

## Human Papilloma Virus (HPV) and the Implications for Oral Cancer Prevention and Treatment:

### Can HPV Vaccination Improve Public Health?

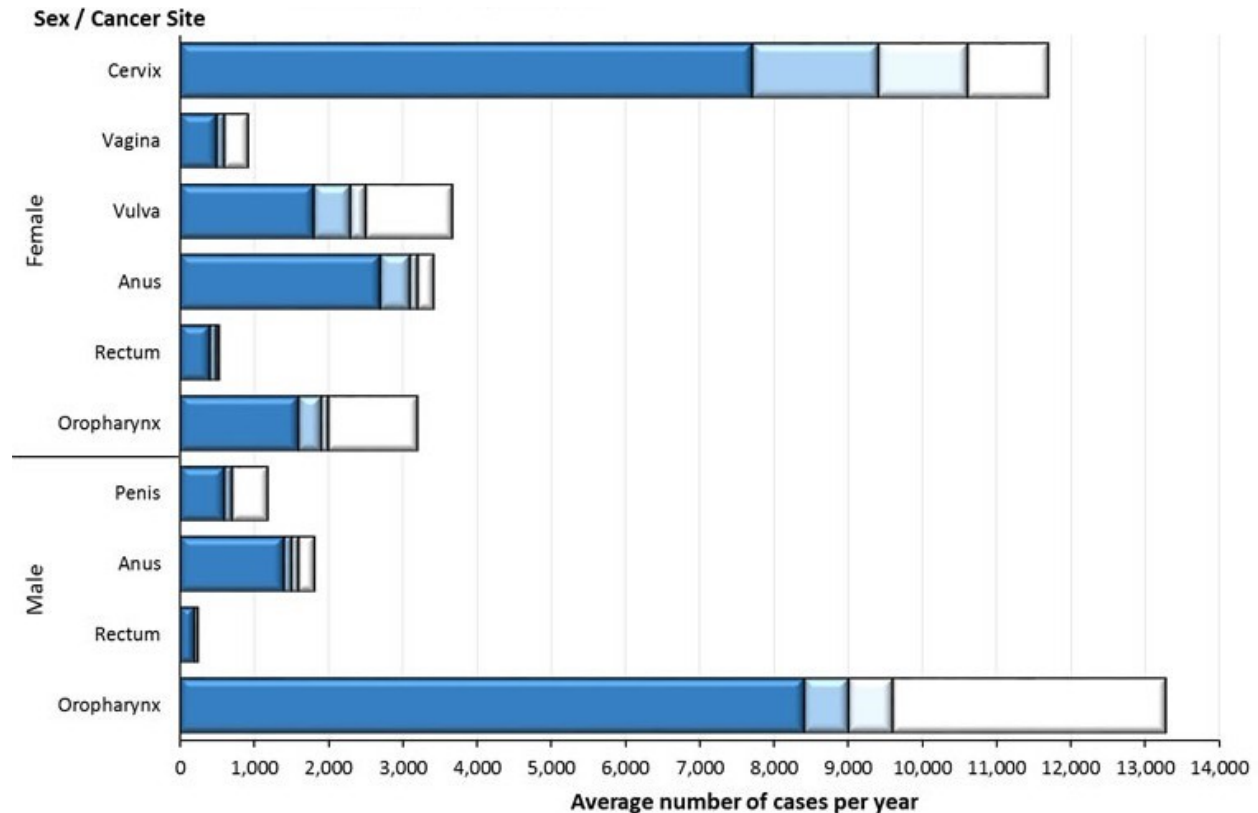
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Human papillomavirus (HPV) is the most commonly diagnosed sexually transmitted disease in the United States. Based on data from 2009 to 2013, approximately 39,800 HPV-associated cancers occur in the United States each year: about 23,300 among women, and about 16,500 among men. Cervical cancer is the most common HPV-associated cancer among women, and oropharyngeal cancers are the most common among men.

Unlike cervical cancer, where all carcinogenic outcomes are attributed to HPV infection, role of HPV in oral cancer development is confounded by its multi-factorial etiology including tobacco and alcohol. Recent studies demonstrated that incidence of HPV-related head and neck cancer is increasing while the prevalence of smoking and alcohol induced cancers has been declining (see Figure 1). Up to 70% of cancers of the oropharynx may be linked to HPV. It is estimated that about 3,200 new cases of HPV-associated oropharyngeal cancers are diagnosed in women and about 13,200 are diagnosed in men each year in the United States.

Figure 1. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. Journal of the National Cancer Institute 2015.



The human papilloma virus is a double-stranded DNA virus that infects the epithelial cells of

skin and mucosa. Over 200 distinct HPV strains have been identified. HPV 16 is the most common viral subtype responsible for oropharyngeal cancer with implications regarding potential preventive measures.

Patients with HPV-positive disease are different from patients with HPV-negative disease. HPV-positive patients are more likely younger, nonsmoker, and have a better prognosis. Studies showed that the risk of cancer progressing for patients with HPV-positive oropharyngeal cancer is significantly reduced compared with HPV-negative patients. Risk stratification by p16 or HPV status has been evaluated and incorporated into clinical trials. For instance, different chemoradiotherapy programs (RTOG 1016), different radiation doses after induction chemotherapy (ECOG 1308) and primary management with trans-oral robotic surgery (ECOG 3311) are studied. Patients with HPV-positive, advanced oropharyngeal carcinoma were treated with chemoradiotherapy with radiation doses reduced by 15- 20% were associated with high progression-free survival and an improved toxicity profile. Radiation de-escalation has potential to improve the therapeutic ratio and long-term function for the patient with HPV-positive oropharyngeal cancer.

American Joint Committee on Cancer (AJCC) staging system in the seventh edition (2010) did not distinguish between HPV-positive and HPV-negative head and neck cancer. In the upcoming eighth edition (2017, to be implemented on January 1, 2018), separate staging systems have been established (see Figure 2). The new system has only three stages for non-metastatic HPV-related oropharyngeal cancer.

Figure 2. AJCC Comprehensive Staging System

AJCC Comprehensive Stage	T and N staging	
	HPV-related ( p16+)	Non HPV-related
Stage I	T0-T2N0-N1	T1N0
Stage II	T0-T2N2 or T3N0-N2	T2N0
Stage III	T4 or N3	T1-3N1 or T3N0
Stage IVA	M1	T1-T3N2a-N2b or T4aN0-N2b
Stage IVB	NA	Either T4b or N2c
Stage IVC	NA	M1

Although HPV-related oropharyngeal cancer is associated with a better prognosis and response to therapy than HPV-negative tumors, current treatment for patients with HPV-related oropharyngeal cancer is essentially same as for those with HPV negative tumors. Multi-center clinical trials are currently underway to determine de-escalation treatment can be applied to HPV positive tumors. In non-oropharyngeal cancer, e.g. tongue, floor of the mouth, or gum cancer. HPV- positivity is less common. Its prognostic implications are unknown at this time for HPV positive non- oropharyngeal cancer.

In the United States, there are only two cancer preventive vaccines are approved. Hepatitis B virus (HBV) vaccine is for prevention of chronic HBV infection which can lead to liver cancer. The other is HPV vaccine. Currently three different vaccines are available which vary in the number of HPV types they contain and target. Among Gardasil, Gardasil 9, and Cervarix, Gardasil 9 is the only HPV vaccine available in the United States as of 2017. Advisory Committee on Immunization Practices recommend 2-dose schedule routine vaccination at age 11 or 12 years up to 26 years since 2006 for females and since 2011 for male. Clinical trials have demonstrated that FDA-approved HPV vaccines can prevent anogenital HPV infections and precancerous lesions that lead to HPV-associated cancers, including cervical and anal cancer; however, potential impact of current HPV vaccines on oral HPV infections that lead to cancer has not yet been tested through clinical trial.

National Health and Nutrition Examination Survey (NHNES) study of more than 2,600 young adults in the United States found that the prevalence of oral infection with four HPV types,

including two high-risk types, was 88% lower in those who reported receiving at least one dose of an HPV vaccine than in those who said they were not vaccinated.

HPV vaccines are strongly recommended for cancer prevention; however, a self-reported survey in 2015 showed only 60% of girls and 50% of boys under age 18 received more than one HPV vaccine dose.

Recently, it has been noted that the incidence of HPV- positive oropharyngeal cancer has been rising, while the incidence of cervical cancer has declined, due to highly effective cervical cancer screening program. There are no formal screening programs for the non-cervical cancers, including oropharyngeal cancer. In the head and neck cancer management, many would agree that early diagnosis and treatment are the most important prognostic factor. Perhaps promotion of universal HPV vaccination could bring even more positive impact on public health, potentially longer life spans and reduction of treatment related morbidity while improving post cancer treatment quality of life.

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