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Review

Oral and laryngeal HPV infection: Incidence, prevalence and risk factors, with special regard to concurrent infection in head, neck and genitals

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ABSTRACT

This review focuses on the importance of oral and laryngeal HPV infection which is present in majority of sexually active individuals at least once in their lifetime. Despite testing, still little is known about prevalence rates, determinants and, especially, the concurrent HPV infection in head and neck, and genitals. The purpose of this review is to clarify some issues of oral HPV incidence, prevalence, and to demonstrate the difficulties in identification of asymptomatic oral HPV carriers. The main premise to take up this topic is the high and still increasing risk for development of oropharyngeal cancer, and potential benefit from screening strategies, education programs and HPV vaccination.

Transmission of HPV to the oral cavity and oropharynx is hypothesized to occur mainly through sexual contact. The exposure of oropharyngeal mucosa to HPV infection with consequence of increased risk for oropharyngeal carcinoma depends on specific sexual behavior. Male gender, older age, race or ethnicity, oral hygiene and current cigarette smoking are independently associated with any prevalent oral HPV infection.

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1. Introduction: The importance and burden of oral HPV infection

Human papillomavirus (HPV) infection is the most common sexually transmitted infection. Persistent high-risk HPV infections are known to be responsible for the development of cervical and oropharyngeal cancers (OPCs) after a long latency period. HPV infections are often asymptomatic, unrecognized and underestimated. The American Center for Disease Control and Prevention (CDC) highlights the fact that the majority of sexually active individuals becomes infected with HPV at least once in their lifetime, often without being aware and not presenting any symptoms.[1] HPV infection is considered the most common sexually transmitted disease among both males and females.[2–4]

Testing for high-risk HPV types is the established procedure in cervical screening context around the world. European Guidelines for Quality Assurance in Cervical Cancer Screening established the principles of organized population-based screening.[5] Still little is known about prevalence rates and determinants of oral HPV infection, etiologically linked with OPCs and other head neck pathologies.[6] There is also a gap in knowledge concerning the incidence of concurrent HPV infection in head and neck, and genitals.

High-risk HPV types 16 and 18 are present in over 70% of cervical cancer cases. The presence of HPV in OPCs is slightly lower: 60% in the USA,[7–9] 40% in Europa[10] and 33% in other parts of the world.[11,12] A global increase of the burden of HPV-related OPC has been observed. Up to the year 2000 the percentage of HPV-related OPCs was 41%. Until 2004 it increased to 72%, and after 2004 there was an increase up to 96% in more recent reviews.[13] High-risk HPV 16 accounts for over 90% of HPV types in OPC's.[14] Low-risk HPV (LR-HPV) types 6 and 11 are responsible for vaginal and genital warts and recurrent respiratory papillomatosis (RRP).[15]

The purpose of this review is to clarify some issues of oral HPV incidence, prevalence, and to demonstrate the difficulties in identification of asymptomatic oral HPV carriers. Our main objectives are to 1) emphasize the high and increasing risk to the development of OPC, 2) highlight potential benefits of screening strategies, 3) provide information on whether, and if, how the HPV carriers are spreading the oropharyngeal infection, 4) summarize the impact of sexual behavior and 5) track the concomitant HPV infection in head and neck, and genitals. These are important directions for the future.

2. Incidence and prevalence of oral HPV infection

Incidence and prevalence estimates for all HPV types in the oral cavity or oropharynx vary substantially (table 1). The variability of data has been attributed to differences in study populations and approaches to specimen collection, processing, and testing.[16] Screening for oral HPV infection among healthy adults using saliva or oral lavage testing, have reported overall prevalence rates close

Table 1
Prevalence estimates for all HPV types in the oral cavity or the oropharynx.

HPV type	Group	Prevalence	Incidence	Reference
All HPV types	Denmark and Japan. Adults without HPV disease.	<1% to >50%		[39,83]
All HPV types	Metaanalysis, healthy persons	7.7%	4.38 cases per 1000 person-months	[84]
All HPV types	Italy. HIV-positive men	20%		[72]
Any oral HPV	USA. Adults aged 14–69 y	6.9%		[8]
Any oral HPV infection (HR-HPVs 16, 18, 58, 59, LR-HPVs 6, 81, 13)	Mexico. All women seeking prenatal care	14%		[41]
Any oral HPV	USA. Men and women 18–69 y	Men 11.5%, women 3.2%		[45]
Any oral HPV	Denmark, USA, Japan. Healthy adults	Higher in women than men		[19,39,40]
Any oral HPV	Southeast Mexico	Higher in women (14.8%) than men		[41]
Any oral HPV	USA. Adults aged 14–69 y	Bimodal age distribution: peak prevalence at age 30–34 and 60–64		[8]
Any oral HPV	USA. HIV-infected male vs. female aged 18–24 years	19.7 vs. 18.6%		[85]
Any oral HPV	USA and South Africa	12–15 year-olds 1.5%; 16–20 year-olds 3.3%		[86]
Any oral HPV	USA and South Africa	Adolescents/young adults 5%		[86–88]
Any oral HPV	Sweden. Women attending a clinic for contraception and sexually transmitted infection treatment	Young females 9.8%		[89]
Any oral HPV	USA. Sexually active urban young ninth-grade women	14–20 year-old 19.6%		[60]
Oral HPV16	USA. Men and women 18–69 y	6 times more common in men than women		[45]
Alpha-genus HPV, oral cavity or oropharynx	USA. Sexually active young men, 18–24 y at enrollment	2.8%		[17]
Alpha-genus HPV, oral cavity or oropharynx	USA. Sexually active young men, 18–24 y at enrollment		12-month cumulative incidence 0.8%	[17]
High-risk HPV	USA. Men and women 18–69 y	4.0%		[3]
High-risk HPV	Finland. Fathers-to-be (average age of 29 y)		12-month cumulative incidence approximately 5%	[90]
HR-HPV	Poland. Respiratory tract in pre-school children	0.0%		[91]
High-risk oral HPV infection	USA. Men and women 18-69y	Men 7.3%, women 1.4%		[45]
Laryngeal HPV6 and HPV11 (recurrent respiratory papillomatosis, RRP)	Netherlands. RRP patients of all ages	Trimodal age distribution: peaks at three median ages 7, 35 and 64		[58]
LR-HPV	Poland. Respiratory tract in pre-school children	19.6%		[91]
Oral LR-HPV	Newborns who are at risk for RRP	0.9%		[60–62]

to gargle/ rinse specimens (1.3–2.8%).[17–19] Oral specimens collected by cytobrush showed higher rates (7%).[20,21] Collection by both gargle/ rinse and directed swab/ cytobrush appears to be more sensitive than collection by a single method.[21]

Low oral HPV viral copy numbers might be missed depending on the sensitivity of the assay.[22] The ability to estimate rates of HPV type-specific acquisition and clearance is limited by the rarity of oral HPV infection.[23] Standardizing methods of oral sample collection and HPV detection would ensure comparability between future oral HPV studies.[24]

2.1. The importance of sexual behaviors for oral HPV exposure

The majority of oral oncogenic HPV infections among both men and women are attributable to sexual behavior.[25,26] The higher burden of oral oncogenic HPV infections and HPV-positive OPC among men arises in part from higher numbers of lifetime sexual partners and stronger associations with sexual behavior among men.[8,27,28] Specific sexual practices (i.e., receptive oral sex) enhance the exposure of oropharyngeal mucosa to HPV infection with consequence of increased risk for OPC.[29,30] A greater number of partners for any and oral sex, a younger age at sexual debut and ever having had oral sex have been shown to be associated with risk of OPC, despite the differences found in gender.[30] Due to their sexual practices, men who have sex with men harbor the highest prevalence of anal HPV[31,32] and show a significantly higher prevalence of oral HPV infection than the general population. This observation is in line with high prevalence of oral HPV infection in women who have sex with women.[33] Sexual habits are also associated with genotype-concordant genital and oral HPV infections among women.[29,32,34] Recent oral sexual exposure was more important for genotype-concordant vaginal and oral HPV infections than the cumulative sexual exposure.[34] Another very strong risk factor for oral HPV infection is commercial sex.[35]

3. Concurrent HPV infection in head and neck, and genitals

To date, few studies have addressed concurrent infection in the head and neck and the genital tracts, although HPV tropism for both sites is a well-known phenomenon.[2,36] Transmission of HPV to the oral cavity and oropharynx is hypothesized to occur mainly through sexual contact (oral sex or open-mouth kissing) but determinants of acquisition have not been fully established through longitudinal studies. The prevalence of HPV infection and HPV types in the oral cavity and cervix of 196 female sex workers in Japan was 12 (6.1%) and 103 (52.6%) respectively, but only two were infected with the concordant HPV genotype in the cervix.[37] The lack of association in HPV positivity and types between the cervix and oral cavity in over 500 pregnant women suggests that self-inoculation is uncommon.[38] The source of infection does not appear to be from oral contact with a current male partner, since there also was no concordance between partners.[38] As well, the presence of HPV infection in the oral cavity was low in the group of women with abnormal cervical cancer screening findings and a high rate of cervical HPV infection.[39] Also among sexual partners in Germany, HPV transmission to the oropharynx by oral-genital sex or by autoinoculation was a rare and unlikely event with low HPV concordance [40] and similarly in male patients in Vietnam.[41].

These findings suggest that oral HPV infection occurs independently of cervical HPV infection.[37] Cervical lesions do not lead to HPV oropharyngeal infection; oral HPV infection may play an independent role in HPV transmission.[42] Therefore either other modes of HPV transmission, or differences in susceptibility to HPV infection or its clearance in the oral cavity and genital mucosa play a role.[38] Another explanation for the low oral prevalence could be an independent clearance of HPV from the oropharyngeal site compared to cervix uteri or clearance at different time intervals.[40] The exception was high prevalence of HPV, multiple infections in both anatomical regions, strongly related to the persistence of the type 16 HPV in cohort of HIV positive women.[43] Therefore, this is univocally high-risk population and it is very important to control and monitor this cohort as well as implement programs for the early detection of HPV and vaccination. Quite the opposite is the case with cervical and anal HPV infections, which are highly correlated; thus HPV-based cervical cancer screening programs might help to stratify anal cancer risk, especially women older than 45 years[44].

4. Non-sexual factors influencing acquisition of oral HPV infection

Besides lifetime number and number of recent sex partners other factors as male gender, older age, race or ethnicity, oral hygiene and current cigarette smoking are independently associated with any prevalent oral HPV infection.[8,27,45] These factors will be discussed below. The associations between non-sexual factors and prevalent infection are consistent with the hypothesis of an altered immune control, which in turn could increase the risk of acquisition or persistence of oral HPV infection.[46,47] Acquisition of oral oncogenic HPV was similar across countries, age groups, and reported sexual habits.

4.1. Gender

As shown in table 1, some studies report oral HPV infections to be higher in men than in women.[46] However, a higher prevalence of any oral HPV infection among women than men has been reported by others.[19,48–50]

Orogenital HPV transmission is higher from women to men than the other way around.[51–53] This is supported by a study stating that among men and women who reported having same-sex partners, the prevalence of high-risk HPV infection was 12.7% and 3.6%, respectively.[54] A logical outline is that the risk of oral HPV infection is reportedly higher among heterosexual than homosexual men.[55] A weaker immune response to HPV among men has been postulated.[32,56–58] This could potentially explain the observations of the later peak in prevalence with increasing number of sexual partners and the stronger increase in oral HPV prevalence with increasing age among men versus women.[27] Some state that males have a significantly higher prevalence of HPV16 infection than females in oral rinse samples indicating a sex-specific susceptibility to HPV16 infection.[59] This is, however, contradictory to statements by others.[19,48–50] In addition, the higher rate of seroconversion in women might lead to stronger protection against extragenital HPV infections.[60] All above mentioned additional gender-specific factors may account for the higher prevalence of oral HPV16 infection in males.[60] In several developed countries worldwide incidence rates for HPV-positive oropharyngeal cancer have substantially increased among men during the past 3 to 4 decades, while rates have only modestly increased among women.[56,61–64] Contrary to this, in a German cohort it was shown that HPV-positive OPC have significantly increased in women during that last years.[65]

4.2. Age

A difference was observed in the HPV infection prevalence by age. Cervical HPV infection was negatively associated with age, but this was not observed for oral HPV infection.[8] Alternatively,

other ongoing modes of transmission (e.g. through saliva exposure) could account for continued oral exposure with age.[66] A bimodal age distribution in oral HPV infection has been noted, with peak prevalence at age 30–34 and 60–64 years.[8] This is remarkably analogous with the clinical presentation of recurrent respiratory papillomatosis (RRP), that shows a trimodal distribution with peaks at three median ages 7, 35 and 64 years.[67] It has been suggested that the increase in detectable HPV infection with older age is due to potential loss of immune control and reactivation of latent HPV infection - which may be site specific.[8] However, this hypothesis was difficult to prove in cross-sectional studies, as there is no mechanism based on attainable data that would allow to distinguish HPV detection due to incident infection, reinfection, or reactivation.[68] Contrary, the oral HPV prevalence (including the HR-HPVs 16, 18, 58 and 59 and the LR-HPVs 6, 81 and 13) in Mexican women ≤20 years of age was higher (24.5%) than in older groups (14%).[50] Interestingly, the sexual behavior was not associated with the presence of genital HPV types in this cohort.[8]

Few studies have examined the prevalence of oral HPV infection in youth, though adolescents/ young adults have the highest age-specific rates of sexually transmitted infection.[17] The prevalence of any oral HPV in this age group ranged depending on age and country (table 1). Other rates of oral HPV infection are mentioned for infants and young children, who are at risk for recurrent respiratory papillomatosis caused by vertically-transmitted low-risk HPV types (LR-HPV) (table 1).[69–71]

4.3. Race and ethnicity

Oncogenic and non-oncogenic oral HPV infections were significantly more prevalent in black subjects in the USA.[72] In another American cohort, non-Hispanic whites were significantly more likely than other races to report oral sexual behavior, but being non-Hispanic white was not independently associated with oral HPV16 after adjusting for oral sexual behavior.[60] The predicted probability of high-risk oral HPV infection was greatest among black participants, especially among those who smoked more than 20 cigarettes per day, current marijuana users, and those who reported numerous lifetime vaginal or oral sex partners.[54,60] Oral HPV infections differ by race for oral HPV types 16 and 51, which were more prevalent in Caucasian subjects, whereas HPV types 35 and 58 were more prevalent in black subjects.[72]

4.4. Oral hygiene

Imbalance in the oral microbiome is a frequent event in oral and oropharyngeal carcinogenesis and the role of HPV has been examined extensively.[73–75] HPV enters epithelial cells of cutaneous or mucosal surfaces through abrasion and infects cells of the basal layer.[2,8,76] In most cases HPV infection is asymptomatic and resolves spontaneously, although in some cases it is accompanied by the appearance of the wound healing response that promotes active cell division and the proliferation of infected cells.[27–29,77]

Periodontal pockets are the source of inflammatory cytokines, bacteria, and viruses in saliva and may provide the perfect environment for HPV infection and persistence and in addition may serve as reservoir for the virus.[78] HPV16 viral load may be related to an increased bacterial number in the oral cavity.[79] The possible role of oral hygiene was examined in a large cross-sectional study, in which four different indicators of scarce oral health have been associated with increased likelihood of any oral HPV.[80] The positive association between severe periodontitis and any oral HPV infection was confirmed by other studies,[59,79] but refuted by others.[81]

Poor oral hygiene, remaining teeth, full-dentures and higher age may serve a vital role in modulation of oral HPV persistence. HPV16 viral load in the oral cavity is associated with specific oral microbiome composition; the levels of oral bacteria in samples from the tongue dorsum were significantly associated with increased HPV copy number,[79,82–84], and a significant correlation between oral hygiene and any HPV load was confirmed. Its improvement may actively reduce the incidence of oral HPV infection.[74,85]

To summarize, the association of demographic and behavioral factors with oral HPV load were multiple: gender, race, older age, smoking and other abuses. They are considered multifactorial in most studies of HPV positive groups, but smoking is the most constant factor apart from the number of partners. The predicted probability of high-risk oral HPV infection was greatest among black, those who smoked more than 20 cigarettes daily, current marijuana users, and those who reported 16 or more lifetime vaginal or oral sex partners.[54] Chaturvedi et al. found that factors independently associated with HPV load above the median included older age and intensity of current smoking.[47] D'Souza proved the strong impact of smoking against sexual habits.[45] Men who currently smoked and had ≥ 5 lifetime oral sexual partners had 'elevated risk' (prevalence = 14.9%). Men with only one of these risk factors (i.e. either smoked and had 2–4 partners or did not smoke and had ≥5 partners) had 'medium risk' (7.3%).[45] Smoking status is also important when analyzing the quality and quantity of HPV types. In the adjusted multinomial logistic regression model, being male (relative risk ratio [RRR] = 3.69; 95% confidence interval [CI], 1.57–8.65), being a current cigarette smoker (RRR = 2.57; 95% CI, 1.23–5.36), and having a new sex partner in the past year (RRR = 2.10; 95% CI, 1.03–4.28) were associated with an increased risk of multiple oral HPV infection over single-type HPV infection.[86]

5. Association between HPV infections and other sexually transmitted diseases

Chlamydia trachomatis infection is much more prevalent in HPV-positive subjects. There is an increased risk for detecting single high-risk HPV genotypes and multiple infections with various HPV-types even in asymptomatic patients.[87,88] A possible association between high-risk HPV and hepatitis C virus was found.

HIV-positivity is a separate risk factor for elevated oral HPV prevalence.[55,89,90] Prevalence rates of oral HPV in HIV-infected persons depends on age and country (table 1).

Immunosuppression may be associated with increased susceptibility to oral virus infection or replication. Higher HPV prevalence Is observed of low and high-risk types in HIV-infected women.[91] This association of HIV-related immunosuppression (CD4+ <350 cells/μL) with oral HPV prevalence is consistent with several other studies[55,57,81].

6. Future direction

To establish the importance of the above considerations, there is great need to identify healthy individuals most at risk of development of OPC to, 1) undertake an educational campaign, 2) develop and implement screening strategies, 3) promote vaccination for both sexes. The incidence of HPV-related oropharyngeal cancer (C01, C09, C10) is increasing and OPC includes the highest number of HPV-associated non-cervical cancers.

Developing cost-effective rules for screening targeting risk groups is difficult. The first group to be tested should be HIV positive individuals, as the risk of developing HPV related OPC has

been clearly demonstrated. They are also a relatively easy accessible group subject to regular medical care.

According to the mosaic of risk factors, the next group should be men with multiple partners/ high risk sexual behaviors, smokers, over 40 years of age, unvaccinated. The incidence and costs of OPC are significantly higher in males than in females [92]. It should be recognized that younger male age cohorts are not fully covered by vaccination and will enter a period of increased risk. In this gigantic group, there is currently no fixed pattern in the conducting of regular examinations. In the authors' view this could be assigned to general practitioners or combined with periodic examinations of employees at work. In conclusion, a more aggressive public health policy towards men may narrow the gender gap of oropharyngeal cancer.[92]

A natural way to test patients would seem to be a combination of simultaneous cervical and oral screening, both for the woman and their partners. Currently, the modifications to a human papillomavirus assay allowed to optimize its utility for cervical cancer screening even in low-resource settings.[93] Scientific rationale for such double screening has been documented in anal cancers. [44] Unfortunately, oral HPV infection occurs independently of cervical HPV infection and routes of transmission seem completely separate.

To sum up, we can define a risk group, but there still a lot of work to provide methods of reaching potentially exposed individuals. Moreover, it would require a multi-year testing schedule due to the episodes of active HPV infection and clearance phenomenon and, above all, the latency of carcinogenesis on the underlying infection. There is no possibility to organize a uniform model. Local financial outlays of the health providers, the needs and the level of education of the society will be decisive. Thus, for now, it is very important to implement educational programs concerning oral HPV infection and promote of vaccination both in girls and boys.

7. Summary and conclusion

The exposure of oropharyngeal mucosa to HPV infection with consequence of increased risk for oropharyngeal carcinoma depends on specific sexual behavior. Apart from the number of sexual partners, current cigarette smoking is the most constant factor. Male gender, older age, race or ethnicity, oral hygiene are independently associated with any prevalent oral HPV infection. Concurrent infection in oropharynx and genitals is rare: oral HPV infection occurs independently of cervical HPV lesions. Either other modes of HPV transmission or differences in susceptibility to HPV infection or its clearance in the oral cavity are suggested.

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Declaration of Competing Interest

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