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The role of sexual behavior in head and neck cancer: implications for prevention and therapy

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Abstract

HPV-positive oropharyngeal squamous cell carcinoma (HPV-OSCC) is associated with oral sexual behaviors. The sharp rise in incidence of HPV-OSCC in the USA has been attributed to changes in sexual norms over the past five decades, with lower age at sexual debut and higher numbers of sexual partners per individual. In addition, variations in HPV-OSCC prevalence by race, age cohort and gender may be attributable to differences in oral sexual behaviors among these groups. Oral HPV infection is the putative precursor to HPV-OSCC. Risk factors for oral HPV incidence, prevalence, clearance and persistence are crucial to understanding how, and in whom, oral HPV infection progresses to malignancy. Future investigation should focus on elucidating the natural history of oral HPV infection persistence and malignant transformation, developing effective screening tools and exploring opportunities for prevention such as vaccination and public health education.

Keywords

head and neck neoplasms; health education; human papillomavirus; human papillomavirus vaccines; oral sex; oropharyngeal neoplasms; sexual behavior; sexually transmitted diseases

Introduction

Oral human papillomavirus (HPV), a sexually transmitted infection (STI), is the etiologic agent for the majority of oropharyngeal squamous cell carcinomas (OSCCs) in the USA and

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other developed countries [1–6]. Although the incidence of head and neck squamous cell carcinoma (HNSCC) overall in the USA has decreased concomitantly with declining tobacco smoking rates [7,8], OSCC incidence has significantly increased in recent years. The proportion of OSCCs caused by HPV has grown from 16% in the early 1980s to nearly 80% [1–3,9–13] in the past decade. The incidence of HPV-positive OSCC (HPV-OSCC) is expected to exceed that of cervical carcinoma, the paradigm of HPV malignancies, by 2020 [3]. HPV-positive HNSCCs of the oral cavity and larynx have also been described; however, the prevalence of HPV-positive tumor status is much lower (less than 10%) than in the oropharynx, and the clinical significance is unclear [14].

The behavioral risk factors for HPV-positive and HPV-negative HNSCC are distinct; sexual behaviors are associated with HPV-positive HNSCCs, but not with HPV-negative HNSCCs, which are chiefly caused by tobacco and alcohol use. HPV-HNSCC primarily affects whites, men and younger individuals of higher socioeconomic status [2,15]. The recent surge in HPV-OSCC has been attributed to the aging of the ‘sexual revolution’ cohort of the 1960s, which had higher average number of sexual partners per individual and younger age of sexual debut than previous age cohorts [16–19]. Indeed, demographic variations in sexual behaviors explain at least in part the distinct epidemiology of both HPV-OSCC and oral HPV infection [20].

The purpose of this review is to describe the association of sexual behaviors with HPV-HNSCC and oral HPV infection, and to explore how variations in sexual practices by age, gender and race contribute to the unique clinical-demographic profile of HPV-HNSCC. Implications for counseling patients with HPV-OSCC will also be discussed.

HPV in carcinogenesis

HPV is a DNA virus responsible for cancers of the anogenital tract and the oropharynx, causing an estimated 5.2% of the global cancer burden [21]. HPV infection is sexually transmitted, and most individuals will have an anogenital HPV infection at some point in their lives, with the majority of infections clearing spontaneously [21].

There are more than 150 types of HPV. Most of these are of low carcinogenic potential based upon early studies of cervical cancer and are therefore referred to as ‘low-risk types’. High-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) are considered definite carcinogens, with several additional types classified as probable or possible carcinogens [21]. HPV16 is responsible for at least 90% of HPV-OSCCs [22,23], while HPV16 and 18 combined cause over 70% of cervical cancer cases [21].

HPV-driven carcinogenesis in the head and neck primarily takes place in the lymphoid tissue of the oropharynx [2,15,24]. HPV16 infects the basal epithelium and may remain episomal, but frequently integrates into the host genome [23]. The resultant over-expression of viral oncoproteins E6 and E7, which cause degradation of tumor suppressor proteins p53 and retinoblastoma, results in cell cycle dysregulation and proliferation [25]. The molecular pathways to malignancy for HPV-positive and HPV-negative HNSCC are distinct. HPV-induced carcinogenesis involves significantly fewer genomic alterations than HNSCC

carcinogenesis independent of HPV, with lower likelihood of p53 mutation, EGFR overexpression and chromosomal aberrations [26–29].

Sexual behaviors, HPV and HNSCC

HPV-positive HNSCC is associated with various collinear sexual behaviors, including oral sex, vaginal sex and oral-anal contact [2,15,30]. Increased lifetime exposure to these behaviors, as measured by number of overall sexual partners, oral sex partners and earlier age at sexual debut is associated with a dose-dependent increase in odds of diagnosis of HPV-HNSCC [2,15,22,30–34].

Early studies that evaluated the relationship between sexual behaviors and HNSCC included heterogeneous anatomic sites and lacked tumor HPV status; however, they hinted at the association of sexual behaviors with a subset of HNSCCs (Table 1 & Figure 1) [35,36]. Schwartz *et al.* in 1998 compared patients with oral cavity and oropharyngeal SCC to matched controls from the general population and found that for males, the odds of malignancy was increased with younger age at first intercourse (adjusted odds ratio [OR]: 3.4; 95% CI: 1.5–7.5) and increased lifetime number of sexual partners (adjusted OR: 2.3; 95% CI: 1.1–5.0). This study was likely underpowered due to the distribution of anatomic sites. Most tumors were oral cavity, which may have attenuated the association [31].

Subsequently, in concert with molecular findings that demonstrated the causative role of HPV in OSCC [37], epidemiologic studies demonstrated a strong association between sexual behaviors and HPV-positive squamous cell carcinoma of the oropharynx (Figure 1 & Table 1).

The relationships of sexual behaviors, biomarkers of HPV oncogenesis and OSCC were definitively demonstrated in a landmark case–control study that compared individuals with OSCC to non-cancer controls [15]. The odds of OSCC was increased with oral HPV16 infection (OR: 14.6; 95% CI: 6.3–36.6), seropositivity to HPV16 L1 capsid protein (OR: 32.2; 95% CI: 14.6–71.3) and higher numbers of lifetime oral sex ($p_{trend} = 0.009$) and vaginal sex partners ($p_{trend} = 0.002$). In addition, HPV16 was detected in 72% of OSCC tumors using gold-standard methods, and when analysis was restricted to HPV16-positive OSCC cases, the association of sexual behaviors with odds of OSCC was further strengthened [15].

HPV-OSCC was subsequently demonstrated to be a distinct disease entity from HPV-negative OSCC. Patients with HPV16-positive and HPV16-negative HNSCC were compared with matched non-cancer controls [2]. Increasing lifetime numbers of both vaginal sex and oral sex partners were associated with HPV16-positive HNSCCs ($p_{trend} < 0.001$ for vaginal and $p_{trend} = 0.004$ for oral sex), but were not associated with HPV16-negative HNSCCs [2]. Conversely, heavier tobacco and alcohol use were associated with HPV16-negative HNSCC ($p_{trend} < 0.001$ for pack-years smoked and $p_{trend} = 0.03$ for years of heavy alcohol drinking), but not HPV16-positive HNSCCs [2]. Patients with HPV-positive HNSCC have also been compared directly with those with HPV-negative HNSCC, with similar findings [32,34] (Table 1).

Sexual behaviors associated with prevalent, incident and persistent oral HPV infection

Oral HPV infection is the putative precursor to HPV-OSCC. The natural history of progression from oral HPV infection to OSCC is under investigation, providing an emerging picture of risk factors for incident, prevalent and persistent infection (Table 2). Based upon limited studies to date, oral HPV infection is relatively uncommon and usually resolves, but a subset of infections persist. Patients with these rare persistent infections are presumably at increased risk for progression to OSCC (Figure 2). Improved understanding of oral HPV infection will clarify the epidemiology and pathogenesis of HPV-OSCC and will have implications for the prevention of and screening for OSCC [38]. Importantly, the natural history of *cervical* HPV infection and cancer has been well elucidated over the past 30 years and serves as a useful benchmark and paradigm for comparison with oral HPV.

Prevalent oral HPV infection—Prevalent oral HPV infection reflects the confluence of acquisition, persistence and clearance rates. A recent analysis of the nationally representative National Health and Nutrition Survey detected prevalent oral HPV infection of any type of 6.9% in the US general population, with a significantly higher prevalence among men than women (10.1% compared to 3.6%) [39]. A meta-analysis including studies of healthy subjects prior to 2009 observed a lower prevalence estimate of oral HPV infection (4.5%, 182 of 4070) [40]. HPV16, which causes the overwhelming majority of HPV-OSCCs in the USA [22,23], is the most common oncogenic oral HPV infection detected [39,40,41], with a prevalence of 1–1.3% [39,40].

Oral HPV infection is significantly less common than anogenital infection for both men and women [42–44]. Among healthy US women, 43% have a prevalent cervical HPV infection [44,45], with an estimated global cervical HPV burden of 12% [46]. The prevalence of anogenital HPV infection among healthy men is less well-studied with estimates ranging from 1.3 to 72.9% [47,48]; however, in studies evaluating multiple sites within individual men, oral infection is consistently less common than anogenital infection [42,43,49].

In addition to male gender, prevalent HPV infection is associated with cigarette smoking, age and immune status. There is a dose-dependent increase of oral HPV prevalence with number of cigarettes smoked per day [39]. Older individuals are more likely to have an oral HPV infection [50–54], although there is evidence for a bimodal age distribution with increased prevalence in younger (30–34 years, 7.3%) and older (60–64 years, 11.4%) age cohorts [39]. HIV seropositivity and, among HIV seropositive individuals, lower CD4 count are also associated with higher prevalence rates [50,51,53–55].

Sexual behaviors are strong risk factors for prevalent HPV infection (Table 2). In non-HIV-infected adults, these behaviors include: lifetime and recent number of oral sex partners [50–52,56], recent number of rimming partners [50] and lifetime number of any sexual partners [39,52] and vaginal sex partners [41,52]. Oral HPV infection has also been associated with surrogates for increased sexual exposure, including history of anogenital warts [42,51] and HSV-2 seropositivity [53].

It is still unclear if deep kissing or ‘French’ kissing is associated with prevalent oral HPV infection. Several studies have associated lifetime [51,52,56] and recent [52] deep kissing

with HPV infection. Others have failed to find an association of oral sex with HPV infection [57], indicating that behaviors such as deep kissing that do not involve oral-genital contact may have the potential for HPV transmission [38].

Incident oral HPV infection—Natural history studies to date have observed an annual incidence rate of oral HPV infection in healthy individuals of 4.4–6.8% when assessed with oral rinses alone, with a higher rate of 12.3% using both oral rinses and self-collected oropharyngeal swabs [56–59]. Oral HPV16 infection incidence rates are 0.6–0.8% per year [57,58]. Most newly acquired infections are cleared rapidly, in less than 1 year [57,58]. Among high-risk (e.g., with high prevalence of risky sexual behaviors and drug use) and HIV-infected populations, incidence rates are higher (17–31 infections per 1000 person-months, or 20.4–37.2% annually), but still with rapid clearance of new infections [43,60,61]. Although less well studied, risk factors for incident infection are similar to those for prevalent infection. In addition to current smoking and HIV infection, recent oral sex, oral-anal contact and open-mouth kissing [56,57,58,60] increase risk for new infection. Genital-oral autoinoculation has also been noted to increase the risk of incident infection in young men [58].

Persistent oral HPV infection—A small subset of oral HPV infections evades clearance for reasons that are unclear. These rare persistent infections are of great interest because they are considered the most likely to eventually become cancer.

The risk of persistent oral HPV infection appears to be increased with male gender, older age and current cigarette smoking [43,60–62]. Seropositivity to low-risk HPV types at baseline [63] and a history of genital warts [62] also increase the risk of persistence, and it has been noted that some people tend to have more frequent infections with multiple types of oral HPV [62], indicating either a broader exposure and/or increased susceptibility to infection in these individuals. Sexual behaviors have not been associated with oral HPV persistence [60,62,63]. Interestingly, HPV viral load measured in oral rinses also has no correlation with sexual behaviors, but does increase with older age and current smoking intensity [64].

Taken together, this evidence suggests that once oral HPV infection occurs due to sexual contact, a constellation of poorly understood host factors including smoking status, age and gender determines the risk of persistence. Further longitudinal studies are needed to clearly define demographic and immunologic variables that place individuals at increased risk for oral HPV persistence and, ultimately, for cancer.

Oral & genital HPV infection in individuals and heterosexual partners

Oral & genital HPV infection concordance within individuals—The risk of concomitant oral and genital HPV infection has mostly been explored in women, in whom cervical sampling is commonly performed for screening purposes. The prevalence of oral infection is increased significantly among individuals with concurrent genital infection, with as much as a fivefold increase in women with cervical infection [44]. This may reflect either dual exposure from sexual behavior as a shared risk factor for infection at each site and/or autoinoculation with infection of different sites within the same individual. Surprisingly, the

rate of type-specific concordance between oral and anogenital sites, while greater than would be expected by chance, is low and represents only a minority of cases [44,49,65–67]. In a sample of women representative of the US population, 3% of women had both cervical and oral HPV infections but only 6.6% of them had complete type concordance (all HPV types found at both oral and genital sites) while 37.7% had partial concordance (at least one but not all types at both sites) [44].

The relatively low type-specific concordance at different sites within individuals may be secondary to different exposures at each site during sexual encounters or may indicate a different susceptibility to and natural history of HPV infection in the oral compared with anogenital sites. A combination of both factors is likely [44]. Indeed, oral and cervical sites are known to be significantly different with regard to the distribution of HPV types, the association of HPV infection with certain risk factors (e.g., age) and local immune environment [44,61,68], supporting a distinct natural history of HPV infection at each site.

Oral & genital HPV infection concordance among partners—Little is known about concordance of oral HPV infection between heterosexual partners, with virtually no data on same-sex couples. A Swedish family study found that baseline oral HPV status was significantly interrelated among heterosexual couples, and persistent high-risk oral HPV infection in one partner increases the risk for persistent high-risk oral HPV infection in the other partner, however, this study did not examine individual type-specific HPV infections [69].

Existing studies of oral and genital HPV infection in heterosexual couples indicate that type-specific concordance of oral HPV infection in one partner with the other partner's oral or genital HPV infection is modest, and lower than genital–genital HPV concordance [70–72]. Among South African couples at an HIV testing clinic in which at least one partner had oral HPV infection, more couples had concordant oral–genital HPV infection (four of nine) than had concordant oral–oral HPV infection (one of nine) [71]. In contrast, a US study found that pregnant women's oral and genital HPV infections were discordant when compared with oral HPV infection in their male partners [72], and among 25 young couples at a family planning clinic, there were only one concordant oral–oral and one concordant oral–genital infection [70]. Again, variability by anatomic site in both exposure to and natural history of HPV infection complicates the study of type-specific concordance among sexual partners, and will require further investigation.

Relevant timeframe for sexual behaviors

Relevant timeframe for sexual behaviors associated with prevalent oral HPV infection—Prevalent infection has been associated with both recent and lifetime sexual behaviors. In a high-risk population of 500 HIV-infected and HIV-uninfected men having sex with men, sexual behaviors were categorized by 0–2 weeks, 2–52 weeks and greater than 1 year previous to the study. After adjustment, only the number of tongue-kissing and oral–penile sex partners greater than 1 year previous to the study were significantly associated with prevalent oral HPV infection [51]. However, other studies of non-immune

compromised adults have identified recent but not lifetime oral sex [50,60], or both recent and lifetime oral sex [52], as risk factors for prevalent infection.

Relevant timeframe for sexual behaviors associated with incident oral HPV infection—Incident oral HPV infection has only been associated with *recent* behaviors in healthy adults, including oral sex, anal sex and open-mouth kissing [56,58,60]. However, in a multinational study with 4 years of follow-up, no association between recent *or* lifetime sexual behaviors with incident infection was detected, although men who were not married or cohabiting did have higher oral HPV incidence rates [57].

In contrast, incident infection for immune compromised individuals appears to be the result of both old and new sexual exposures, which suggests reactivation of prior latent infections. A large study of HIV-infected and at-risk HIV-uninfected individuals found that incident oral HPV infection was associated with *recent* oral sex for HIV-uninfected individuals, but *lifetime* number of oral sex partners for HIV-infected individuals. Further, there was a similar cumulative incidence for abstinent compared with sexually active participants during the study period [60]. This may indicate that the immune-compromised state unmasks cumulative exposures and allows for reactivation of latent infections acquired from previous exposures. Reactivation of cervical HPV infection has also been described for HIV-infected women [73,74]. The potential for oral HPV reactivation may impart a greater importance to lifetime than recent sexual exposures in immune compromised individuals.

Relevant timeframe for sexual behaviors associated with HPV-HNSCC—The precise length of time from the sexual transmission of oncogenic oral HPV infection to the development of HPV-positive HNSCC is unknown, but suspected to be on the order of decades. Serologic studies of antibodies to HPV antigens as a measure of exposure to oncogenic HPV in individuals who later developed oropharyngeal cancers detected seropositivity to HPV16 oncoprotein E6 and capsid proteins L1 and L2 in samples collected a decade or more prior to the diagnosis of OSCC [75,76]. This indicates that the relevant timeframe for the sexual behaviors that lead to oral HPV infection and are associated with HPV-HNSCC is likely greater than 10 years before the development of malignancy.

Risks associated with sequence of initiation of sexual behaviors

The *sequence* of debut of specific sexual behaviors has been postulated to be an important determinant of susceptibility to oral HPV infection. The potential significance of ordering of sexual behaviors is attributed to variations in the vigor of the systemic immunologic response to antigens presented to the oropharyngeal compared with anogenital mucosa. It is known that different anatomic sites respond differently to HPV exposure, eliciting variable levels of serologic response [77]. In addition, HPV expertly evades immune activation when establishing infection in basal epithelial cells [78], and only a fraction of infections result in seroconversion [79,80]. It is conceivable that initial genital exposure may provoke a relatively more robust immune response, compared with oral exposure, which then protects from infection during oral exposure later in life. Conversely, exposure to HPV of the oral mucosa without the protection afforded by previous genital exposure may increase the risk of oral HPV infection and perhaps persistence, increasing the risk of malignant

transformation [81]. This possibility is supported by epidemiologic findings that OSCC incidence is increasing in whites, men and younger age cohorts [82], populations that are more likely to participate in oral sex at or around the time of sexual debut [20].

Differences in sexual behaviors by race, age cohort & gender

The increasing incidence of HPV-OSCC predominantly affects whites and men, while sparing blacks and women, and is more pronounced among younger age cohorts [3,82]. This unique demographic profile can be explained at least in part by variations in sexual behaviors by race, age and gender [20].

Race—OSCCs are more likely to be HPV-positive in whites (21–64%) than blacks (0–35%) [2,3,11,13,83,84], and in the USA the incidence of OSCC has increased in whites but has decreased in blacks, which is likely due to higher rates of HPV-OSCC in whites compared with blacks [85].

Whites and blacks in the USA are consistently found to have distinct patterns of sexual behaviors. Common findings in population-based studies of sexual behaviors by race are that whites are more likely to engage in oral sex [20,86,87], with more partners [20] and at a younger age than blacks [88,89]. In contrast, blacks are less likely to participate in oral sex and have fewer oral sex partners [87,89] than whites, but initiate vaginal sex earlier [20] and have more lifetime partners for any sexual act [87,88,90]. Blacks are also more likely than whites to report having fewer oral sex than vaginal sex partners [20].

The higher likelihood of having oral sex, and at a younger age than vaginal sex, in whites compared with blacks may explain the white predominance of HPV-OSCC patients in the USA. Prevalence ratios (PR) for oral sexual behaviors in white men compared with black men were similar to the incidence rate ratios for OSCC derived from the Surveillance, Epidemiology and End Results database in the same year [20]. Although this analysis was limited by the lack of HPV tumor status available from Surveillance, Epidemiology and End Results data, the argument that differences in oral sexual behaviors are responsible for the differences in HPV-OSCC incidence by race is compelling.

It is interesting that the pattern of oral HPV *infection* prevalence by race does not consistently follow the white predominance noted in OSCC. Oral infection with any type of HPV is actually higher among blacks in the USA (10.5%) compared with whites (6.5%, $p = 0.06$), and there is no significant difference in prevalence of high-risk infections by race [20]. Among men only, the prevalence of oral HPV16 is higher in whites than blacks, but the difference is not statistically significant (2.37% compared with 1.88%; PR: 1.26; 95% CI: 0.56–2.85) [39].

Reasons for this discrepancy between infection and cancer epidemiology are unclear, but a potential explanation is the variation in sequence of sexual debut in whites (more likely to begin with oral sex) compared with blacks (more likely to begin with vaginal sex). While it is hypothesized that genital exposure to HPV elicits a more robust serologic response than oral exposure [81], the immunologic protection afforded may not necessarily impact the acquisition of *new* oral HPV infections, but rather may improve an individual's ability to

clear oral HPV infections, thus preventing progression to cancer. At present, these theories are speculative and remain unvalidated.

Age cohort—Individuals diagnosed with HPV-OSCC are significantly younger than those with HPV-negative OSCC [11,91–95], which is reflected in the increasing incidence of OSCC in younger patients in developed countries [3,4,82]. Although the incidence of OSCC is six- to eight-times higher in middle-aged (ages 45–59) individuals than younger adults (ages 30–44) [20], the rate of OSCC has nearly doubled in the 35- to 44-year age group from 0.79 to 1.39 per 100,000 during the time period from 1973 to 2009, almost exclusively due to increased incidence among white men [96].

This pattern is thought to be a manifestation of evolving sexual practices and norms in the past several decades, with decreased age of sexual debut and more lifetime sexual partners per individual [16–18]. Recent analysis of nationally representative US survey data indicates that younger age cohorts are significantly more likely to perform oral sex, and to have a younger age of oral sexual debut, than older age cohorts [20,39]. Another study found that adolescents in 2004 were three-times more likely to participate in oral sex than they were in 1994 [97], potentially due to perceptions among adolescents of oral sex as a relatively low-risk activity [98].

Oral HPV infection prevalence varies significantly by age cohort. Analysis of the National Health and Nutrition Survey data from 2009 revealed a bimodal distribution with the highest prevalence of oral HPV infection in individuals aged 60–64 years (11.4%; 95% CI: 8.5–15.1%) and a smaller peak in the 30–34 years age cohort (7.3%; 95% CI: 4.6–11.4%) [39]. This bimodal distribution persisted after adjustment for other factors including number of lifetime sexual partners (not limited to just oral sex), but only for high-risk HPV types and only among men.

The peak at 30–34 years likely represents increased sexual behaviors in young adulthood. There are several potential explanations for the increased prevalence with older age, which has been described in other studies as well [50,53,54]. The peak at 60–64 years may be due to birth cohort-specific sexual behaviors, that is, individuals in their fifth and sixth decades of life were adolescents or young adults just after the sexual revolution of the 1960s; or there may be a role for viral reactivation or increased persistence due to age-related immune suppression [99], as has been described for cervical HPV infection [100]. A subset of HPV infections in this age cohort may in fact represent viral shedding from undiagnosed OSCCs [101]. In another analysis of the same data with broader age categories, there was no association of any HPV or HPV16 infection with age after adjustment for oral sexual behaviors, indicating that oral sexual behavior may be the driving factor behind age-cohort differences in oral HPV16 infection, and therefore HPV-OSCC [20].

Gender differences—A significantly higher proportion of individuals with HPV-related HNSCC compared with HPV-unrelated HNSCC are men (73% compared with 62%; $p < 0.001$) [82]. Although men report more risky sexual behaviors than women with higher number of lifetime partners for any sex and oral sex, differences in reported behaviors do not fully account for the gender disparities seen in both oral HPV infection and HPV-OSCC

incidence rates [20,39]. Gillison *et al.* estimated that differences in sexual behaviors and other covariates only accounted for approximately 16% of the infection prevalence differences observed by gender [39]. Comparison of sexual behaviors by gender range from PR of 1.03 (95% CI: 1.01–1.05) for ever performing oral sex to 1.84 (95% CI: 1.54–2.20) for five or more lifetime oral sex partners. However, the prevalence of oral HPV16 infection (PR: 6.79; 95% CI: 2.07–22.26) and the age-adjusted incidence rate ratio of OSCC (4.71; 95% CI: 4.42–5.02) for men relative to women, are much higher than would be expected based on sexual behaviors alone [20].

There are important differences in the susceptibility to HPV infection, and in the immune reaction elicited by HPV infection, by gender and anatomic site (e.g., oral, anal, cervical and penile) that are speculated to help explain these gender differences. Performing oral sex on a woman may confer greater risk for oral HPV acquisition than oral sex on a man due to either higher prevalence of HPV infection among women or increased viral load in the cervical mucosa [61,43,47,65,68,77]. Indeed, genital HPV infection prevalence is lower in men than women in most populations studied [102], and the transmission of HPV from the cervix to the male genitalia occurs with significantly greater frequency than vice versa [103]. When oral HPV infection was assessed in a group of women, men who have sex with men and heterosexual men, the highest rate of oral HPV infection acquisition was detected among heterosexual men [104], presumably because their sexual partners were more likely female.

Men also have a significantly lower seroprevalence to HPV than women [43], even though only a subset of cervical infections in women lead to seroconversion [47]. The lower seroprevalence in men is speculated to be the result of less robust systemic immunological response elicited by infection of the keratinized squamous epithelium of the male genitalia compared with the mucosal lining of the cervix [79,80]. The increased prevalence of oral HPV infection among men may be in part a result of weaker immunologic memory for the virus and therefore impaired clearance upon oral mucosal exposure.

Counseling patients with HPV-OSCC

HPV-OSCC is cancer that results from an STI, which introduces complex psychosocial concerns that can deeply affect patients and their loved ones. In the field of head and neck oncology, counseling patients about an STI is a relatively new responsibility and a departure from the traditional smoking-and alcohol-dominated conversation about disease etiology and modifiable risk factors. Patients may be concerned about the role of HPV in their disease, how and when they acquired HPV and the risk of transmitting the infection to current or future partners [105]. However, these questions often remain unasked and unanswered [106,107].

A significant proportion of patients with HPV-OSCC are uncertain about the role of HPV in their cancer, with only one-third of patients in a recent study identifying HPV as the cause of their disease, and the majority reporting confusion about the transmissibility of the virus [108]. When asked if their oncologists had discussed issues related to HPV and head and neck cancer, 84% reported it was not discussed or only somewhat discussed [108]. Despite our incomplete knowledge of HPV natural history, it is important to educate patients regarding what is known, in order to alleviate spoken and unspoken anxieties and fears.

HPV and promiscuity or unfaithfulness—Although HPV-OSCC is associated with sexual behaviors, a diagnosis of HPV-OSCC does not necessarily indicate promiscuity. HPV is a common infection among US adults [21] and while the risk of infection is associated with higher lifetime numbers of sexual partners, many patients with HPV-OSCC do not have excessively high numbers of sexual partners and some report never having had oral sex [2,15]. In addition, the relevant sexual encounters leading to the transmission of oral HPV infection likely occurred many years – a decade or more – prior to OSCC diagnosis [75,76].

Transmissibility of HPV-OSCC—Individuals with HPV-OSCC are approximately eight-times more likely than those with HPV-negative HNSCC to have HPV detected in oral rinses, and some patients have persistent detectable HPV DNA after treatment [101]. Male partners of women with *cervical* cancer, which is almost always HPV related [21], have a 2.4- to 2.7-fold increased risk for tonsil and tongue cancer [109], so there is concern that this increased risk may also apply to partners of individuals with HPV-OSCC. However, partners of individuals with HPV-OSCC have likely already been exposed to HPV infection in the past, either from their current or past partners [110]. New evidence shows that partners of individuals diagnosed with HPV-OSCC have a very low incidence of oral HPV infection comparable to that of the general population [111]. Currently, there is no reason to recommend altering sexual practices when one partner is diagnosed with HPV-OSCC in an established relationship [107]. Likewise, the utility of vaccination for partners of patients with HPV-OSCC is unknown, but unlikely to afford protection given their high likelihood of prior exposure to oncogenic HPV.

Psychosocial concerns—The increasing incidence of HPV-OSCC and the excellent prognosis conferred by HPV-positive tumor status mean that the population of HPV-OSCC survivors is growing, and survivorship care will become increasingly important.

There is limited research examining the psychosocial concerns of patients with HPV-OSCC; however, psychosocial concerns surrounding HPV-related *genital* lesions have been extensively studied. A diagnosis of an HPV-related genital lesion is associated with anxiety, depression, anger and shame, increased concern about sexual relationships and decreased sexual enjoyment and activity, and decreased quality of life [112–114]. The CDC have issued guidelines for counseling patients with HPV-related genital lesions that include patient education and discussion of sexual and psychological issues [115].

Preliminary studies of HPV-OSCC indicate that patients may experience feelings of guilt, self-blame and embarrassment due to their diagnosis, along with a sense of anger, sadness or helplessness [106]. While patients with HPV-OSCC have higher baseline quality-of-life (QOL) scores than those with HPV-negative disease [116,117], they may suffer greater *decreases* in QOL so that their post-treatment scores are not significantly different [116], although there is conflicting evidence in this area [117]. Long-term (>1 year) QOL trajectories and determinants have not yet been explored.

Sexual functioning is an element of cancer survivorship that requires specialized rehabilitation [118]. A majority of HPV-OSCC patients in an interview-based study reported

decreases in sexual intimacy due in part to the HPV-related diagnosis [106], but little is known about sexual behaviors or changes in intimacy after treatment for these individuals.

Given the high emotional stakes of an STI-related cancer diagnosis, it is imperative to acknowledge the potential psychosocial impact of HPV-OSCC and to frankly discuss what is known and unknown so that unfounded fears are dispelled. Future research is indicated to explore QOL and sexual intimacy during survivorship, and to develop a rehabilitation framework to meet the complex needs of this unique and growing population [107]. Importantly, there is evidence that psychosocial counseling for survivors of cervical cancer can increase QOL [119], a possibility that should be investigated for HPV-OSCC patients.

Screening

Although partners of individuals with HPV-OSCC have likely been exposed to high-risk oral HPV infection [110], and screening for HPV-related *cervical* lesions has had great success [120], there are currently no validated or recommended screening algorithms for HPV-OSCC. Several screening methods have been evaluated, but low sensitivity and difficulty accessing the crypts of the tonsillar epithelium have prevented their implementation [121,122]. In addition, the prognostic value of prevalent or persistent HPV detection in oral rinses in predicting risk for OSCC is entirely unknown. It has been suggested that partners of HPV-OSCC patients may be reassured by routine oral cavity and oropharynx screening [123], but there is no evidence to support this recommendation. Indeed, the US Preventive Services Task Force issued a statement in 2013 describing inadequate evidence to recommend screening for oral cancer [124]. Further research is necessary to develop effective screening techniques.

Prevention

The prevention of HPV-OSCC will be through vaccine and education initiatives. There are two HPV vaccines available in the USA. Both prevent against HPV types 16 and 18 (oncogenic types), and one also covers types 6 and 11 (which cause genital warts) [125]. These vaccines were developed for the prevention of cervical cancer and have a 98% efficacy against cervical lesions [126]. Although initial recommendations were for girls only, guidelines were expanded to include boys for the prevention of HPV-associated anal cancer [127]. Vaccination is intended for administration prior to sexual debut in order to prevent sexually transmitted HPV and is currently recommended for boys and girls 11–12 years old with catch-up vaccinations up to 26 years old [125,127]. A trial of the quadrivalent vaccine in older women (aged 24–45 years) demonstrated high immunogenicity and efficacy in preventing cervical intraepithelial neoplasia [128], however, the population-level significance of these findings is unclear [129].

It is not yet known if vaccination prevents oral HPV infection or OSCC; however, results from oral rinses obtained during a cervical HPV vaccine trial are encouraging. Among 5840 women in a randomized, controlled, blinded trial of the bivalent HPV16/18 vaccine, 4 years after vaccination, there were 15 oral HPV16/18 infections in the control group compared with only one infection in the vaccine group, resulting in an estimated vaccine effectiveness of 93.3% (95% CI: 63–100%) [130].

Should vaccination prove efficacious in preventing oral HPV infection and OSCC, there are several important considerations. Although HPV vaccination is recommended for boys as well as girls, only 21% of boys aged 13–18 were vaccinated in the USA compared with 54% of girls in 2012 [131], potentially due to a perception that the vaccine is not directly beneficial for men [132,133]. Public health efforts to increase the awareness of vaccination benefits for both genders are imperative to increase vaccination coverage of young boys as well as girls. In addition, if oral HPV is indeed acquired through deep kissing – as is suggested in several studies – a younger age of vaccination should be evaluated in order to allow for coverage prior to initiation of kissing, which often occurs at a younger age than riskier sexual behaviors [134].

In addition to vaccination, education is another important component of HPV-OSCC prevention. Oral sex is seen as ‘low-risk’ by adolescents [98], who may be well-educated regarding the risks of vaginal intercourse and therefore purposefully engage in oral sex rather than other behaviors in order to avoid STIs [135], especially in the post-HIV era. However, while oral sex is indeed associated with a significantly lower risk of STIs when compared with vaginal sex, it is not a risk-free behavior. In addition to oral HPV infection, oral sex has been associated with the transmission of gonorrhea, syphilis, chlamydia and even HIV [136,137]. Although there are no strong data at this time to recommend changes in sexual practices specifically for prevention of oral HPV infection and HPV-OSCC, the risk of HPV transmission via oral sex should be addressed in public health education efforts and preventive strategies should be explored.

Palatine tonsillectomy is an interesting, but unlikely, prevention idea highlighted by a recent study that found significantly reduced oral HPV infection in individuals whose tonsils had been removed [60]. This is unlikely to become a feasible strategy both because of the morbidity of tonsillectomy, and because many HPV-OSCCs originate in the lingual rather than the palatine tonsils.

Conclusion

HPV-positive head and neck cancer is a distinct and growing disease entity with strong ties to sexual behaviors and oral HPV infection. It remains unclear how the sexually transmitted nature of oral HPV will impact developing preventive, diagnostic and treatment paradigms. Future research should proceed with careful consideration of the psychosocial dynamics inherent to an STI-associated malignancy.

Expert commentary

HPV-OSCC and oral HPV infection are unequivocally associated with sexual behaviors, and the increase in incidence of HPV-OSCC in the USA and other developed countries is almost certainly secondary to changes in sexual norms in recent decades. However, much remains unknown about the progression from oral HPV infection to malignancy on the molecular level, the unique psychosocial needs of patients with HPV-OSCC on the individual level, and the potential for effective evidence-based approaches to screening and prevention on the population level. Future research in each of these areas is indicated in order to better

understand this epidemic, improve care for the growing number of HPV-OSCC patients and survivors and ultimately decrease the disease burden of HPV-OSCC for future generations.

Five-year view

The incidence of HPV-positive HNSCC is expected to continue rising. Public awareness and the mandate for research into this relatively new disease entity will likewise continue to grow. The next 5 years will bring about important advances in our understanding of oral HPV natural history, for example, how and in whom oral HPV infection progresses to HPV-HNSCC. Ultimately, improved understanding of oral HPV natural history may translate into the development of efficacious HPV-HNSCC screening methods, as well as potential preventive strategies. Finally, the psychosocial impact of STI-related cancer has not been well studied. Survivorship considerations, such as QOL determinants and relational health, will become an increasingly important area of investigation as the population of HPV-HNSCC survivors continues to grow.

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Key issues

- Human papillomavirus (HPV) is etiologically responsible for a rising proportion of head and neck squamous cell carcinomas (HNSCCs), primarily tumors arising in the oropharynx. Approximately 80% of oropharyngeal squamous cell carcinomas are HPV-positive. HPV-positive HNSCC is epidemiologically and molecularly distinct from HPV-negative disease.
- Oral sexual behaviors are associated with HPV-positive HNSCC (HPV-HNSCC).
- The epidemiology of HPV-HNSCC, which affects mostly middle-aged individuals, whites and men, can partially be explained by variations in oral sexual behavior by age cohort, race and gender.
- Oral HPV infection is the putative precursor to HPV-HNSCC. Elucidating risk factors for incident, prevalence and persistent oral HPV infection is important to our understanding of the natural history of progression from infection to malignancy.
- Risk factors for incident and prevalent oral HPV infection include sexual behaviors, cigarette smoking, male gender, older age and immune deficiency.
- Persistent oral HPV infection is hypothesized to increase risk for progression to cancer. Risk factors for persistent oral HPV infection are poorly understood, but may include cigarette smoking, male gender and older age. Sexual behaviors have not been found to increase risk for persistent infection.
- The psychosocial needs of patients with HPV-HNSCC are likely distinct from the needs of patients with HPV-negative disease due to the sexually transmitted nature of HPV-HNSCC, but this has not been well studied.
- Counseling for patients with HPV-HNSCC should acknowledge the potential psychosocial impact of the diagnosis, and frankly address what is known and unknown about oral HPV transmission.
- There are no evidence-based screening methods available for oral HPV infection or HPV-related head and neck cancer.
- The efficacy of HPV vaccination in preventing oral HPV infection is unknown, but preliminary studies indicate that vaccination may be a viable prevention strategy.

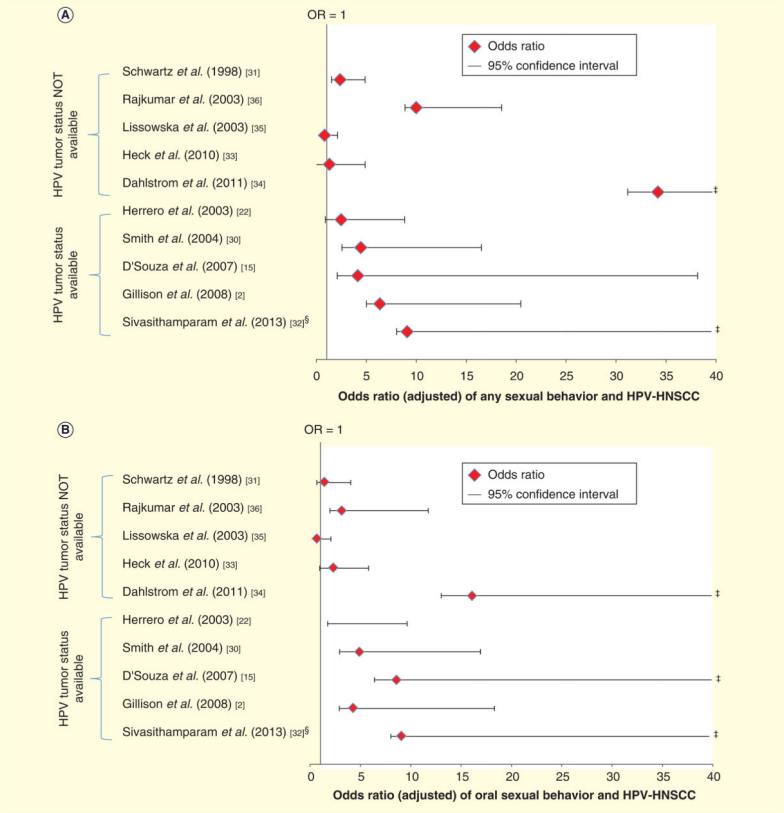

Figure 1. Association of sexual behavior and diagnosis of HPV-related HNSCC†

(A) Association of *oral* sexual behavior and diagnosis of HPV-related HNSCC. **(B)** Association of *any* sexual behavior and diagnosis of HPV-related HNSCC.

†See Table 1 for numerical ORs.

‡Upper limit of 95% CI is greater than 40.

§Combined oral and vaginal sexual behavior, unadjusted OR.

HPV: Human papillomavirus; HNSCC: Head and neck squamous cell carcinoma; OR: Odds ratio.

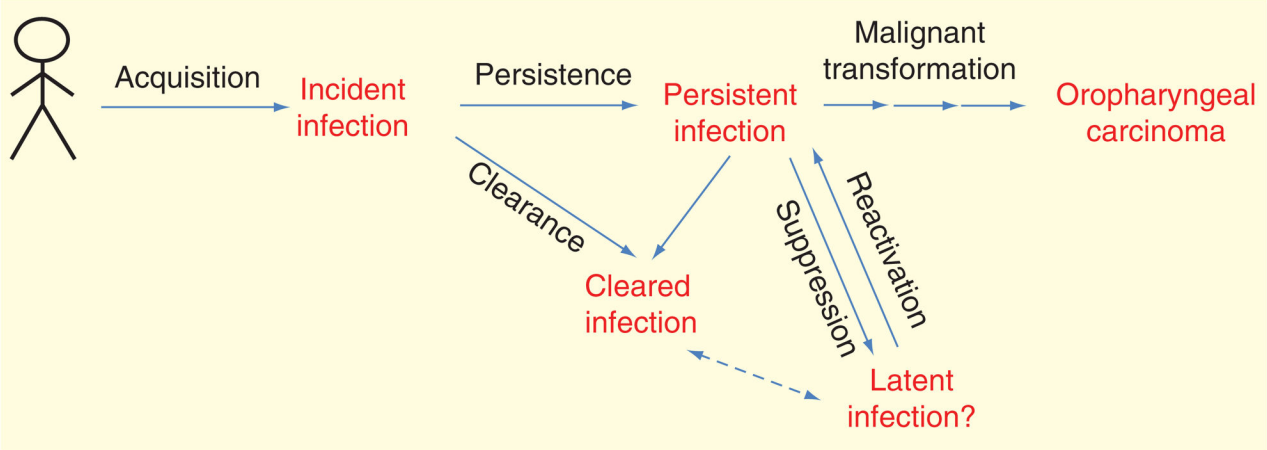

Figure 2. Proposed oral HPV natural history

Oral HPV infection is acquired through sexual contact. Most incident infections are cleared or alternatively may become latent, but a subset persists. Persistent infection is the putative precursor to oropharyngeal squamous cell carcinoma. Risk factors that have been identified for persistent infections are male gender, smoking and older age. The natural history of the progression from infection to cancer is not well understood. There may be a role for latent infection that is reactivated in individuals who are immune suppressed. Prevalent oral HPV infection estimates, that is, the percentage of individuals infected at any given time in cross-sectional studies, are determined by rates of incidence, clearance and persistence. Prevalence is increased among individuals reporting higher lifetime and recent numbers of oral sexual partners, men, smokers and older individuals.

Table 1

Associations between sexual behaviors and HPV-related HNSCC in selected studies.

Study (year) (location)	Groups compared[†]	Oral sexual behaviors[‡] Adjusted odds ratio (95% CI)	Any sexual behaviors[‡] Adjusted odds ratio (95% CI)	Ref.
HPV tumor status not available				
Schwartz *et al*. (1998) (USA)	Oral SCC[‡] male cases (n = 154) vs non-cancer male controls (n = 294)	OR 1.4 (0.8–2.6)[§#]	OR 2.3 (1.1–5.0)[§#]	[31]
Rajkumar *et al*. (2003) (Southern India)	Oral SCC[‡] cases (n = 591) vs non-cancer controls (n = 582)	OR 3.14 (1.15–8.63)[§††]	OR 9.93 (1.57–62.9)[¶#]	[36]
Lissowska *et al*. (2003) (Poland)	Oral cavity and pharyngeal SCC (n = 122) vs non-cancer controls (n = 124)	OR 0.71 (0.25–1.31)[††]	OR 0.76 (0.76–3.31)[#]	[35]
Heck *et al*. (2010) (INHANCE Consortium, 12 countries)	Oropharynx SCC (n = 1282) vs non-cancer controls (n = 6069)	OR 2.25 (1.42–3.58)[#]	OR 1.25 (1.01–1.54)[#]	[33]
Dahlstrom *et al*. (2011) (USA)	Oropharynx SCC (n = 165) vs 87 non-oropharynx SCC (n = 87)	OR 16.0 (3.0–86.0)[#]	OR 34.2 (7.0–166.3)[#]	[34]
HPV tumor status available				
Herrero *et al*. (2003) (IARC, 9 countries)	HPV-positive (n = 56) vs HPV-negative (n = 852) oral cavity and oropharynx SCC	OR 3.2 (1.5–6.4)[††]	OR 2.4 (1.0–5.7)[#]	[22]
Smith *et al*. (2004) (USA)	HPV-positive (n = 38) vs HPV-negative (n = 155) oral cavity and oropharynx SCC	OR 4.8 (1.9–12.1)[††‡‡]	OR 4.4 (1.5–12.5)[#‡‡]	[30]
D'Souza *et al*. (2007) (USA)	HPV16-positive oropharynx SCC (n = 72) vs non-cancer controls (n = 200)	OR 8.6 (2.2–34.0)[#] $p_{trend} < 0.001$	OR 4.2 (1.8–9.4)[#§§] $p_{trend} = 0.001$	[15]
Gillison *et al*. (2008) (USA)	HPV16-positive HNSCC (n = 92) vs non-cancer controls (n = 184)	OR 4.3 (1.4–14)[#] $p_{trend} = 0.004$	OR 6.4 (1.9–22)[#§§] $p_{trend} < 0.001$	[2]
Sivasithamparam *et al*. (2013) (USA)	HPV-positive (n = 32) vs HPV-negative (n = 11) oropharynx SCC	OR 9.00 (0.98–82.50)[#¶¶]	OR 9.00 (0.98–82.50)[#¶¶]	[32]

[†]The authors' original terminology for cancer site (e.g., oral, oral cavity, pharyngeal, oropharynx) is listed.

[‡]Odds of having HPV-related SCC as described in "Groups Compared" compared with odds of being in comparison group in association with highest intensity category of oral or any sexual behaviors compared with the lowest intensity category in each study. Where p_{trend} is listed, there is a significantly increased association of HPV-related SCC with increasing number of sexual partners.

[§]Men only.

[¶]Women only.

[#]Odds associated with increased number of sexual partners (treated as categorical outcome).

[††]Odds associated with history or practice of sexual behavior (treated as binary outcome).

[‡‡]Stratified by age; ORs given for age ≤55 and increased intensity of sexual behaviors compared with age >55 and reference group of sexual behaviors.

[§§]Vaginal sex only.

[¶¶]Combined variable of >10 vaginal and 5 oral sexual partners, unadjusted odds ratio.

HNSCC: Head and neck squamous cell carcinoma; INHANCE: International Head and Neck Cancer Epidemiology; IARC: International Agency for Research on Cancer.

Table 2

Sexual behaviors and other commonly identified risk factors for incident, prevalent and persistent oral HPV infection.

Factors associated with increased risk of oral HPV infection	**Type of oral HPV infection**		
	Incident infection	***Prevalent infection***	***Persistent infection***
Sexual behaviors†	Oral sex [58,60] Oral-anal contact [60] Deep kissing [56] Not married or cohabiting [57]	Oral sex [56,50–52] Oral-anal contact [50] Vaginal sex [52] Any sex [41,39] Deep kissing [56,51,52] Not married or cohabiting [41]	
Other commonly identified factors†	Smoking [57] HIV seropositivity [60]	Male gender [39,53] Older age [50–53,138] (or bimodal pattern [39]) Smoking [50–52,39,139] HIV seropositivity [50,51,53,138]	Male gender [60] Older age [60,61] Smoking [62]

†Other than HIV seropositivity, limited to analyses of non-immune compromised individuals.

HPV: Human papillomavirus; HIV: Human immunodeficiency virus.