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Review

Human papillomavirus in oropharyngeal cancer: The changing face of a disease

Jon Mallen-St Clair MD, PhD [a,1], Mustafa Alani DMD [b,1], Marilene B. Wang MD [a,c,d], Eri S. Srivatsan PhD [c,d,*]

[a] Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[b] UCLA School of Dentistry, Los Angeles, CA, United States
[c] Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System/David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[d] Member of Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA, United States

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ABSTRACT

The last decade has brought about an unexpected rise in oropharyngeal squamous cell carcinoma (OPSCC) primarily in white males from the ages of 40–55 years, with limited exposure to alcohol and tobacco. This subset of squamous cell carcinoma (SCC) has been found to be associated with human papillomavirus infection (HPV). Other Head and Neck Squamous Cell carcinoma (HNSCC) subtypes include oral cavity, hypopharyngeal, nasopharyngeal, and laryngeal SCC which tend to be HPV negative. HPV associated oropharyngeal cancer has proven to differ from alcohol and tobacco associated oropharyngeal carcinoma in regards to the molecular pathophysiology, presentation, epidemiology, prognosis, and improved response to chemoradiation therapy. Given the improved survival of patients with HPV associated SCC, efforts to de-intensify treatment to decrease treatment related morbidity are at the forefront of clinical research. This review will focus on the important differences between HPV and tobacco related oropharyngeal cancer. We will review the molecular pathogenesis of HPV related oropharyngeal cancer with an emphasis on new paradigms for screening and treating this disease.

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* Corresponding author at: Department of Surgery, VAGLAHS/David Geffen School of Medicine at UCLA, Los Angeles, CA 90073, United States.
E-mail address: esrivats@g.ucla.edu (E.S. Srivatsan).
[1] Equal contribution by these two authors.

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cause of cancer in the world. Mortality rates are high, with more than 200,000 deaths attributed to the disease annually [1]. While early stage HNSCC can often be cured with surgery and adjuvant radiation, the 5-year survival of patients with locally advanced or metastatic disease is 48% and 26% respectively [2,3]. The disease is characterized by high recurrence rates and nodal metastases, both of which are thought to have a profound effect on mortality, as the 5-year survival rate is reduced by approximately 50% in patients with cervical lymph node metastases [4].

Traditional treatment of HNSCC is associated with considerable morbidity. Surgical therapy for advanced stage disease can be disfiguring. Furthermore, all commonly used treatment modalities—surgery, chemotherapy, and radiation therapy are associated with adverse outcomes on speech and swallow function [5]. In the past decade, HNSCC associated with known risk factors, such as tobacco, alcohol, and poor oral hygiene has been declining in incidence [6,7]. In contrast, infection with HPV has been shown to be a new risk factor for HNSCC, more specifically the base of tongue, soft palate, tonsils, and pharyngeal wall in younger adults. The prevalence of HPV associated HNSCC has been increasing at epidemic proportions in multiple populations including the United States, Western Europe, and Australia [6,7]. The prevalence of HPV infection in oropharyngeal SCC (OPSCC) has been estimated to range from 45 to 90% depending on the study and method of detection [6]. High risk HPV 16 is the dominant subtype that has been identified, and is thought to represent 90% of OP cancers that are HPV positive [6]. The increasing incidence of HPV is associated with alterations in the sexual practices of these populations, over the past 40 years. Specifically, there has been a trend toward increased number of sexual partners and increased number of orogenital partners [8]. In addition, to the increased incidence of HPV associated OPSCC there has been a concomitant rise in the seroprevalence of HSV 1 infection, which is likely reflective of these alterations in sexual practices [9]. The incidence of HPV associated OPSCC is a unique clinical entity. This review will focus on the important differences in HPV associated HNSCC, with an emphasis on how these differences affect diagnostic screening and treatment. The molecular pathogenesis of HPV associated OPSCC will also be reviewed in detail.

1.1. HPV associated HNSCC: a distinct clinical entity

HPV positive HNSCC appears distinct from the HPV negative HNSCC in multiple clinical presentations (Table 1). The molecular mechanism of transformation and tumor progression in HPV associated HNSCC are unique. There is an epidemiological profile that is distinct, with the majority of patients with HPV associated HNSCC being young, white, and male. The clinical behavior of HPV associated HNSCC is unique as well, with the majority of patients presenting with an early T stage, but with advanced nodal disease. Perhaps most importantly, patients with HPV associated HNSCC have an improved prognosis [6,7,10]. The HPV status of SCC has been demonstrated to be a prognostic factor for overall survival, as well as progression free survival [11]. Specifically, HPV associated OPSCC is associated with a 28% reduced risk of dying, and a 49% reduced risk of local regional recurrence [11,12]. Studies have also indicated that HPV status may be a predictive marker of response to treatment, associated with an improved response to both radiation therapy and chemotherapy [13]. All of this information is indicative that HPV associated OPSCC is a distinct clinical entity and currently efforts are being made to develop novel screening methodologies and therapeutics to target HPV associated OPSCC.

1.2. Molecular pathogenesis

HPV is a member of the Papillomavirus family. It has a circular double strand DNA encoding eight early genes (E1–E8) that are involved in host cell transformation, and two late genes (L1 — L2) which are involved in producing structural proteins for the viral capsid. There are over 100 subtypes of HPV viruses; these are typically classified as low risk or high risk subtypes. Common high risk subtypes include HPV16, 18, 31, and 33 [14]. However, both low risk and high-risk subtypes of HPV can cause the abnormal growth of epithelial cells [15]. Infection with HPV results in a large spectrum of epithelial lesions. These are typically benign hyperplastic lesions; however, infection with high-risk subtype is associated with transformation to cancer [16,17]. HPV 16 is the most common sub-type associated with head and neck cancer and is estimated to be present in 90% of HPV associated HNSCC samples [18]. Papillomaviruses typically infect basal epithelial cells through a localized wound or abrasion [17]. Within the oropharynx, HPV associated OPSCC occurs most commonly in the lingual and palatine tonsils. The uvula, soft palate, and posterior pharyngeal wall are less frequent subsites of this disease. Infection typically targets the reticulated epithelium that lines the tonsillar crypts [14]. The tonsillar crypts are susceptible to transformation with HPV virus and may be analogous to the transformation zone of the uterine cervix [14].

1.3. HPV structure

The HPV 16 virion is 55 nm in diameter and has an icosahedral capsid T = 7 that is composed of two capsid proteins, the L1 major capsid, and the L2 minor capsid (Table 2). The fully formed viral capsid has 360 L1 capsid proteins that are organized into pentamers with L2 proteins incorporated into the center of the pentamer structure [19]. L2 binds directly to the L1 by means of hydrophobic interactions. Most of the L2 protein is hidden within the capsid except for its N terminus,

Table 1
– Differences between HPV positive and negative HNSCC.

Tumor Characteristics	HPV positive tumors	HPV negative tumors
Molecular Signature	p53 wild type, increased p16 expression, decreased Rb expression, p53 degraded	p53 mutated, genomic instability, harbor more mutations
Pathogenesis signature	Direct transformation by oncoproteins E6 and E7	Ethanol and Tobacco use, poor oral hygiene - chronic inflammatory state with free radicals → favors DNA damage
Cellular composition	T-cells (CD3 +, CD4 +, CD8 +, CD34 +, γδ, regulatory), NK-cells, B cells, and monocytes [85].	Endothelial cells, epidermis, dermis, keratinocyte, and fibroblast.
Epidemiologic signature	Younger, white, male, high number of oral/vaginal sexual partners, marijuana use, better oncologic outcome	Older, African American population, ethanol and tobacco use and poor oral hygiene, poor oncologic outcome
Clinical signature	Early T stage with extensive nodal involvement. Cystic and multilevel tumor phenotype	Late T stage. Typically less nodal disease
Histologic signature	Lobular growth, permeated by lymphocytes, non-keratinization, and considered well or undifferentiated. Basaloid morphology [7].	Keratinizing, moderately differentiated
Metastasis signature	Distant metastasis occurs post chemo therapy with a distinct pattern to Lung, liver, bone, and other tissues. Requires alternative surveillance strategies [87].	Local and lung metastasis. Reduced distant metastasis pattern to bone liver and other sites [87].