the clinical manifestation of HPV infection [1]. The incidence of HPV-related anal squamous cell carcinoma is increasing [9]. In general, anal HPV is more common in women as in men, and significantly more women than men carry multiple HPV types [9-12]. However, both MSM and heterosexual men showed a remarkable prevalence of anal HPV infection [7]. HIV-infected MSM and heterosexual HIV-infected men were also at risk for acquiring and sustaining persistent high-risk HPV types at the anal and penile sites and are also at risk for developing dysplasia at these sites in the future [18]. Unlike women, prevalence rates in men are steady at all ages, suggesting that men do not develop effective protection against reinfection [5]. Anal intraepithelial neoplasia (AIN) are very common throughout a wide range of
ages in both HIV-negative and HIV-positive MSM [6]. The few studies on the natural history of AIN in HIV-infected men suggest that high-grade AIN is a precursor to invasive anal cancer. The incidence of anal cancer in men has increased near three-fold in three decades in the United States [5].

Sexual behavior is a primary risk factor associated with anogenital tract among both men and women. A recent study demonstrated that persistence of high-risk HPVs was directly associated with the number of male anal sex partners and inversely associated with the number of female sex partners [11].

There are no clear guidelines over recommendation on the treatment and surveillance of patients with high-grade AIN [13,14]. Anal cytology as the solitary screening tool for anal cancer fails to detect anal dysplasia in a considerable number of patients [15,16]. HPV16 and HPV51 infections were associated with high-grade squamous intraepithelial lesions [12,14]. HPV16 DNA load was significantly associated with p16 (INK4a) expression, a biomarker for cancer [17,18]. The tumor cells positive for p16 are also positive for high-risk types of HPV [19].

Low sero-conversion rates following HPV infection in men may contribute to their susceptibility to recurrent infections that can progress to HPV-related cancers [20]. Recurrence rates remain high regardless of the treatment delivered, and surveillance is paramount, although optimal surveillance regimens have yet to be established [16].

HPV-ASSOCIATED ORAL CANCER

Head and neck cancers represent a unique challenge to clinicians because of their invasive, metastatic and highly recurrent nature [21]. Investigation of the prevalence of oral HPVs in the United States showed that among men and women aged 14 to 69 years the overall prevalence of oral HPVs was 6.9% [8,22]. HPV-positive oral cancer more commonly affects the oropharynx, specifically tonsils and base of tongue [21]. More than 90% of oropharyngeal cancers are associated with oncogenic type HPV16 infection [21]. Oral HPV infections are notably more frequent in men than in women, and the incidence of HPV-positive oropharyngeal squamous cell carcinomas [HPV-OSCC] has increased, predominantly among middle-aged adult men [3,24]. Significantly higher detectable HPV antibodies are found among women compared to men [20]. This may explain the differences in age-specific HPV prevalence and incidence patterns observed by gender [23]. The prevention of high risk HPV infection may result in a 4.7% reduction in the incidence rate of head and neck cancer in the United States [24].

The sharp rise in the incidence of HPV-OSCC in the United States has been attributed partially to changes in sexual norms over the past five decades, with a younger age at sexual debut and higher numbers of sexual partners per individual [17]. HPV-OSCC is associated with oral sexual behaviors [24,25]. Oral HPV was uncommon among sexually inexperienced individuals and increased significantly with the number of sexual partners [26,27]. A population-based cross-sectional study in rural China showed that the risk of oral HPV infection was significantly higher in the men with genital infection than the men uninfected [28]. This finding indicates that oral to oral and sexual transmission is the important route of oral HPV transmission. Additionally, increasing ultraviolet light exposure is also found significantly correlated to pharyngeal cancer in white males [29]. Although oral HPV incidence increased in both sexes, it was more than two times higher in men than in women [25].

The host immunity has been known to play an important role in the persistence of HPV infection. A recent study identified that several innate and adaptive immunity factors, including the cyclic guanosine monophosphate-adenosine monophosphate synthase (Cgas), and an adapter protein STING, form a critical viral sensing mechanism that detects intracellular DNA and initiate antiviral response [30]. For cancer development, expression of p16 (INK4a) has been identified as one of changes in the samples [31]. A recent study showed a combination of HPV DNA and p16 (INK4a) detection is a more accurate and reliable way for active HPV infection in the head and neck squamous cell carcinoma when compared with either one of the factors alone [32]. Several Toll-like receptors (TLR 4, 5 and 9) are also de-regulated during the progression of HPV-associated neoplasia [33,34].

SUMMARY

Sexual behavior changes in the general population contribute to the epidemic HPV infection at the oral and anal sites. The incidence of anal squamous cell carcinoma is predominant in women while the incidence of oral squamous cell carcinoma is more than two times higher in men. Most studies in human populations are retrospective, and the causal effect could not be established. Our recently established oral and anal papillomavirus mouse model will help us to explore the mechanisms of HPV-associated anal and oral cancer development [35-38].

The incidence of HPV-associated anal and oral cancers is increasing in high-risk populations including MSM, HIV-positive and immunocompromised individuals. A routine detection of the anal canal and oral sites are highly recommended in each clinic visit of HIV-infected men independently of their sexual behavior [23]. Despite discrepancies in the reported studies, several biomarkers (p16(INK4a), TLRs, etc.) together with viral DNA detection are useful predictors of HPV-associated oral and cancer development.

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