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# Epidemiology of oral human papillomavirus infection

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SUMMARY

*Objective:* To describe what is known about the epidemiology of oral human papillomavirus (HPV) infection.
*Methods:* In this article we review current data on HPV prevalence, natural history, mode of acquisition, and risk factors for oral HPV infection.
*Results & Conclusion:* Over the past several years new studies have informed our understanding of oral HPV infection. These data suggest oral HPV prevalence is higher in men than women and support the sexual transmission of HPV to the mouth by oral sex. Data is emerging suggesting that most oral HPV infections usually clear within a year on and describing risk factors for prevalent and persistent infection. Recent data support likely efficacy of the HPV vaccine for oral HPV, suggesting vaccination may reduce risk of HPV-related oropharyngeal cancer.



## Introduction

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 US, 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, 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

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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% to 43% among US females aged 14–59 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 4581 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 US population [25]. The study population included 5579 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 review [35] 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 US. 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 30–34 year olds (7.3%; 95% CI, 4.6–11.4%) and then a second, higher peak among 60–64 year olds (11.4%; 95% CI, 8.5–15.1%; Fig. 1).

In a study by Pickard et al., a population of 1000 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 1688 healthy men aged from 18 to 74 with a median age of 31 years in the US, 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 US 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 population [39] 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 in-

**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] | 1000 | 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% |