Published in final edited form as:

Oral Oncol. 2014 May ; 50(5): 364–369. doi:10.1016/j.oraloncology.2013.09.003.

Epidemiology of oral human papillomavirus infection

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Abstract

Human papillomavirus (HPV) infection is known to cause a subset of oropharyngeal cancers. Data regarding oral HPV infection is limited but emerging. HPV infection of the genital tract has been more thoroughly researched and helps inform our understanding of oral HPV infection. In this article we review current data on HPV prevalence, natural history, mode of acquisition, and risk factors for oral HPV infection.

Keywords

human papillomavirus; oral infection; oropharynx cancer; prevalence; incidence; natural history

Human papillomavirus (HPV) infection accounts for approximately 5.2% of the worldwide human cancer burden including the cancers of the anus, genital tract and oropharynx.^{1,2}

While the epidemiology, natural history and molecular biology of the HPV infection and subsequent development of cancers in the genital tract have been extensively studied in the past, there are many unknowns in oral HPV infection and its role in development of oropharynx cancer. The etiologic role of HPV infection in oropharynx cancer has now been firmly established.²⁻⁵ In the U.S., HPV now causes the majority of oropharynx cancer and the total number of the cases is expected to surpass the number of cervical cancers by the year 2020, if the current trend of increasing incidence of oropharynx cancer continues.²

In this review, we will highlight lessons learned from investigations of HPV infection of the genital tract and provide insight into interpretation of the current data in prevalence,

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Conflict of Interest: CHC served on an ad hoc scientific advisory board for Merck and received an honorarium. GD has research support from Merck.

incidence, natural history, mode of acquisition and risk factors of oral HPV infection. Because molecular mechanism, epidemiology, screening and prevention specific to HPV-related oropharynx cancer are reviewed in separate sections of this special issue, we will only briefly summarize the pertinent points in these topics for completeness of this review. Further understanding of epidemiology and natural history of the oral HPV infection can inform prevention strategies and screening of oropharynx cancer.

Biology of HPV infection

There are over 150 types of HPV, which have been categorized into “high-risk” and “low-risk” types based on their potential to induce malignancy in cervical cancer. The eleven HPV types currently classified as high-risk include: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, while oncogenic potential of 7 additional HPV types has been suggested in some studies, but not established.^{6,7} A single type, HPV 16, is responsible for the majority of HPV-associated cancers, and causes more than 90% of HPV-positive oropharynx cancer.³ Most HPV types are considered low-risk, including types 6 and 11 which cause anogenital warts and laryngeal papillomatosis.⁸⁻¹²

Human papillomavirus are small, non-enveloped DNA viruses, including oncoproteins (E5, E6 and E7) and capsid proteins (L1 and L2).¹³⁻¹⁶ Among the HPV proteins, E6 and E7 are the key drivers of carcinogenesis in oropharynx cancer by eliminating two of the most important tumor suppressors, p53 and Rb.¹⁵⁻¹⁹ Lack of p53 and Rb functions alter the genes regulating cell cycle resulting in deregulated cellular proliferation, anti-apoptosis as well as genetic instability, and subsequent formation of epithelial lesions of the skin or mucosa.^{15,16} Current data indicate that the reason low risk HPV types do not cause malignancy may be explained by weaker binding of their E6 and E7 to their target proteins, differences in promoter positioning and regulation, and pattern of mRNA splicing compared to E6 and E7 from the high risk HPV types.^{20,21}

In the cervix, HPV enters and infects the keratinocytes in the basal layer upon trauma to the cervical epithelium and exposure of the basement membrane.²² In the oropharynx, it is speculated that HPV enters the basal layer of the tonsillar epithelium and infects the crypt cells exposed by disruption of the epithelium and basement membrane that naturally occurs while trafficking of antigens, lymphocytes and antigen-presenting cells.^{16,23}

Prevalence of oral HPV infection

Epidemiology and natural history of oral HPV infection have not been well established. However, recent studies suggest oral HPV prevalence is substantially lower than genital HPV infection.²⁴⁻²⁹ In epidemiologic studies cervical HPV prevalence ranges from 27-43% among U.S. females aged 14 to 59 years.^{26,28} While oral HPV infection in the comparable age group is lower ranging 0.9-7.5% (Table 1).^{25,30-34} In a systemic review of the literature including 18 published studies between 1997 and 2009 that detected oral HPV DNA, the pooled prevalence of oral HPV infection in 4,581 healthy individuals were determined.³⁵ The prevalence of any HPV infection was 4.5% [95% confidence interval (CI), 3.9%–5.1%], and prevalence of high-risk (oncogenic) HPV was 3.5% (95% CI, 3.0%–4.1%). Prevalence of oral HPV16 in this study was 1.3% (95% CI, 1.0%–1.7%).³⁵

A recent cross-sectional study conducted as a part of the National Health and Nutrition Examination Survey (NHANES) between 2009 and 2010 examined the prevalence of oral HPV infection in the general U.S. population.²⁵ The study population included 5,579 men and women, aged 14-69 years. Extracted DNA from mouthwash samples of each subject was tested for 37 types of HPV to determine presence of oral HPV DNA. Overall prevalence of oral HPV infection for any HPV type was 6.9% (95% CI, 5.7%–8.3%).²⁵ This study provides an estimate of oral HPV prevalence in the general U.S. population, and the prevalence in this 2009-2010 study is slightly higher than that observed in the systematic review³⁵ which had data from 1997-2009. In this population based NHANES study, the prevalence of 18 high-risk HPV types was 3.7% (95% CI, 3.0%-4.6%) and of 19 low-risk HPV types was 3.1% (95% CI, 2.5%-3.9%). The most common high-risk HPV type was HPV16, with a prevalence of 1.0% (95% CI, 0.7%-1.3%) corresponding to approximately 2.13 million infected individuals in the U.S. While the prevalence of genital HPV infection in the general population is highest among young adults (20-24 years), the prevalence of oral HPV infection in the general population seems to follow a bimodal pattern by age more similar to that of anal and penile HPV infection, peaking first in 30 to 34 year olds (7.3%; 95% CI, 4.6%-11.4%) and then a second, higher peak among 60 to 64 year olds (11.4%; 95% CI, 8.5%-15.1%; Figure 1).

In a study by Pickard, *et al.*, a population of 1,000 men and women college students between ages of 18 and 30 years were studied.³⁰ The prevalence of oral HPV infection was 2.4% (95% CI, 1.4%-3.4%) and HPV16 infection was rare at 0.2% (95% CI, 0%-0.4%).³⁰ HPV prevalence was higher in another recent study explored oral HPV infection in 1,688 healthy men aged from 18 to 74 with a median age of 31 years in the U.S., Mexico and Brazil. The prevalence of all 38 tested HPV types was 4.0% (95% CI, 3.1%-5.0%).²⁹ The prevalence of 12 high-risk HPV types was 1.3% (95% CI, 0.8%-2.0%) and similar across countries. Again the most common high-risk HPV type was HPV16 in all three countries; however, interestingly HPV55 was more common in Mexico compared to the U.S. or Brazil suggesting the prevalence of common HPV types may vary depending on populations.²⁹ The variations in oral HPV prevalence among different studies may be attributed to differences in study populations, sampling and testing methods, and possibly the time periods studied.

Oral HPV Transmission

It is not yet fully understood how oral HPV infections are transmitted, although data strongly support sexual transmission. Cross sectional data suggests oral HPV infection is usually spread from performing oral sex on an infected genitals, or rimming an infected anus.³⁶ It is not clear whether HPV can be spread through deep kissing (French kissing). Some initial evidence suggests that vertical transmission might be possible. For example, persistent oral HPV infection in mothers was associated with an increased risk of persistent oral HPV infection in their infants in one study, suggesting a possible non-sexual route of oral HPV transmission.³⁷ There is no evidence for auto-inoculation or other non-sexual transmission, although we cannot yet exclude this possibility.

Identical HPV strains have been reported in one couple who both had oropharynx cancer, supporting the hypothesis of oral HPV transmission between the couple.³⁸ However, sexual behaviors (e.g. number of oral sex partners, number of vaginal sex partners) are co-linear, and it can therefore be difficult to differentiate which behaviors transmit HPV infection to the oral cavity. Partners of women with cervical cancer also have a higher incidence of oropharynx cancer than the general population³⁹ supporting the transmission of HPV from the genital region of an infected woman to the oral cavity during oral sex.

In addition, oral HPV prevalence has also been explored in women with a cervical HPV infection, with widely varying results between studies, from 2.6% to 50%.⁴⁰ Women with concurrent oral and genital HPV might have an increased susceptibility to HPV infection through either hereditary or immune deficit vulnerability, or the co-infection might be explained by overlap in sexual behaviors that increase the risk of oral and cervical HPV, or that infections could be acquired orally and genitally from the same infected partner during oral and vaginal sex. Several studies, however, have found low agreement of oral and cervical HPV infections within the same individual. A meta-analysis of women with cervical HPV infection estimated that 27% of the women displayed type-specific concordance between oral and cervical HPV DNA.⁴⁰ Several reports on type-specific concordance have similarly found no significant association between cervical and oral HPV infection or anal and oral HPV infection.^{41,42} This low concordance of oral and anogenital HPV infection, specifically a lack of type-specific concordance, suggests that self-transmission of oral HPV infection from the anogenital region within the same individuals to the mouth is uncommon, if it occurs at all.

While oral sex has been significantly associated with oral HPV prevalence in most studies, some studies have not shown any association. In the cohort of pregnant women and their spouses, Rintala, *et al.* found that the partner's genital HPV status did not predict acquisition of oral high-risk HPV.⁴³ Similar results were found in a study on the epidemiology of oral HPV infection among a multinational sample of healthy men, in which Kreimer *et al.* found that individuals who reported never performing oral sex had a similar prevalence of oral HPV infections compared with those who reported ever having oral sex (3.8% vs. 4.1%, respectively).^{29,44} However, both these studies included large numbers of married couples. In some recent studies, oral HPV infection was associated with higher number of open-mouthed kissing partners, even when restricted to subjects who had never performed oral sex (although the number of these participants was limited).^{30,32} Thus we cannot exclude the possibility that other behaviors, such as kissing, may be relevant to the transmission of HPV infection.

Natural history of oral HPV infection

Natural history of oral HPV infection such as incidence, duration of infection and ultimate development of oropharynx cancer is not yet well understood. Initial studies suggest that most oral HPV infection are likely cleared within a year.^{25,29,30,36,45} In a study of college students, followed at a 3 month interval, oral HPV incidence was 5.67 per 1,000 person-months (95% CI, 3.12-8.16/1,000 person-months).³⁰ In a recent prospective cohort study of 404 HIV-infected men incidence of oral HPV was 31 per 1,000 person-months.³⁶

Initial studies of oral HPV clearance suggest most infections clear. Sixty five percent of prevalent infections and 85% of incident infections in a study of adult men cleared within 12 months.⁴⁶ Among HIV-infected adults clearance was lower, with 47% percent of prevalent infections and 60% of incident infections cleared within 12 months.³⁶ Interestingly, this clearance was significantly quicker than anal HPV infections in these same participants. Another study of 733 HIV-positive men, reported that 44% of infections cleared (defined among those with prevalent baseline infections, as absence of that HPV type in the follow-up samples).⁴⁵

While oral HPV natural history data is limited, we can also refer to what is known about genital HPV infection as a model of what may be generally expected for oral HPV. In a prospective cohort study of female adolescents, aged 13-18 years, 50% of incident cervical infection were cleared within 8-12 months of infection and only approximately 10% of the individuals had persistent infection beyond 2.5 years.⁴⁷ Persistence was higher among subjects co-infected with HIV.⁴⁷ Initial studies suggest that oral HPV natural history is similar, with most infections clearing on their own within a year or two.

Risk factors for oral HPV infection

Numerous cross sectional studies which have explored oral HPV prevalence have also examined risk factors associated with oral HPV infection.^{25,29,30} The most consistent risk factors associated with prevalent oral HPV infection in these cross sectional studies are male gender, sexual behaviors and tobacco exposure. In the NHANES study, oral HPV prevalence was notably higher in men than women (10.1% vs. 3.6%).²⁵

Prospective studies suggest that HPV acquisition increases around sexual debut with prevalent oral HPV detected in 1.5% of 12–15 year olds and 3.3% of 16–20 year olds, supporting oral HPV infection is a sexually transmitted disease; therefore, it is not surprising to see the strong association with sexual behaviors and oral HPV infection.³³ Performing oral sex has been strongly associated with oral HPV in most studies. For example, in the NHANES study, oral HPV prevalence was 8-fold higher among participants who reported ever having had sex than for those who reported having had no sexual activity (7.5% vs. 0.9%; $P<0.001$) and increased with number of lifetime or recent sexual partners for any kind of sex, vaginal or oral sex.²⁵ As expected, the prevalence of HPV infection was the highest among participants with more than 20 lifetime sexual partners with a prevalence of 20.5% (95% CI, 17.4-23.9).²⁵ In addition, tobacco use is strongly associated with the risk of oral HPV infection. Use of ≥21 cigarettes per day was strongly associated with increased prevalence at 20.7% (95% CI, 12.6-32.0) compared to a prevalence of 1.1% (95% CI, 0.6-2.3) in individuals with 0 cigarette use per day in the NHANES study.²⁵ Also, in the study of 1,680 healthy men, the strongest association for oral HPV was seen with current tobacco use which increased the odds of the infection by 2.5-fold (95% CI, 1.4-4.4).²⁹

Other studies have reported that the prevalence of oral HPV infection is higher among HIV-infected individuals.⁴⁸ When 379 HIV-positive and 266 at-risk HIV-negative individuals were tested for oral HPV infection, the prevalence among the HIV-positive group was 40% while prevalence in the at-risk HIV-negative group was 25%.⁴⁸

Common risk factors between oral HPV infection and oropharynx cancer

Several studies have also looked at the prevalence of oral HPV infection among patients with oropharynx cancer. HPV16 DNA is detected in oral rinses of ~50% of cases with HPV-16-positive oropharynx cancer patients.⁴⁹ Patients with HPV-positive oropharynx cancer in particular are significantly more likely than individuals without cancer to have oral infection (OR~12), and the association is even stronger for HPV type 16 (OR~15).⁴ Higher number of sexual partners is associated with increased odds of HPV-positive oropharynx cancer.^{4,25,32,50,51} However, as sexual behaviors are co-linear, many sexual behaviors are similarly associated with increase odds of HPV-related oropharynx cancer, and we cannot distinguish which behaviors transmit oral HPV from these cross sectional studies.⁵¹⁻⁵³ Tobacco use has also been associated both with increased oral HPV prevalence and with increased oropharynx cancer. The effect of tobacco specifically on HPV-positive oropharynx cancer is less clear, with some studies suggesting increased risk⁵⁴, but others suggesting no association.^{51,55} While median tobacco use is less among HPV-positive than those with HPV-negative oropharynx cancer, more than half of HPV-related oropharynx cancer patients has significant history of tobacco use.^{4,25,56}

Trends in oropharynx cancer incidence

The incidence of HPV-related oropharynx cancer has significantly increased over the last three decades in several countries.^{2,57-60} A U.S. cancer registry study found that the incidence of HPV-negative head and neck cancer declined by 50% from 2.0 cases per 100,000 to 1.0 per 100,000 between 1988 to 2004.² Over the same time period, the incidence of HPV-positive HNSCC instead increased by 225% from 0.8 per 100,000 to 2.6 per 100,000. This increase was only observed among men and was primarily among younger individuals. Also, within this study, 271 oropharyngeal cancer tumors were available to test for presence of the HPV DNA and related biomarkers. They found that the proportion of oropharyngeal cancers that were caused by HPV increased dramatically from 16.3% to 71.7% between 1984 and 2004.² Similar increases have been reported in some European countries.⁶¹

Prevention of oral HPV infection

There is currently no validated screening method for HPV-related oropharynx cancer which has been shown to be effective. Although HPV DNA can be detected in oral rinses, and is associated with increased odds of HPV-related oropharynx cancer in case-control studies, cohort studies suggest most oral HPV infections clear quickly and thus may not be useful for screening. In the cervical cancer model, persistent HPV infection is an established risk factor for developing high-grade cervical intraepithelial neoplasia⁶² and cervical HPV testing is being incorporated into cervical cancer screening algorithms. The potential public health benefit of screening for oral HPV infection and HPV-related oropharynx cancer is unknown.

For oral cancers (oral cavity and oropharynx), current recommendation is visual examination often performed by a dentist in the general population, and additional examination with a laryngoscope by head and neck surgeons in patients with previous history of pre-malignant and malignant diseases.⁶³ In addition, step-wise epithelial changes

from normal, cellular atypia, dysplasia, carcinoma *in situ* to invasive carcinoma in cervical cancer are well delineated.²² However, premalignant lesions of oropharynx cancer have not been identified; therefore, involved cellular changes from oral HPV infection leading to invasive oropharynx cancer are entirely unknown. The lack of visible pre-malignant lesions for HPV-related oropharynx cancer make visual exam ineffective in screening for these cancers. It is hopeful that the HPV vaccines will prevent oral HPV infection and thus decreased HPV-positive oropharynx cancer rate. Indeed while initial randomized control study data evaluated efficacy for only cervical and anal HPV endpoints, recent data supports the efficacy of the vaccines for oral HPV as well.⁶⁴

Summary

It is clear that the disease burden caused by HPV infection in certain subgroups is significant.¹ Increasing amounts of data indicate that oral HPV infection is relatively common, but that like anogenital HPV infections, most oral HPV infections likely clear on their own within a year or two. While our current knowledge of epidemiology, natural history and prevention of oral HPV infection remains limited, studies show that oral HPV infection is sexually transmitted and that male gender, current tobacco use, and HIV infection are associated with increased prevalence.

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Figure 1. Modeled HPV prevalence across age in the U.S. population aged 14 to 69 years by sex and HPV types.²⁵ (Reprinted with permission. Journal of American Medical Association. All rights reserved.)

Table 1

Summary of oral HPV prevalence estimates among young adults in the United States.

Author (Year)	Sample Size	Study Population	Oral HPV Prevalence Estimate
Gillison et al (2012) ²⁵	792	18-24 year old convenience sample of men and women from general population (NHANES)	5.6%
Pickard et al (2012) ³⁰	1,000	18-30 year old male and female convenience sample from Ohio State University	2.4%
Edelstein et al (2012) ³¹	212	18-24 year-old men within ongoing male HPV cohort study at the University of Washington	7.5%
D'Souza et al (2009) ³²	210	18-23 year old college-aged men in Maryland/Baltimore area	18-19 year olds: 0.9% 20-23 year olds: 5.0%
Smith et al (2007) ³³	336	16-20 year old men and women from a pediatric clinic within the University of Iowa medical system	3.3%
Summersgill et al (2001) ³⁴	97	13-20 year old girls and boys seen in Family Practice or Pediatric outpatient clinics of the University of Iowa Health Care system	5.2%