Human Papilloma Virus and Oral Cancer
Joseph Califano, MD
Oral Cancer Committee, Maryland Comprehensive Cancer Control Plan

One of the most well studied biomarkers of HNSCC is human papilloma virus integration in oropharyngeal squamous cell cancers. Human papillomavirus (HPV) is a ~ 7.9-kb, nonenveloped, double-stranded, circular DNA virus that has been implicated in a variety of anogenital and aerodigestive diseases, ranging from common warts to laryngeal papilloma to cervical cancer. Currently, sequences for over 320 different types of HPV have been identified, with several additional poorly characterized types described. These viruses infect cells in the basal layer of squamous epithelium, and the different types have been traditionally separated based on tropism for cutaneous and mucosal sites, as well as high, intermediate, and low risk, depending on their association with malignancy. This review will focus on mucosal high-risk types, known to be significant in the head and neck, predominantly HPV 16 and HPV 18, although other, rarer, subtypes may be carcinogenic.

As a biomarker, HPV infection and the subsequent genomic integration in HNSCC offers diagnostic, prognostic, and possibly therapeutic opportunities. Multiple studies have shown that HPV infection is present in a subset of oropharyngeal cancers but at different rates. In a recent meta-analysis, HPV genomic DNA was detected in approximately 26% of all HNSCC by sensitive polymerase chain reaction (PCR)-based methods. However, in the majority of studies, 50% or more of oropharyngeal tumors contained the HPV genome. A multinational study conducted by the International Agency for Research on Cancer (IARC), only 18% of oropharyngeal tumors were HPV positive, indicating that this proportion likely varies by geography. Regardless of the study population, high-risk HPV16 accounts for the overwhelming majority (90% to 95%) of HPV-positive tumors. In addition to being able to reliably detect HPV in a subset of oropharyngeal cancers, when HPV is detected in cervical lymph nodes of patients presenting with an occult primary, it may be used to establish with high specificity, the location of the primary within the oropharynx. Tonsillectomy has been shown in retrospective analyses to identify the primary site of cervical metastases as the contralateral or ipsilateral tonsil in approximately 10% and 30% of cases, respectively. Therefore, HPV-related cancer is a distinct entity that can be reliably diagnosed.

With regard to prognosis, patients with HPV-positive tumors have improved prognosis when compared with patients with HPV-negative tumors in the majority of studies, with as much as 60% to 80% reduction in risk of dying from their cancer when compared with the HPV-negative patient after controlling for other risk factors. The reason for the improved survival is unclear; however, improved radiation responsiveness, immune surveillance to viral antigens, and the absence of field cancerization in these patients who tend to be nonsmokers, have been postulated as possibilities. In addition, E6-related degradation of p53 in HPV-positive cancers may not be functionally equivalent to HPV-negative p53 mutations and therefore, HPV-positive tumors may have an intact apoptotic response to radiation and chemotherapy.
Therapeutic implications of an HPV-positive diagnosis are an active area of investigation. The Eastern Cooperative Oncology Group is studying the impact of HPV presence on oropharyngeal organ preservation therapy. It is believed that HPV-HNSCC will perform better than HPV negative HNSCC. A clinical trial of an HPV16-specific therapeutic vaccine is also currently being evaluated. The vaccine is administered in the adjuvant setting and is intended to enhance the cytotoxic T-cell response to the HPV16 oncoproteins. With regard to prevention, a prophylactic vaccine composed of the HPV16 viral capsid protein has recently been shown to prevent persistent HPV16 infection and the development of cervical dysplasia. However, the clinical trials have not included an evaluation of the impact of the vaccine on oral HPV infection. The vaccine does have the potential to have an impact on HNSCC incidence because the current vaccines are targeted to HPV16 and there are animal models that demonstrate a protective effect and a reduction in the development of HPV-related oral lesions.

Possible future diagnostic tests that would likely have high specificity but low sensitivity for a diagnosis of HPV-associated HNSCC will include the detection of HPV16 DNA in plasma which can be used for surveillance. Other screening tests like fluorescence ISH or ISH on papanicoloou smears obtained directly from tumors and HPV16 E6 and E7 seroreactivity are other tests currently being tested. The impact of a positive test for a patient’s risk for the development of cancer is unclear. For instance, there was a recent study that demonstrated oral sex as a risk for HPV infection and subsequent development of cancer, but this risk has proved challenging to quantitate.

Finally, within the state of Maryland, a retrospective cohort study showed that disease-free survival was significantly greater in white than in black SCCHN patients treated with chemoradiation, the greatest difference occurring in the oropharyngeal subgroup. Further analysis of these data showed a worse overall survival for black head and neck patients that was driven by oropharyngeal cancer treatment outcomes since black oropharyngeal cancer patients have a lower prevalence of HPV infection.

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