Human Papillomavirus and Oropharyngeal Cancer

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KEYWORDS

• Human papillomavirus • Oropharyngeal cancer • Oral squamous cell carcinoma
• Tonsillar cancer • HPV 16 • p16

KEY POINTS

- Human papillomavirus (HPV) infection is a distinct risk factor for oropharyngeal squamous cell carcinoma (OPSCC), and HPV 16 is associated with most HPV-OPSCC cases.
- Incidence rate of HPV-OPSCC, particularly tonsillar cancer, has been rapidly increasing for the past 2 decades, whereas tobacco-related head and neck squamous cell carcinoma rates are decreasing worldwide.
- Typical patients with HPV-OPSCC are described as men, white, younger than 60, healthier individuals with no or little tobacco exposure, and having a higher socioeconomic status.
- Strong association between orogenital contact and OPSCC was found in a hospital-based, case-control study. A recent systematic review in 2014 found 50% to 80% of adolescents and young adults reported participation in oral sex.
- The potential benefit of HPV vaccination to reduce the risk of HPV-OPSCC has been suggested.

INTRODUCTION

The link between human papillomavirus (HPV) infection and head and neck squamous cell carcinoma (HNSCC) was first described by Syrjanen and colleagues[1] in 1983. However, in some of the historic HPV literature, distinctions were not made between cancers arising in the oral cavity and oropharynx. It is now well established that HPV infection is a significant risk factor for the development of oropharyngeal squamous cell carcinoma (OPSCC); furthermore, HPV-associated OPSCC (HPV-OPSCC) is recognized as a unique subtype of HNSCC comprising approximately 25% of all

Disclosure Statement: The authors have no commercial or financial conflicts of interest and no funding sources to disclose.
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Dent Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cden.2017.08.008 **dental.theclinics.com**

HNSCC.[2] Epidemiologic studies have shown increasing incidence rates of HPV-OPSCC for the last 2 decades, whereas tobacco-related HNSCC rates are decreasing worldwide.[3–5] In the near future, the global burden of HPV-OPSCC is predicted to surpass that of cervical cancer, in which HPV infection is also known to be etiologic.[6]

It is estimated that approximately 70% of all OPSCC are linked to HPV infection.[7] In contrast, HPV is not considered to be a major risk factor for the development of *oral cavity* squamous cell carcinoma (OSCC). A meta-analysis (from a total of 4680 samples from 94 studies) reported the probability of detecting HPV in benign leukoplakia as 22% and in dysplastic lesions as 26.2%.[8] However, studies suggest that HPV contributes to the pathogenesis of only a very small subset (1%–10%) of all OSCC.[4,9,10] Tobacco and alcohol remain the major risk factors for OSCC. The important distinctions between OPSCC and OSCC are now reflected in the recently published 4th edition of the World Health Organization (WHO) Classification of Tumours of the Head and Neck[11] as well as in the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual.[12] The clinical staging criteria for HPV-OPSCC have been significantly revised to accommodate current understanding of these cancers. The changes reflect the uniqueness of HPV-OPSCC, including site specificity, demographics, clinical features, and response to treatment when compared with non–HPV-OPSCC. This review describes current understanding of the link between HPV infection and OPSCC, with updated biological and clinical evidence.

HUMAN PAPILLOMAVIRUS–ASSOCIATED HEAD AND NECK SQUAMOUS CELL CARCINOMA: EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS

HPV is a small (8-kb), nonenveloped circular DNA virus with epithelial tropism.[13] The HPV family comprises approximately 200 viral strains with more than 40 being transmitted through direct contact with the skin and mucous membranes.[13,14] To this end, HPV infection is the most common sexually transmitted disease in the United States. According to the Centers for Disease Control and Prevention (CDC), approximately 20 million Americans are currently infected with HPV with 6 million newly infected each year.[7] Nearly all sexually active individuals will acquire an HPV infection at some point in their lives.[3] Although most HPV infections are typically cleared by the host's immune system within 1 to 2 years without causing any symptoms, some persist for months to years.[15]

Depending on its ability to persist and transform infected epithelial cells, HPV is divided into 2 broad subtypes: high-risk and low-risk HPV.[15] Low-risk HPV, including HPV 6 and 11, is associated with benign lesions such as verruca vulgaris or condyloma acuminatum (**Fig. 1**). High-risk HPV is associated with malignancy, mostly in the cervix, vulva, vagina, penis, anus, rectum, and oropharynx, including the base of tongue and tonsil.[16] The WHO currently identifies 12 HPV strains (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) as high-risk cancer-causing types.[15]

HPV types 16 and 18 are associated with the vast majority of HPV-related cancers in the United States; HPV 16 is now recognized as a carcinogenic agent for OPSCC.[16–19] In contrast, HPV types 31, 33, 45, 52, and 58, combined, are linked to approximately 10% of all HPV-positive cancers.[17] A recent CDC study reported that almost 39,000 HPV-associated cancers (11.7 per 100,000 persons) were annually diagnosed during the period from 2008 to 2012; approximately 40% of these were diagnosed as OPSCC[20] (**Fig. 2**). Collectively, the incidence rates of HPV-OPSCC have been increasing for the last 3 decades, whereas tobacco-related HNSCC rates are decreasing worldwide.[3,4] The increase in incidence of OPSCC in relation to all HNSCC is significant; HPV-OPSCC increased at a rate of 2.5% per year in the United States