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Oral HPV infection and head and neck cancers in HIV-infected individuals

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Abstract

Purpose of review—HIV-infected individuals are living longer due to effective antiretroviral therapy and may therefore have a greater opportunity to develop HPV-associated malignancies. This review describes the risk factors and burden of oral HPV infection and HPV-associated Head and Neck Cancer (HNC) among HIV-infected individuals.

Recent findings—Oral HPV infection is commonly detected in HIV-infected individuals and is elevated among those with a higher number of lifetime oral sexual partners, current tobacco use, and immunosuppression. There is limited data on the natural history of oral HPV, but initial studies suggest the majority of infections clear within two years. While HIV-infected individuals are at much higher risk of most HPV-associated cancers than the general population, studies suggest HIV-infected individuals have a more modest 1.5-4 fold greater risk for HPV-associated HNC.

Summary—HIV-infected individuals are living longer, have a high prevalence of oral HPV infection and have many of the currently determined risk factors for HPV-associated HNC.

Keywords

Head and Neck Cancer; HIV; oral HPV; risk factors

Introduction

Human Papillomavirus (HPV) infection, a commonly detected DNA virus widely known as the necessary cause of cervical cancer,[1] has been established as a major etiologic factor for head and neck cancer (HNC).[2] Research suggests that HIV-infected individuals are at higher risk for oral HPV infection and HPV-associated HNC.[3,4] In this article, we review the literature on the risk factors and burden of oral HPV and HPV-associated HNC among HIV-infected individuals, discuss cancer prevention possibilities, and suggest future research directions.

HPV and Head and Neck Cancer Overview

HNC is a heterogeneous group of cancers which includes cancer of the oral cavity, pharynx, and larynx, and is the sixth most common cancer worldwide with an annual incidence of over 400,000.[5] HPV is known to cause a subset of HNCs, with HPV-associated HNCs having distinct genetic, clinical, and epidemiological characteristics from HPV-unassociated HNCs.[6] HPV-associated HNCs represent approximately 25% of all HNCs in the general population,[7,8] and usually arise in the oropharynx, which includes the base of the tongue

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and the lingual and palatine tonsils.[9] These HPV-associated cancers are independently associated with sexual behavior including recent and lifetime number of oral sex partners.[6] In contrast, the majority of HPV-unassociated HNC occurs in the oral cavity and larynx and is primarily associated with tobacco and alcohol use.[6]

Control of the cell cycle is impacted in both HPV-associated and HPV-unassociated cancers. HPV-associated HNCs involves E6 and E7 oncogene expression which functionally inactivate tumor suppressor genes p53 and pRB, while HPV-unassociated HNCs mutationally inactivate p53 and p16 which can lead to unregulated cell growth.[10,11] HPV-associated HNCs, which now account for many of the HNCs diagnosed before age 60, have shown better response to chemotherapy and radiotherapy, and improved survival compared to HPV-unassociated HNCs. [12,13]

The incidence of HPV-associated HNC has increased in the general population of many developed countries over the past several decades.[14*,15] This increase could be explained by generational differences in sexual behavior or increased persistence or progression of oral HPV due to changes in co-factors. Despite this increasing trend of HPV-associated HNC, the natural history of oral HPV has been largely unexplored.

Oral HPV infection among HIV-infected individuals

Several cross-sectional studies have observed that HIV-infected individuals have a 2-3 fold higher odds of prevalent oral HPV infection compared to HIV-uninfected individuals, even after adjustment for sexual behavior and other relevant factors.[3,16**] Recent studies suggest HIV-infected individuals have an overall oral HPV DNA prevalence between 20% and 45% (in the alpha genus), and an oncogenic oral HPV DNA prevalence between 12% and 26%,(Table 1).[3,16**,17] HPV16, which causes more than 80% of HPV-associated oropharyngeal cancers,[7,18] is the most commonly detected oral HPV type in HIV-infected individuals with a prevalence around 2-6%.[16,19-21*] In contrast, a study utilizing a representative population of the United States (US) found that 7% of healthy adults have a detectable oral HPV infection, while about 1%have detectable oral HPV16.[22*] Estimates of oral HPV prevalence among HIV-infected individuals likely vary because of multiple factors including differences in sample collection, processing, number of HPV types tested, DNA detection methods, and the study participant characteristics (Table 1).

The natural history of oral HPV has been largely uninvestigated. Preliminary studies suggest that similar to anogenitial HPV, a substantial proportion of oral HPV infections clear within one or two years.[21*,23*,24] In fact, oral HPV has been observed to clear modestly faster than anal HPV,[21*,23*] potentially due to local mucosal immunity differences in the anatomic sites. Oral HPV infection has also been observed to be intermittently detected among HIV-infected individuals who are recently sexually abstinent[23*] suggesting that oral HPV may be variably expressed or re-expressed from a prior latent state similar to anogenital HPV.[25]

Head and Neck Cancer in HIV-infected individuals

The risks of several different cancer types are elevated in HIV-infected individuals due to behavioral and biological characteristics, immunodeficiency, and potentially chronic inflammation and immune dysfunction/senescence.[26*] Indeed, HIV-infected individuals in developed countries are at modestly increased risk of both HPV-associated and HPV-unassociated HNCs compared to the general population. AIDS-cancer registry match studies have found that the standardized incidence ratios (SIRs) for HNC is between 1.5 and 4 fold higher among HIV-infected individuals compared with the general population (Table 2).[4,27-29] HIV-infected individuals are also at increased risk of laryngeal, oral cavity and

other HPV-unassociated HNCs,[4] which is likely due to their high prevalence of tobacco use,[30*] the strongest risk factor for these cancers.[31] While these registry match studies are not adjusted for various potential confounders other than age, one study which did control for risk factors including tobacco and alcohol use recently found a non-significant risk of oral cavity/pharynx cancer overall comparing HIV-infected and HIV-uninfected individuals in California (aRR=1.4, 95%CI=0.9-2.1).[32**]

While most studies have considered all HNC sites together, several registry-match studies attempting to approximate the risk of HPV-associated HNC have explored cancer risk in specific anatomical subsites and found that HIV-infected individuals have a 1.5-4 fold higher risk of oropharyngeal or tonsillar cancer compared to the general population (Table 2).[4,27,33,34] While estimates suggest that half or more of oropharyngeal cancers are HPV-positive in the general population,[14**,15] the proportion of HPV-positive oropharyngeal tumors in HIV-infected individuals is unknown. While their exact level of risk is unclear, HIV-infected individuals appear to be at moderately increased risk of HPV-associated HNC compared to the general population based on the modestly higher oropharyngeal cancer incidence. Interestingly, the magnitude of this increase (SIR∼1.5-4) is lower than other HPV-associated cancers such as anal, cervical, vulvar, and penile cancer which each have SIRs≥5.[4,27]

Impact of Sexual Behavior

An increased number of oral sexual partners is a risk factor for both oral HPV infection[16,35] and HPV-associated HNC.[6] Given the high number of lifetime sexual partners among many HIV-infected individuals,[16**,36] one might expect the incidence of HPV-associated HNC among HIV-infected individuals to be higher than what is currently observed; particularly among the most sexual active groups such as men who have sex with men (MSM).[16**,37] However, several registry based studies have found a non-significantly *lower* incidence of oropharyngeal cancer in HIV-infected MSM compared to HIV-infected injection drug users and heterosexual men (Table 2).[27,28,34] One potential explanation for this relatively modest HNC incidence among HIV-infected MSM is that the probability of acquiring oral HPV from performing oral sex on a man (fellatio) may be lower than when performing oral sex on a woman (cunnilingus). Indeed, a recent study we performed involving HIV-infected individuals suggests that heterosexual males have a higher incidence of oral HPV infection compared to MSM and heterosexual females after adjusting for relevant factors such as number of sexual partners.[23*] Two large studies also recently suggested that oral HPV DNA prevalence[22*] and HPV-associated oropharyngeal cancer[14*] are considerable higher in males compared to females in the US general population.

There are at least two hypotheses on why oral HPV may be more transmissible when performing oral sex on women. One hypothesis is that the female genital region may have a greater HPV viral load than the male genitals [38-41] despite having similar genital HPV DNA prevalences,[42-44] and this higher viral load in the female genitals could increase the likelihood of oral HPV acquisition. In contrast, a second hypothesis suggests that the keratinized epithelium from male genitals may be less likely to induce an immune (antibody) response than mucosal surfaces such as the cervix or the anal canal.[45,46*] Thus, the high level of natural antibodies developed after a cervical or anal HPV infection in women and MSM might conceivably be more likely to protect them from acquiring subsequent oral HPV infections.[45,47-49*] Further investigation is necessary to explore these hypotheses.

These hypotheses coupled with the demographics of the HIV-epidemic in developed countries may in part explain the moderate risk of HPV-associated HNC seen in the HIV-

infected population. In the US, approximately half of HIV-infected individuals are MSM, while a little over a quarter are women (who are almost all heterosexual).[50] This suggests that the proportion of heterosexual males (who perform oral sex on women) is lower among the HIV-infected population than the general population. If the risk of acquiring oral HPV infection is truly highest among heterosexual males, then this could help explain the relatively moderate risk of HPV-associated HNC (compared to other HPV-associated cancers) seen in HIV-infected individuals in developed countries.

Impact of Immunosuppression and Antiretroviral Therapy (ART) Use

HIV-related immunosuppression may be a strong risk factor for oral HPV incidence or persistence given the 2-3 times higher adjusted odds of oral HPV prevalence in HIV-infected individuals compared to HIV-uninfected individuals.[3,16**] Advanced stage of HIV disease, characterized by low CD4 T cell count and high HIV viral load, has also been associated with increased oral HPV prevalence which may reflect a loss of viral control in those with compromised immune systems (Figure 1).[3,16**]

The direct effect of immunosuppression on oral HPV persistence and HPV-associated HNC is currently less understood, but research on other HPV-associated cancers suggest immunosuppression may act more on the *earlier* stages of the HPV carcinogenesis process.[34,51] Oral cavity/pharynx cancer is elevated among both HIV-infected individuals and solid organ transplant recipients (another immunosuppressed population) suggesting a potential link between immunosuppression and HPV-associated HNC.[52] In addition, three studies have found that the incidence of oral cavity/pharynx cancer was non-significantly higher among those with a reduced CD4 T cell count,[28,32**,53] with Engels et al also finding a higher risk of oral cavity/pharynx cancer in individuals with AIDS relative to HIV-infected individuals who have not developed AIDS.[53] However, another recent study suggested reduced CD4 at AIDS diagnosis was associated with a *reduced* risk of oropharyngeal cancer among patients 28-60 months after AIDS offset.[27] One explanation for this heterogeneity in results could be from a higher proportion of HPV-unassociated HNCs in certain populations, as HPV tumor status has not been explored and HPV-associated and unassociated HNC might be differentially related to immunosuppression. These registry based studies also lack detailed covariate information such as sexual behavior and smoking status and cannot comprehensively evaluate the effect of cumulative and recent immunosuppression.

Effective antiretroviral therapy (ART, also known as HAART) has greatly improved the life expectancy of HIV-infected individuals while reducing viral-related malignancies such as Kaposi Sarcoma and Non-Hodgkin's lymphoma.[54] However, the incidence rates of HPV-associated malignancies have remained stable in the ART era, or have increased in the case of anal cancer. A preliminary study suggested ART use was associated with increased six month oral HPV persistence,[55] and other studies have suggested ART use is associated with an increase in oral lesions/warts.[56,57*] However, these studies may be prone to confounding by indication, as ART is more likely to be indicated for sicker individuals.

The role of ART on cervical HPV and related squamous epithelial lesions (SILs) has been more extensively explored with the majority of well-designed studies suggesting a benefit.[58-60] While some of the initial studies suggested a similar cervical HPV persistence and progression of SILs comparing ART users and non-users,[61,62] more recent reports suggest ART reduces the incidence of cervical HPV,[59] decreases the incidence of squamous epithelial lesions[58,60] and increases the regression of these lesions.[58,59] However, if ART use does not fully recover oral HPV-specific immunity it may not be able to substantially modify the elevated oral HPV incidence or persistence seen in HIV-infected individuals. Therefore, HPV-associated HNC could pose a further increasing threat for

immune-competent HIV-infected individuals, if ART improves survival but did not improve control of oral HPV infections.

Tobacco use and other co-factors for HPV-associated HNC

Although HPV-associated HNC has often been described as a cancer among non-smokers and non-drinkers, there is growing evidence that tobacco may play a substantial role in the development of some of these cancers.[63] Tobacco use is an established risk factor for cervical cancer,[64] and is associated with oral HPV prevalence [22*,35,65,66] and six month oral HPV persistence[67] in HIV-infected and HIV-uninfected individuals. Other studies have shown tobacco use can reduce the innate and cell-mediated immunity at the systemic level and in the local oral region[68,69], suggesting an immunosuppressive effect of tobacco.

The direct role of tobacco on HPV-associated HNCs is less clear as several studies have found an association,[18,70-72] while others have not.[6,73] This question is particularly important for HIV-infected individuals, as the prevalence of tobacco use in this population is considerable higher than the general population with estimates suggesting 40-70% of HIV-infected individuals in developed countries may be current smokers.[30,74]

There are several other factors being investigated that may increase the risk of HPV-associated HNC including marijuana and alcohol use. While there is a lack of data on these factors in HIV-infected individuals, epidemiologic studies among HIV-uninfected individuals have found inconsistent results between risk of HPV-associated HNC and both marijuana [6,75-77] and alcohol use [6,70] as some have observed an association and others have not.

Future steps and challenges

While prevention of HPV-associated HNC is a developing research area, screening for HNC remains a challenge. A recent study found that feasibility of an oral Pap smear equivalent remains poor in HIV-infected individuals, as the limited number of cytopathologic abnormalities observed were not associated with HPV16.[78**] Fakhry et al suggest that this potential screening tool may not be feasible due to anatomic sampling limitations and the relatively low incidence of HNC.[78**]

Although prophylactic vaccination is an effective tool to prevent other HPV-associated cancers, its efficacy in preventing HPV-associated HNC among HIV-infected individuals has not yet been evaluated. The recently developed HPV vaccines likely have the potential to protect against HPV-associated HNC, considering they include prevention of HPV16 which accounts for over 80% of HPV-associated HNCs.[7,8,18] While rigorous efficacy studies have not been performed, initial observational data suggest the vaccine may provide protection against prevalent oral HPV16 and HPV18 in young HIV-uninfected women.[79] The quadrivalent vaccine has been shown to be safe and immunogenic among HIV-infected individuals,[80,81] and is recommend by the American Council on Immunization Practices for HIV-infected individuals aged 11-26.[82] Efficacy studies for anogenital HPV are currently being performed in older HIV-infected individuals.[83*]

There are still several other unknowns regarding oral HPV infection and HPV-associated HNC among HIV-infected individuals. First, the proportion of HNCs cancers caused by HPV among HIV-infected individuals is currently unknown and would help to understand its etiology and identify who is at the greatest risk for this disease. In addition, it is not clear what factors increase the risk of oral HPV incidence, persistence and progression to subsequent HNC. The relative effects of HIV, reduced immunity, tobacco use, sexual behavior and other factors on the natural history of oral HPV are still not well understood.

Long term longitudinal studies are needed to further explore these factors and how they differ between HIV-infected and HIV-uninfected individuals.

Conclusion

HIV-infected individuals are living longer and therefore may have the opportunity to acquire more slowly developing HPV-associated malignancies. Indeed, HIV-infected individuals currently appear to have a moderately increased risk of HPV-associated HNC, which might potentially increase as this population ages. In addition, HIV-infected individuals have many of the potential risk factors for this disease (immunosuppression, increased sexual partners, tobacco use) and thus should be further studied and considered for future potential preventative measures.

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Key points

- HIV-infected individuals are at increased risk for all HPV-associated cancers, including HPV-associated head and neck cancercompared to the general population.
- Oral HPV infection is commonly detected in HIV-infected individuals, but the vast majority of infections appear to clear or be controlled within two years.
- Risk factors for oral HPV infection include immunosuppression, increased number of oral sexual partners and tobacco use.
- HIV-infected heterosexual males may be at higher risk of oral HPV and subsequent HPV-associated HNCcompared to heterosexual women and men who have sex with men with similar number of sexual partners.

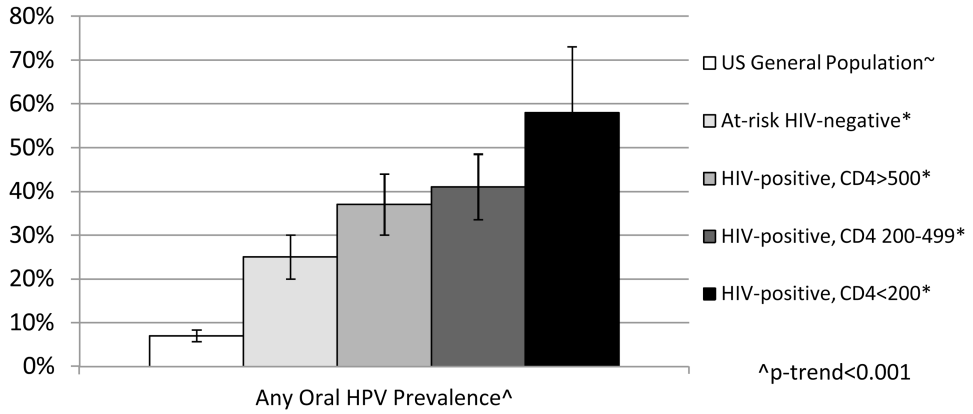

Figure 1. Impact of immunosuppression on oral HPV prevalence

∼Data from a representative sample of the US population, from the National Health and Nutrition Examination Survey (NHANES)[22*]

*Data from the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study(WIHS),[16**] HIV-uninfected individuals in this study were are at-risk for oral HPV due to their higher number of sexual partners and higher use of tobacco

Table 1

Summary of results from studies reporting prevalence of oral HPV DNA among HIV-infected adults, contrasted with US general population results

Study	Description	Sample Size	Sample Method	Any HPV*	Oncogenic HPV&	HPV16	Multiple types
Coutlee STD 1997[19]	US men and women	201	oral brush	14%	12%	3.0%	0.5%
Kreimer et al JID 2004[3]	US men and women	190	oral rinse/brush biopsy	25%	14%	---	5.8%
Cameron STD 2005[17]	US men and women	98	Saliva	37%	26%	6.1%	7.0%
Marais JMV 2008[23]	South African women	33	oral brush	33%	12%	3.0%	9.1%
Richter JOPM 2008[24]	South African women	30	oral brush	20%	7%	0.0%	6.7%
Fakhry Plos One 2010~[25]	US men and women	112	oral rinse	45%	26%	5.9%	---
Parisi BMCID 2011[26]	Italian MSM	166	oral swab	20%	1.5%	0.8%	---
Beachler et al CEBP 2012[16**]	US MSM and women	379	oral rinse	40%	21%	6.1%	19%
Read et al Plos One 2012[20*]	Australian MSM	249	oral rinse/brush	19%	8%	4.4%	7.2%
Del Mistro STD 2012[27*]	Italian men and women	100	Saliva	37%	13%	3.0%	6.0%
Steinau et al JOPM 2012[28**]	US men and women	100	oral rinse	39%	24%	3.0%	17%
Fatahzadeh et al OOOOE 2013 [29*]	US men and women	52	oral rinse	38%	23%	6.0%	---
Videla et al STD 2013[21**]	Spanish men	650	oral brush/rinse	16%	15%	5.2%	3.8%
Beachler et al JID 2013[30*]	US men and women	404	oral rinse	28%	13%	2.3%	11%
------	*HIV+ Summary*^	*2764*	-----	*26%*^	*15%*^	*4.2%*^	*8.5%*^
Gillison et al JAMA 2012[22*]	*US General Population*+	*5501*	*oral rinse*	*7%*	*3.7%*	*1.0%*	---

*Number of total alpha HPV types tested varied from 9 (Coutlee 1997) to 47 (Parisi 2011) although untyped genotypes were included in the prevalence estimates for several studies (Coutlee 1997, Cameron 2005, Del Mistro 2012). Cutaneous HPV types were not included in this summary.

&Number of oncogenic types varied from 7 (Coutlee 1997) to 22 (Kreimer 2004, Marais 2008) while most considered 13-14 types to be oncogenic

~Average point prevalences reported

^ Pooled oral HPV prevalence summary includes studies with differences in sample collection, processing, number of HPV types tested, DNA detection methods, and the study participant characteristics

+ Data from a representative sample of the US population, from the National Health and Nutrition Examination Survey (NHANES)

Table 2

Increased risk of Head and Neck Cancer comparing HIV-infectedindividuals with the general population

Study	Study Population	Type of Cancer	Standardized Incidence Ratios (SIRs) and (95%CIs)	
			Overall	HIV-Transmission Subgroup[#]
Shiels et al. JAIDS 2009[4][&]	Meta-analysis of developed countries (1980-2007)	Head and Neck	2.0 (1.1-3.6)	---
Simard et al. AIM 2010[34][^]	United States (1996-2006)	Oral Cavity and Pharynx	1.8 (1.5-2.0)	---
Silverberg et al. CEBP 2011[35**]	United States (1996-2008)	Oral Cavity and Pharynx	aRR[*]=1.4 (0.9-2.1)	---
Shiels et al. JAIDS 2009[4][&]	Meta-analysis of developed countries (1980-2007)	Oropharyngeal	1.9 (1.2-2.5)	---
Chatervedi et al. JNCI 2009[36]	United States (1980-2004)	Oropharyngeal	1.6 (1.2-2.1)	MSM: 1.1 (0.7-1.8), IDU: 2.1 (1.3-3.2), Hetero:3.2 (1.6-5.7)
Clifford et al. JNCI 2005[37]	Switzerland (1985-2002)	Lip, Oral Cavity and Pharynx	4.1 (2.1-7.4)	MSM: 2.0 (0.4-5.8), IDU: 13.7 (4.9-30.1), Hetero: 2.9 (0.3-10.5)
Frisch et al. JNCI 2000[38][^]	United States (1987-1996)	Tonsillar	2.6 (1.8-3.8)	Hetero Men: 5.3 (1.1-15.4)

[&] Meta-analysis included three studies considering oropharynx cancers and four studies exploring head and neck cancer.

[^] Both studies used data from the US HIV/AIDS Cancer match study

[*] Relative Risk based on an observational study controlling for potential risk factors such as tobacco and alcohol use

[#] MSM= Men-who-have-sex-with-men, IDU=Injection drug user, Hetero=Heterosexual