Human papillomavirus (HPV), a sexually transmitted infection, is now responsible for the overwhelming majority of oropharyngeal squamous cell cancers (OSCCs) in the United States (U.S.). Historically, tobacco and alcohol use accounted for the majority of head and neck cancers. However, with the decline of tobacco use in the U.S., the incidence of smoking-related (HPV-negative) oropharyngeal malignancies has decreased [1]. The proportion of oropharyngeal cancers attributable to HPV (HPV-positive OSCC; HPV-OSCC) has risen substantially in the U.S. Indeed, while only 16% of OSCCs in the 1980s were HPV-positive, approximately 73% of tumors in the 2000s were HPV-positive. Not only is the proportion of OSCCs that are HPV-positive rising, but the incidence of OSCC is also rising. From 1988 to 2004, there was a 28% increase in incidence of OSCC in the U.S., which was primarily among younger men, ages 50–59 [1]. Currently, the incidence of OSCC in the U.S. is 6.2 per 100,000, and 1.4 per 100,000 among men and women, respectively [2]. There is also data emerging that HPV is etiologically associated with a smaller subset of oral cavity tumors [3].

HPV-OSCC has been recognized in the past 10 years as a distinct disease entity. These cancers are associated with oral HPV infection and sexual behavior (a surrogate for oral HPV exposure), although HPV-OSCC is diagnosed in many people who have a modest number of lifetime sexual partners. Individuals with HPV-OSCC, compared to those with HPV-negative tumors, tend to be white, male, non-smokers and non-drinkers [4]. Patients with HPV-OSCC have significantly better prognosis than those with HPV-negative OSCC [5,6]. Given its prognostic significance, HPV tumor detection has been integrated into National Comprehensive Cancer Network (NCCN) guidelines in the diagnostic evaluation of patients with OSCC, thus establishing HPV detection as a clinical standard of care for oropharyngeal malignancy [7].

**Nuances in discussing the diagnosis of HPV-OSCC with patients**

Despite the recognition of a HPV-OSCC “epidemic” among head and neck oncology, the impact of providing a HPV-related diagnosis to OSCC patients has not been studied to date. This diagnosis is complex and multi-faceted. The diagnosis of HPV-OSCC impacts upon a patient a cancer diagnosis coupled with the diagnosis of a sexually transmitted infection (STI). The former part of the diagnosis is similar to diagnoses the oncologic team routinely provides and has been trained to discuss. However, the etiologic association of a STI and cancer is one that has emerged on the doorstep of the head and neck care team in the last decade, without education regarding the psychosocial ramifications of STI diagnoses. As opposed to gynecologic-oncologists, for instance, who discuss cervical cancer with patients routinely and are trained in diagnosing and treating STIs (cervical dysplasia, Chlamydia, etc.) head and neck surgical, radiation, and medical oncologists currently have no training in discussing STIs. Yet, the head and neck team is now in a position to not only discuss the etiology of a STI-related malignancy, but to counsel their patients and partners regarding
complex social and behavioral questions outside the realm of oncology, as patients and partners wrestle with the knowledge that the malignancy was caused by a STI.

Clinically, the multidisciplinary head and neck cancer team is reasonably equipped to counsel patients on the link between tobacco, alcohol and cancer, as well as tobacco and alcohol cessation, although studies show low physician compliance and low levels of confidence to counsel patients [8–11]. The psychosocial distress of a cancer diagnosis has long been recognized, especially in the head and neck patient population [12]. By contrast, there is a paucity of head and neck literature regarding counseling of patients with a diagnosis of a STI-related cancer. Therefore, this manuscript is intended to address concerns of patients with HPV-OSCC and their families, and the behavioral questions that frequently arise among practitioners diagnosing, treating, and following this unique patient population.

Few resources currently exist to answer HPV-OSCC patients' behavioral questions about how, when, and why they got this cancer. The answers to these questions have implications for past, present, and future relationships and must therefore be carefully considered before providing advice to patients. Because these issues have not been well explored in an evidence-based method, it is important in discussions with patients to contextualize many of these answers with "we do not know, however, initial evidence suggests that..." Therefore, we present our best answers to these difficult questions with the caveat that in many cases, the answers to these questions are not yet established and can currently only be extrapolated from related research on anogenital HPV infection, initial oral HPV literature, and an understanding of the distinctions between oral and cervical HPV infection.

This manuscript addresses common patient concerns related to behaviors associated with HPV-OSCC and oral HPV infection, and reviews what is currently known and what remains unknown about oral HPV acquisition and transmission. A patient brochure with commonly asked questions and answers is also included (Fig. 1), which providers may give to their patients to supplement and reinforce their counseling regarding HPV-OSCC.

Discussing tumor HPV status in OSCC

Despite inclusion of HPV detection in NCCN guidelines for cancers of the oropharynx, there are no formal recommendations at present for when and how to discuss HPV test results with patients. Given that cervical HPV and cervical cancer literature has been used as the paradigm for oral HPV and HPV-OSCC research, until a similar body of literature is generated for HPV-OSCC, we can use the cervical HPV counseling messages created by the CDC as a starting point.

The cervical HPV counseling guidelines generated by the CDC suggest that physicians discuss the significance of cervical HPV infection and reasons for the test before performing the test [13]. In addition to the verbal conversation, the guidelines recommend that physicians provide patients with documentation in layman's terms to summarize HPV and how it is associated with cervical cancer [13]. When delivering HPV test results, physicians are recommended to summarize why the test was performed and contextualize a positive result in a neutral, non-stigmatizing fashion that reinforces the high prevalence and transience of HPV infection, as well as acknowledge potential concerns of transmission to partners. Providing information in print at the time of delivery of results is also recommended.

In delivering HPV results, communication style is highlighted to be as important as the content of the message. CDC guidelines have the following evidence-based recommendations for physicians delivering the diagnosis of cancer (not site-specific): recommend that clinicians slow down, adjust language to the literacy of the patient, supplement facts with stories, anecdotes or pictures, limit the topics covered at each visit, and use the so-called "teach back" method to assess the comprehension of patients at the end of a conversation [14,15].

By analogy, at the time of requesting HPV testing in OSCC, as with any diagnostic test, providing both verbal and print education may result in improved communication and understanding (see brochure provided in Fig. 1) [16]. When sharing with a patient that their OSCC is HPV-positive, providing both verbal and written education may be helpful in light of the questions that sometimes ensue after the initial relief of improved prognosis associated with HPV-OSCC, i.e. sexual intimacy, transmission, and/or infidelity.

Reaction to HPV-positive test

Patients may react differently to finding out their OSCC is HPV-positive, as some may experience anxiety and confusion about the behavioral aspects of infection (i.e. how, when or why they acquired the infection). The NCCN panel for head and neck cancers acknowledges that HPV testing of OSCC may lead to questions regarding prognosis and sexual history, which clinicians should be prepared to discuss [7]. In its discussion of HPV infection, the NCCN panel cautions "HPV information may add anxiety and stress for some patients. Alternatively, gaining an understanding of the etiology for one’s cancer can result in reduced anxiety for some patients [4]."

Based upon the cervical literature, some patients presented with a diagnosis of cervical cancer (the overwhelming majority of which are HPV-related) have significant psychosocial sequelae including anxiety, depression, and sexual dysfunction [17]. It has been suggested that psychosocial counseling in this patient population may lead to improvement in quality of life [18]. Women who are diagnosed with a cervical HPV infection and/or premalignant lesions have been found to report self-blame, grief, concern, anxiety, shock, fear, shame, sexual dysfunction, and distress [19,20]. Commonly, women express concerns regarding disclosure of results to partner or partners, fear of future transmission, partner rejection, and questions over the source of infection [14,21,22]. Individuals report angst about the underlying infection that cannot be treated, the stigma of a STI, and questions regarding progression from infection to cervical pre-malignancy and/or malignancy. Along with clinical counseling, addressing patients' behavioral questions may help to reduce the aforementioned psychological sequelae of this complex diagnosis. Patients experience emotional reactions at the time of a cancer diagnosis which may interfere with comprehension [23], and these issues may be amplified with the additional diagnosis of HPV.

Below we discuss common patient questions and what is known and unknown in response to these questions.

How did I get an oral HPV infection?

- HPV is a sexually transmitted infection that can infect the epithelium of the oropharynx, oral cavity, and anogenital tract [24].
- Genital HPV natural history is well understood and serves as the paradigm against which we compare oral HPV natural history. Genital HPV infections, including cervical, vaginal, and penile infection, are common among sexually active young adults. More than 80% of sexually active young adults are infected with a genital HPV infection at some point during their lifetime, although many of these people will never know they were infected [25,26]. Most people clear these genital infections within a year or two on their own [25,27]. Among those who do not clear their infections, persistent infection can lead to pre-malignant and malignant genital lesions [28–30].
• Oral HPV infection is significantly less common than genital HPV infection, and infections are more common among men than among women [31–35]. Initial studies suggest that most people clear their oral HPV infections within a year or two on their own, but some oral HPV infections persist [36,37].
• Oral HPV infection is more common in individuals who have ever performed oral sex, and who have a higher number of lifetime and recent oral sexual partners [31,38,39]. However, oral HPV infection has also been (more rarely) detected in some people who report never performing oral sex [31,37,38,40].
• Oral HPV infection is more likely to be found in individuals with a higher number of lifetime and/or recent vaginal sex partners. Many sexual behaviors are related and on average, people who have a high number of sexual partners for one act have higher numbers of partners for other acts as well (i.e. the relevant sexual exposures are collinear) [31].
• The presence of oral HPV infection is not a marker of promiscuity. Some people with an oral HPV infection report never having performed oral sex, or have only had a few lifetime oral sex partners [31,38,39,41]. Current estimates indicate that about 10% of all men and 4% of all women ages 14–69 in the general U.S. population have a prevalent oral HPV infection [31]. It is believed, though it has not been shown, that many more sexually active individuals are exposed to oral HPV infection in their lifetime [36,37,42], although some people may never have an oral HPV infection.

Are oral HPV and HPV-positive head and neck cancers caused by oral sex?

As summarized below, studies consistently show that oral sex is strongly associated with oral HPV infection and increased odds of HPV-OSCC.

• Oral-genital contact:
  • Several studies have shown that individuals with a higher number of oral sex partners are more likely to have:
    - Prevalent oral HPV infection [38,39].
    - Incident oral HPV infection [43].
    - HPV-associated head and neck cancer [44,45].
  • This suggests that HPV is likely transmitted by oral sex. However, it is important to understand that many sexual behaviors are collinear (i.e. people with higher numbers of partners for one type of sexual behavior often have higher numbers of partners for other types of behavior). Therefore, it is difficult to determine which behaviors specifically are responsible for the presence of HPV in the mouth and/or pharynx.

• Oral-anal contact:
  • Anal HPV is common and it is possible that oral-anal sexual contact (rimming) may be associated with transmission of oral HPV [46–48].
  • One study of gay men showed that an increased number of rimming partners is associated with higher oral HPV prevalence [49]; however, further research is needed to conclusively elucidate the role of rimming in oral HPV transmission.

• Oral-oral contact:
  • It is not known whether open-mouth kissing (i.e. deep kissing or French kissing) can transmit oral HPV infection. Three studies reported an association between open-mouth kissing and oral HPV prevalence, even among those who reported never having performed oral sex [31,38,50]. However, these studies were limited by small sample sizes and could be explained by confounding or mis-reporting of behavior. Other studies have not found any associations with kissing [49,51]. Oral HPV has been detected in youth, but prevalence among younger adolescents (12–15 years old, 1.5%) and older adolescents (16–20 year olds, 3.3%) is relatively low despite the common practice of deep-kissing among these populations [40,52].

When did I get an oral HPV infection?

• We do not know the time from the acquisition of an oral HPV infection to the time of diagnosis with HPV-OSCC. However, extrapolating from what is known about anogenital HPV natural history we believe that individuals presenting with HPV-OSCC today likely acquired these infections many years (possibly decades) previously [53,54].
• Oral HPV infection is not only detected in individuals in their 20s, at the peak time of sexual activity for most individuals, but has even higher prevalence among older age groups [31]. In a recent U.S. population-based study, oral HPV prevalence in both men and women was most common among 30–34 year olds (7.3%) and 60–64 year olds (11.4%), though these estimates do not necessarily reflect the time an infection was initially acquired. Whether the second peak in oral HPV prevalence among 60–64 year olds is related to recent sexual activity, presence of pre-cancer, immune-related factors (i.e. re-activation) or generational differences, is presently unknown.
• We expect that oral HPV infection must persist for many years for cancer to occur, though the data we currently have on natural history of oral HPV infection is limited [53,54]. A recent study detected antibodies to HPV oncogene E6 in HPV-OSCC cases more than 10 years before cancer was diagnosed, while a nested case control study in Nordic countries found HPV16 antibodies 15 years or more prior to diagnosis [53]. These studies suggest that oral HPV infections were acquired many years before development and diagnosis of malignancy. However, we do not know exactly how long it takes for HPV to cause oropharyngeal cancer.

Does diagnosis of HPV-OSCC indicate past or present promiscuity?

• It is important to remind patients that being diagnosed with HPV-OSCC does not imply that either partner was/is unfaithful. Based upon CDC recommendations for discussion of presence of an oncogenic cervical HPV infection, “emphasis should be placed on the fact that HPV is a common infection that is often shared between partners and can lie dormant for many years. [13]”
• An HPV-OSCC diagnosis does not imply that either partner has a “risky” sexual past. Although HPV-OSCC is strongly associated with sexual behaviors and with a higher number of lifetime sexual partners, many patients have a modest number of lifetime sexual partners [44,55]. Indeed, while a higher number of sexual partners increases one’s odds (chances) of acquiring a sexually transmitted infection such as HPV, and thus is associated with increased odds of HPV-OSCC, it only takes one partner who is infected to acquire the infection [44]. Around half of HPV-OSCC patients have had five or fewer lifetime oral sex partners and some report never having performed oral sex [4].
• While not as common as genital HPV infections, many people will likely have been exposed to oral HPV infection during their lifetime [31]. We suspect that while many people are exposed to oral HPV infection, few become infected and even fewer develop malignancy.
6. When did I get this infection?

- We do not know the time from first oral HPV infection to cancer but it takes many years.
- We know that some people have infection 15 years or more before cancer.

7. What does having HPV in my tumor mean?

- Oropharyngeal cancer patients with HPV in their tumor live longer, on average, than people without HPV (i.e. HPV-positive tumors usually respond well to therapy).
- However, patients who currently smoke tobacco or have smoked for a long time in the past, do not live as long as patients who never smoked. Patients who are current smokers should consider quitting.

8. Will the HPV vaccine help me?

- The HPV vaccine prevents people from getting new HPV infections.
- The vaccine will not help you clear an infection you already have.
- The vaccine is recommended for people ages 9-26 years old.

9. Will my spouse/partner also get HPV-OSCC?

- The risk of HPV-OSCC may be slightly higher among spouses of HPV-OSCC but this cancer remains rare among spouses.
- There are no recommended screening tests for HPV-OSCC.

For additional information

A comprehensive list of references is available in:
1. What is Human Papillomavirus (HPV)?

- HPV is a sexually transmitted infection that can infect the oropharynx (tonsils and back of throat), anus, and genitals.
- There are many types of HPV. HPV can cause cancer, warts or have no effect.
- HPV is very common in the U.S. Over 20 million Americans have some type of genital or oral HPV infection.
- In some people, oral HPV infection leads to HPV-OSCC after many years.

2. What causes oropharyngeal cancer?

- HPV now causes most oropharyngeal cancers in the U.S.
- It is recommended that oropharyngeal tumors be tested for HPV.
- Smoking and alcohol use can also cause oropharyngeal cancer.

3. How did I get an oral HPV infection?

- HPV is transmitted to your mouth by oral sex. It may also be possible to get oral HPV by other ways.
- Performing oral sex and having many oral sex partners can increase your chances of oral HPV infection.
- Having an oral HPV infection does not mean your partner was/is unfaithful and does not suggest promiscuity.
- Many people with HPV-OSCC have only had a few oral sex partners in their life.

4. Who has oral HPV infection?

- Many people will likely be exposed to oral HPV in their life.
- Around 10% of men and 3.6% of women in the U.S. have HPV in their mouths and HPV infection is more commonly found with older age.
- Most people clear the infections on their own within a year or two, but in some people HPV infection persists.

5. Can I transmit oral HPV infection to others?

**Family and friends:**
- Oral HPV is not casually transmitted by sharing drinks or kissing on the cheek.
- We do not know if open mouth kissing can transmit HPV.

**Partners of people with HPV-OSCC:**
- You have already likely shared whatever infections you have.
- You do not need to change your sexual behavior.
- Female partners should have regular cervical Pap screening.

**New sexual partners in the future:**
- Many patients with HPV-OSCC no longer have HPV detectable in their mouth after treatment, while others do.
- With new partners, discuss protection methods (e.g., condoms and barrier protection).
**Will I transmit this infection to others?**

- **Transmission to family and friends:**
  - Oral HPV does not appear to be casually transmitted.
  - There is currently no evidence for non-sexual transmission of oncogenic HPV to the mouth or oropharynx, except for the possibility that it may be transmitted through open-mouth kissing.

- **Transmission to spouse or long-term sexual partners:**
  - HPV is a sexually transmitted infection across couples that have been intimate have likely already exposed each other to their sexual infections [56]. Therefore, we do not recommend changing current sexual behaviors in established relationships.
  - Spouses of patients with HPV-OSCC have likely been exposed to HPV themselves (from current and/or former partners), though they usually do not have detectable oral HPV infection (D’Souza, unpublished results [79]). Thus, there is no need to change sexual behavior with a current spouse or long-term partner.
  - Female partners with HPV-OSCC and female spouses/partners of patients with HPV-OSCC should undergo routine cervical screening per NCCN guidelines (as currently indicated for all women over 21 years of age) [57].

- **Transmission to future partners:**
  - Many patients with HPV-OSCC do not have detectable viral DNA after treatment and therefore likely cannot transmit the infection after therapy [58]. On the other hand, some patients continue to have HPV detectable in exfoliated oral cells after therapy, although this likely represents integrated (non-infectious) HPV DNA [58].
  - There is a possible risk of transmission to future partners, though the level of risk is not known.
  - As is the case for prevention of any sexually transmitted infection, discussion of appropriate protection is advised with new partners.
  - Inconsistent condom use or lack of condom use and barrier protection during oral-genital and genital-genital contact has been associated with increased odds of oral HPV infection and HPV-OSCC [31,44,59]. The use of barriers during new sexual encounters may decrease the risk of transmitting genital HPV infection to the mouth or oropharynx during oral sex [60]. Research has not yet evaluated whether oral HPV infection can be transmitted to the genital area during oral sex.

**Is my spouse/partner at increased risk of this cancer? What should they do?**

- Some studies have suggested that spouses of cervical cancer patients are at ~2–3-fold increased risk of HPV-OSCC [61–63]. There are also a limited number of case reports in the literature of couples where both members were diagnosed with HPV-OSCC [64].
  - Partners of patients with HPV-OSCC may have slightly higher rates of HPV-associated cancers such as anal, penile, and/or oropharyngeal than the general population, but these are still rare cancers and the chances of developing these cancers remain low overall [65]. Cervical pre-cancerous lesions are more common among female spouses. Women with HPV-OSCC or female partners of HPV-OSCC patients should follow cervical cancer screening guidelines [57].
  - There are presently no screening guidelines for HPV-associated malignancies of the head and neck. Therefore, with the exception of cervical cancer screening guidelines, there are no additional recommendations for sexual partners or spouses of patients of HPV-OSCC specifically regarding head and neck cancer.

- In the context of genital HPV, the CDC recommends that both patients and partners receive counseling which addresses the potential psychological and sexual issues that arise with the diagnosis of a lesion that is associated with HPV [13]. Physicians of patients and partners diagnosed with genital HPV infection are recommended to acknowledge tension regarding past experiences, effect on present intimacy and other practical solutions to cope with the tension, which may arise from the diagnosis of HPV [13,66]. However, it should be noted that partner notification is voluntary (analogous to other sexually transmitted infections such as HIV). Indeed, as these HPV infections were acquired many years previously and most individuals clear HPV infections on their own, there are no clear guidelines for partner notification. Partner notification could pose more harm than benefit. In the CDC’s counseling messages for genital HPV, the potential for negative partners reactions (rejection and abuse) are highlighted.
  - An oropharyngeal “Pap-test equivalent” has recently been evaluated in high-risk populations, though the study suggests it may not be useful for early detection of oropharyngeal cancers [67]. More research is needed to explore viable secondary prevention mechanisms for oropharyngeal cancers.

**Will I always have this oral HPV infection?**

- Before treatment, many patients with HPV-OSCC have HPV DNA detectable in their oral exfoliate cells; this DNA is likely sloughed off from the tumor and does not necessarily represent a virus capable of infecting someone else [44,58,65].
  - After treatment, some patients no longer have HPV DNA detectable in their oral exfoliate cells, while others do. We do not know whether the infection is “cleared” (gone) or “latent” (controlled by the immune system but not eliminated) [58].

**What does being HPV-positive mean about my disease?**

- Patients diagnosed with HPV-OSCC have significantly better overall survival than patients with HPV-negative OSCC [5,6]. Three-year overall survival for patients with HPV-OSCC is 82% as opposed to 57% among HPV-negative OSCC patients [5]. In population-level data in the U.S., more than half of patients with HPV-OSCC were alive ten years after diagnosis [1].
  - Patients with HPV-OSCC also have improved progression-free survival [6]. The improved prognosis of HPV-associated tumors is believed to be due to increased radiosensitivity conferred by HPV [68].
  - Given this strong prognosis, current trials are evaluating therapy de-escalation, with the hope that side effects from treatment could be reduced without compromising survival; however, we do not yet know the results of these trials.
  - It should be highlighted that current NCCN guidelines caution against the use of HPV tumor status in clinical decision making outside the context of a clinical trial [7].

**Does current or past tobacco use affect oral HPV infection and HPV-OSCC?**

- Current tobacco use has been associated with increased prevalence of oral HPV infection in several studies, suggesting that it may increase either the likelihood of becoming infected when exposed or increase the persistence of oral HPV infection [31,49,69].
Can the HPV vaccines help?

- There are currently two HPV vaccines licensed to prevent new HPV infections in the U.S. The quadrivalent HPV vaccine (Gardasil, made by Merck) protects against HPV types 6, 11, 16, and 18. The bivalent HPV vaccine (Cervarix, made by GSK) protects against HPV types 16 and 18. Both vaccines are currently recommended for all girls and boys around 11–12 years old, as well as “catch-up” vaccination of individuals up to 26 years of age who have not been vaccinated [71,72].
- HPV vaccines prevent individuals from becoming infected with these HPV types if/when they are exposed to the virus [73,74]. These vaccines are designed to be administered before sexual debut, i.e. before exposure to the HPV types targeted. Unfortunately, these vaccines do not help individuals clear an infection they have already acquired prior to vaccination.
- The efficacy of these vaccines in prevention of oral HPV infection has not been evaluated. Existing clinical trials of the HPV vaccines have focused on their impact on HPV-associated anogenital diseases like cervical and anal cancer, and their utility against oral HPV infection is unknown [73,74]. However, given that such a high proportion of head and neck cancers are caused by HPV16 (which the vaccines target), researchers are hopeful that the vaccine might be beneficial in the prevention of future HPV-OSCC as well [75,76]. Several studies using animal models do suggest that HPV vaccination could provide protection against oral HPV infection with vaccine-type HPV strains [77,78].
- It is not known whether the vaccines might have an effect on disease recurrence in the oropharynx. Women treated for vulvar or cervical HPV-related lesions during a randomized blinded placebo controlled study of the quadrivalent HPV vaccine were retrospectively analyzed for subsequent disease. Risk of subsequent HPV-related disease was lower among those who received the vaccine than those in the placebo group. While this is seemingly promising, the benefits and risks of vaccination in people with HPV-OSCC are unknown and need further research.
- Some patients wonder if their spouse should get the HPV vaccine. Spouses have likely already been exposed to HPV and would therefore likely not benefit from vaccination.

Conclusion

HPV confers a unique demographic and prognostic profile upon patients with OSCC; however, the personal and social implications of this diagnosis have not been studied to date. It is important that we acknowledge the strengths of our current knowledge base as well as the unknowns when we counsel patients regarding this diagnosis. While aspects of oral HPV infection and HPV-OSCC are well understood, there are gaps in our present knowledge base, some of which are of great interest to patients and their partners. Ongoing work in risk factors, natural history, psychosocial effects, and therapies for oral HPV infection and HPV-OSCC will inform counseling guidelines of this patient population.

Conflict of interest

G D’Souza has research support from Merck.
