Third Ediiton

Quality Resource Guide

HPV and Oral Cancer

Author Acknowledgements

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Educational Objectives

Following this unit of instruction, the practitioner should be able to:

1. Understand the changing epidemiology of oral cancer and the emergence of HPV as a risk factor.
2. Discuss the signs, symptoms and location of HPV-associated oral cancer.
3. Understand the prognosis for HPV-associated oral cancer.
4. Understand the relationship between specific sexual practices and increased risk for HPV-associated oral cancer.
5. Recognize the critical points of an oral screening for HPV-associated oral cancer.
6. Respond to patient questions about HPV infection and oral cancer and HPV vaccination.

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The content of this Guide is subject to change as new scientific information becomes available.

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Introduction

Oral cancer, primarily consisting of oral squamous cell carcinoma, is predominantly a disease of men and is the eighth most common cancer in the U.S. in this cohort. Disease in women is approximately half that of men. Currently there are estimated to be a total of 55,000 cases with 12,000 deaths annually. Oral cancer is commonly diagnosed late in its course and has only 68% five-year survival.[1] The typical oral cancer has been described as presenting with red and/or white lesions in an elderly male who has been a long-term cigarette smoker and heavy alcohol drinker. Smoking and drinking remain risk factors for oral cancers; however, Human Papilloma Virus (HPV) has emerged as another significant risk factor and is changing the epidemiology of oral cancer, primarily in the oropharynx.

HPV is a small double stranded DNA virus that infects the basal cells of stratified epithelium. More than 200 types of HPV have been identified and cause a variety of human lesions such as verruca vulgaris and various oral epithelial hyperplasias. HPV has been shown to be causative in several cancers including cervical, anal, penile, and more recently oropharyngeal cancer.[2] The two virus types most associated with this cancer and considered high risk for malignant transformation are HPV 16 and 18; with HPV 16 causing 80% and HPV 18 causing 3% of HPV-associated oral cancers.[3]

HPV associated oral cancers most commonly occur as oropharyngeal cancers (OPC) and do not commonly affect the rest of the oral cavity. The term "oral cancer" in this review will include OPC and oral cavity cancers that occur anterior to the oropharynx (lips, buccal mucosa, anterior 2/3 of the tongue, gingiva, and hard palate). OPCs occur in a characteristic location, the posterior oropharynx, the region described as Waldeyer's Ring, including the lymphatic tissue of the palatine and lingual tonsils. Therefore, the common location for HPV oral cancer is between the tonsillar pillars and at the base of the tongue (**Figure 1**). This posterior location often makes these tumors difficult to see. The associated red sore throat is often misdiagnosed as an upper respiratory infection.[4] The most common presenting signs and symptoms with these tumors are dysphagia, odynophagia, and a neck mass, so they are typically large and/or have lymph node involvement before being first diagnosed.[5]

Figure 1

HPV-associated squamous cell carcinoma of the right palatine tonsil (Photo provided by Dr. Michaell Huber).

Epidemiology

The epidemiology of oral cancer in the US has changed dramatically over the last 40+ years. The prevailing risk factors for oral cancer have classically been described as long-term tobacco use, primarily cigarettes and cigars, and heavy alcohol consumption. However, the incidence of these cancers is falling while those caused by HPV infection are increasing. From 1973 to 2008 HPV positive OPC of the lingual tonsil and palatine tonsil increased at a combined rate of 1% per year whereas the rate of HPV negative oral cavity cancer decreased almost 2% per year. From 1988 to 2008, the prevalence of oral cancers associated with the traditional risk factors of smoking and drinking alcohol decreased by 50% whereas the prevalence of those associated with HPV infection increased by 225%. 70% of OPC cancers are now associated with HPV infection.[6,2]

From 2015 to 2019 overall oral cancer rates were largely stable. However, OPC linked with HPV infection increased 1.3% in women and 2.8% in men each year. Mortality for cancers of the mouth and throat increased 0.4% from 2009 to 2020 after decades of decline due to reduction in tobacco use. This is due to an increase of OPC cancer mortality of 2% per year over this period.[7] Currently cancer within the oral cavity with traditional risk factors is more common than HPV-associated OPC, however, with the current trends it is estimated that HPV OPC will become the predominant oral cancer in the near future.[8] Cervical cancer has typically been recognized as the most common cancer caused by HPV. However the incidence of HPV-associated OPC is now higher than cervical cancer in the United States.[9]

There are additional factors that distinguish HPV OPC from traditional oral cancer. The most common age for occurrence (40 to 59 years) is lower for HPV OPC than for traditional oral cancer (over 60 years).[10] As described previously, HPV OPC is usually diagnosed at advanced stages. Late diagnosis usually means a poor prognosis for traditional oral cancer. However, patient three-year survival (82%) is considerably higher for HPV-associated OPC than for traditional oral cancer (57%).[11]

There are population differences in risk for HPV OPC with the following relationships:

- Men > Women
- Caucasians > Blacks
- Non-Latinos > Latinos, including Mexican-Americans

Caucasian men are at particular risk and account for most of the increase in HPV-associated OPC incidence in recent years. These trends are mirrored by oral infection rates with HPV. Seven percent of the U.S. population has an oral HPV infection and one percent has an oral HPV 16 infection. Oral sex activity appears to be key to oral infection and eventual development of OPC, as risk increases with the number of oral sex partners. It also appears that performing oral sex on a woman results in a higher risk than performing oral sex on a man. This explains the increased risk for men but not for the racial and ethnic differences. The differences in risk for different ethnic groups appears to reflect differences in oral sex practices among these groups.[12]

It appears that immune function plays a critical role in HPV oral infection and its progression to HPV OPC in a small number of patients. As mentioned earlier, the HPV tumors largely occur in areas of dense lymphoid tissue, the palatine and lingual tonsils. Immunosuppression raises the potential for infection. Patients who are infected with HIV are four times as likely to have oral infection with HPV as the general population. They also have increased risk for HPV OPC.[13]

Prevention

Recommendations for prevention of HPV OPC are challenging, as we know so little about progression from infection to development of cancer. Most people will clear the virus after infection with 90% clearing the virus within one year.[14] Why do only 10% of patients retain infection for more than one year, and who of this group are at risk to ultimately develop cancer? How long does it take the average patient to develop cancer? What role does the immune response play in this progression? These questions have yet to be answered.

Should patients be screened for oral HPV infection? There are several commercial tests available that are being marketed to screen all patients with the goal of preventing oral cancer. Unfortunately, we do not know what a positive test means for an individual patient. As mentioned previously, 7% of the US population has an HPV oral infection, and 90% of these patients will clear the virus by one year. Therefore, only a very small number of these patients will go on to retain HPV and potentially develop OPC, and these HPV tests do not help us identify who those patients will be. Also, these tests screen for viral DNA present in the oral cavity and not for cell integrated DNA known to cause malignant transformation. Routine testing for oral HPV infection is not currently warranted.

What is the role of vaccination in preventing HPV OPC? There is currently one vaccine (Gardisil 9-Merck) commercially available in the US, and it covers HPV 16, HPV 18, and seven other HPV strains. Will vaccination be effective in preventing HPV OPC? This is a difficult question to evaluate, because it appears that OPC develops many years after the period that patients would be most sexually active and acquire HPV infection, usually in their teens and 20s. However, studies evaluating vaccination against HPV in women to prevent cervical infection have been very effective.[15,16] Also multiple studies have shown that HPV vaccination significantly reduces oral infections with HPV.[17, 18] As a result the FDA has given Merck conditional approval to market Gardisil 9 to prevent HPV OPC while they conduct further studies of efficacy until 2025. A decision will then be made whether or not to continue approval.[19]

Dental Considerations

HPV OPC is changing the face of oral cancer. It is critical that dental providers understand this and interact with patients accordingly. It appears this professional understanding is currently not in place.[20,21] A 2014 study of the knowledge of dentists, dental hygienists, and dental students showed some concerning trends. Over half of respondents in all three groups misidentified data on location of lesions in the oral cavity, age at occurrence, and patients at risk for HPV OPC.[22] It is critical that dental educational programs and continuing education programs modify their curricula to reflect the current information. **Table 1** provides a comparison of characteristics between traditional oral cancer and HPV-related oropharyngeal cancer.

A thorough oral soft tissue exam using a good light source is always the most important intervention to discover oral cancer. The examination needs to include more emphasis on the posterior oropharynx and base of tongue. This location where HPV

Table 1 - Comparison Between Traditional Oral Cancer and HPV-Related Oral Cancer

	Traditional Oral Cancer*	HPV-Related oral Cancer†
Location	Oral cavity	Posterior Oropharynx, palatine and lingual tonsils
Description	Ulcerated mucosal lesion, pain variable	Neck mass, pain common
Risk Factors	Tobacco and alcohol	HPV infection
Common Age	> 60 y	40-59 y
Three-year Survival	57%	82%
Gender	Males	Males, particularly white males

* Oral cancer with tobacco and alcohol use as primary risk factors

† Oral cancer with HPV infection as primary risk factor

OPC typically occurs is commonly "glossed over" because of its posterior location and concern about the patient's gag reflex. Often these tumors cannot be seen even with a thorough oral examination due to their posterior location. Examination of the neck is more critical with these patients, as a neck mass with pain is often the first sign of malignancy. With these findings referral should be made to a head and neck surgeon for fiberoptic evaluation of the oropharynx.

Does dentistry have a role to educate patients about the role of HPV in OPC? Dentists need to be able to answer a patient's questions about HPV OPC being a sexually transmitted disease. This can be a delicate discussion, but as with HIV in the 1980s, dentists must be able to give patients accurate information about the natural history of this disease. A 2019 publication has shown that most dental patients are comfortable discussing the risk factors, including sexual history, for HPV OPC.[23] It is important to explain that HPV infection is very common, but HPV OPC is very uncommon. The vast majority of HPV infected patients will not develop OPC. There is an excellent article by Fakhry and D'Souza that addresses patient questions for professionals about HPV infection and oral cancer.[24]

What about vaccination against HPV infection? It is currently approved and recommended for multiple groups of females and males to prevent cervical, anal, and penile cancers. Even though the efficacy of the vaccination to prevent OPC is undetermined, as mentioned earlier the FDA has given conditional approval to prevent HPV OPV.[19] Therefore widespread HPV vaccination could have a dramatic impact on preventing multiple cancers, including HPV OPC.

HPV vaccination recommendations now include patients up to 45 years of age. The Centers for Disease Control and Prevention now recommends the following: "vaccination for all boys and girls at ages 11-12 to protect against HPV-related infections and cancers. Some adults age 27 through 45 years who are not already vaccinated may decide to get HPV vaccine after speaking with their doctor about their risk for new HPV infections and the possible benefits of vaccination. HPV vaccination in this age range provides less benefit, as more people have already been exposed to HPV. Anyone starting the series before their 15th birthday receives two doses of HPV vaccine, with at least six months between the first and second dose. Adolescents who receive their two doses less than five months apart will require a third dose of HPV vaccine. Teens and young adults who start the series at ages 15 through 26 years will need three doses of HPV vaccine. Also, three doses are recommended for people with certain immunocompromising conditions aged 9 through 26 years." (**Table 2**)[25] HPV vaccination rates for children and teens have improved significantly over the last several years with 76.9 receiving at least one dose in 2021.[26]

What is the role of dentists in advocating for HPV vaccination? All practicing dentists should be able to respond to patient questions about vaccination. In dental practices that treat children, this discussion with parents would be particularly important. The American Dental Association has adopted a policy encouraging dentists to support and promote HPV vaccination and has published a brochure entitled *Oral Health and the HPV Vaccine*.[27] In addition, the American Academy of Pediatric Dentistry has adopted a "Policy on Human Papilloma Virus Vaccinations" which strongly encourages promotion of HPV vaccination.[28] Again, this may be a delicate discussion with parents. However, the public health impact would be enormous if dental practices could help significantly raise the rate of vaccination.

Table 2 - Current HPV Vaccine[25]

Vaccine	Manufacturer	HPV Types	Recommended Doses	Recommended Ages
Gardasil 9	Merck	6, 11, 16, 18, 31, 33, 45, 52, 58*	2 or 3+	11 to 45#

* HPV 6 and HPV 11 cause genital warts and precancerous lesions and HPV 31, 33, 45, 52 & 58 cause cervical, vulvar, vaginal, and anal cancer.

+ 2 doses up to age 15, 3 doses after age 15 or in certain immunosuppressed groups.

Vaccination should begin at age 11 to 13, older groups can consider vaccination up to age 45 after discussion with health care provider.

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POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the "Online Exam." We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.0 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. **What HPV type is most commonly associated with oropharyngeal cancer?**
   a. Type 1
   b. Type 9
   c. Type 16
   d. Type 21

2. **Oral HPV infection can cause which of the following conditions?**
   a. Warts
   b. Hyperplasias
   c. Cancer
   d. All of the above

3. **What is the primary location for HPV associated oral pharyngeal cancer?**
   a. Dorsal tongue
   b. Lips
   c. Tonsils
   d. Floor of the mouth

4. **Which is a common clinical presentation for HPV associated oropharyngeal cancer?**
   a. Neck mass
   b. Tongue ulcer
   c. Leukoplakia of buccal mucosa
   d. Lip swelling

5. **Which oral cancer diagnosis has a better three year survival?**
   a. Floor of mouth cancer
   b. HPV Oropharyngeal cancer
   c. Gingival cancer
   d. All are equal

6. **Which group is at highest risk for HPV associated oropharyngeal cancer?**
   a. Black women
   b. Black men
   c. Caucasian women
   d. Caucasian men

7. **Which condition is associated with increased risk for HPV oral infection?**
   a. Herpes Simplex
   b. HIV
   c. COVID
   d. Candidiasis

8. **What percentage of patients with HPV oral infection will not clear the virus within one year?**
   a. 40%
   b. 60%
   c. 30%
   d. 10%

9. **The FDA has approved HPV vaccination for which of the following cancers?**
   a. Oropharyngeal cancer
   b. Cervical cancer
   c. Anal cancer
   d. All of the above

10. **What is the recommended number of doses of HPV vaccine for 11 to 12 years olds?**
    a. 1
    b. 2
    c. 3
    d. 4

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