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Oral HPV: An Overview of the Disease and its Role in the Development of Oral Cancer

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What is oral HPV?

Oral HPV (human papillomavirus) is a clinical manifestation of the HPV infection in regions of the ororespiratory tract, which includes the entire oropharyngeal complex, tongue, tonsils, and buccal and lingual mucosa. HPV is one of the most common sexually transmitted diseases in the United States.[1-3] The prevalence of HPV is large and growing; according to the National Institute of Allergy and Infectious Diseases, a branch of the Centers for Disease Control, at least 20 million people in the U.S. are infected with HPV, and there are approximately 5.5 million new cases per year.[4]

The genetics of HPV involve a double-stranded DNA genome that is then enveloped in a protein capsid comprised of 2 proteins. These capsid proteins impart to the various HPV types the capacity to infect epithelium from a variety of body sites, but most importantly, the skin and mucosa of the genital and ororespiratory tracts. There are more than 100 different human papillomavirus types.

Each type is defined first by differences in the sequence of its DNA and second by its tendency or risk to be associated with malignant tumors of the infected tissue. Low-risk HPVs such as HPV-6 and HPV-11 typically induce benign lesions such as warts or papillomas. High-risk oncogenic types, such as HPV-16, -18, -31, -33, and -35, are defined by their strong epidemiologic association with cervical cancer.[5]

Like its counterpart in the genital tract, HPV infection of the head and neck region is now also recognized to be associated with squamous cell carcinomas of the skin and oral mucosa.[6-8] As far as the oropharyngeal complex is concerned, the prototype high-risk types (HPV-16 and HPV-18) are known experimentally to cause cells in culture to undergo malignant transformation, corresponding to the common finding of these viruses in clinical cancers as well.[9]

How HPV infection leads to oral cancer

The initial effect of HPV infection is to take control of the cell's mechanisms for growth and differentiation. Longstanding and continued expression of the viral genes, in particular the so-called E6 and E7 genes, causes destabilization of the cell's genome that in turn makes permanent the deregulation of the cellular proliferation.

This step is often referred to as cellular immortalization. The subsequent steps that lead to cancer are evidenced in clinical samples as histologic progression and, at the molecular level, integration of the HPV genome into the cell's chromosomes and the amplification of various cellular oncogenes.[10-13] In other words, the HPV virus must be present in the host cell; and once there, its viral genetic material in effect "takes control" over the host cell, leading to a cascade of events we see as the clinical manifestation of a tumor.

Oral HPV frequency

In a 2003 multinational study conducted by the International Agency for Research on Cancer, only 18% of oropharyngeal tumors were HPV-positive, indicating that this proportion likely varies by geography.[14]

A 2005 study based on the meta-analysis of several studies estimated that HPV is associated with approximately 26% of all head and neck squamous cell carcinomas. These more sensitive studies employed the laboratory technology called the polymerase chain reaction, or PCR.[15]

The data linking HPV to oropharyngeal cancers is even more strong, with various published series showing detection of HPV in 50% or more of cases.[16] Regardless of the study population, HPV-16 accounts for the majority—90% to 95%—of HPV-positive tumors, whereas other high-risk types (-31, -33, and -35) account for the minority.[14,15]

The importance of early detection

Dental professionals are on the front lines of oral cancer detection and diagnosis. Since the oral cavity is one area of their expertise, patients should turn to these healthcare providers to advise them on concerns of the "nonhealing" sore in the mouth, or the firm lump, or areas of red or white change in their cheeks or on the gums. These are clinical signs of a cancer or a cancer precursor.

Unfortunately, squamous cancers of the oral cavity can be variably slow-growing or highly aggressive; while at the same time, these cancers are insidious and typically present at an advanced stage. This fact limits treatment options. This is why early detection is imperative, and today can be achieved even before a lesion is noted on

careful visual examination. Testing for HPV is central to an early detection strategy, and the use of PCR is the most sensitive way to find HPV.

The dental professional's role in overall wellness

Although oral HPV infection occurs frequently, it uncommonly leads to cancer. However, the effect of offering HPV testing from an oral rinse sample makes simple the prospect of identifying patients at risk for this serious disease. A positive HPV test is further analyzed to look for the specific HPV type.

The finding of an HPV high-risk infection signifies a patient who should be watched closely for the emergence of a lesion, and these patients should be counseled about other factors that add to their risk, including the use of tobacco and the practice of oral sex. Since the majority of cancerous and pre-cancerous oral HPV-related lesions are associated with the genital HPV types (-16 and -18), a test that offers HPV typing is a key step in determining the patient's risk profile for oral cancer.[14,15]

While there is no cure for HPV, close surveillance can clearly prevent the development of a more serious HPV-associated cancer. HPV infection most often occurs with no outward signs, and when there are "warts" or "sores" in the oral cavity, these lesions may go through periods of dormancy and reactivation. It is during these periods of activity that the process of "transformation" may persist.

Keeping this in mind adds to the spectrum of services that dental professionals are best at offering. In a larger sense, taking the patient's overall health and wellness into consideration now includes a careful oral cancer exam that should be conducted at every dental appointment, on a 6-month recall basis, or more frequently, to be determined by the clinician.

Ways to detect oral HPV

The sporadic nature of the virus is one of the reasons why the HPV-positive patient should remain closely monitored by the dental professional on an ongoing and regularly scheduled basis. Outward signs of oral HPV may manifest themselves as pre-cancerous, cancerous, or benign lesions of the oral epithelium.

Oral cancer in its earliest stages has always been difficult to discern from healthy normal tissue. By the time the lesion is visually or symptomatically apparent, it is often “too late” and requires surgical removal. There are several devices available to assist in detecting possible cancerous lesions in the mouth.

Tissue fluorescence devices shine light of a specific wavelength onto the oral mucosa. The light interacts with dysplastic tissue differently than with normal tissue, and therefore fluoresces differently than normal tissue. Depending on the individual risk factors of the patient, the suspect lesion can then be monitored over time for changes or symptoms, or a biopsy can be taken and tested for cancer.

Brush biopsy devices employ tiny wire brushes that scrape off the top layers of skin of suspect lesions, the cells of which are analyzed in a laboratory and described on a pathology report.

It must be noted that these two methods are used to screen for oral cancer, which may or may not be attributed to the oral HPV virus. They do not directly screen for HPV. The most convenient non-invasive way to definitively detect oral HPV is through a salivary diagnostic test.

Salivary diagnostics

Although the most commonly used laboratory diagnostic procedures involve the analysis of the cellular and chemical constituents of blood, saliva is making strong inroads into the field of diagnostic medicine, as it has proven to be a useful medium from which to measure a wide range of hormones, pharmaceuticals, and antibodies.

Saliva has also proven to be a convenient source of human, bacterial, and viral DNA. Thus, it is an ideal source of diagnostic information, and serves as the basis for salivary diagnostic tests.

One such salivary diagnostic test is the OraRisk[sm] HPV test by OralDNA[®] Labs. The OraRisk[sm] HPV test identifies the presence of HPV DNA in a patient’s saliva sample using a laboratory process called polymerase chain reaction (PCR).

In molecular biology, PCR is a technique for amplifying a particular segment of DNA. In order to perform PCR, a laboratory must know a portion of the sequence of the DNA molecule they wish to replicate.

In the case of the OraRisk[sm] HPV test, the laboratory can positively identify oral HPV through the analysis of a few drops of saliva, and comparing the DNA contained in that sample to the DNA of specific types of oral HPV. If there is a match, then the person is positive for that particular type of HPV.

Salivary diagnostics has great advantages and benefits to both the health care practitioner who administers the test and the patient who is being tested. Completely non-invasive, the OraRisk[sm] HPV test is easy and comfortable for the patient and clinician.

The patient simply swishes (vigorously) and gargles a sterile saline solution in the mouth for approximately 30 seconds, then expectorates into a funnel-top collection tube. The funnel is removed, the collection tube is sealed with a cap, and that concludes the in-office part of the test.

The sample is then labeled, placed in the provided specimen transport bag, and shipped via FedEx® standard overnight (at no extra cost) to OralDNA® Labs for PCR analysis. An e-mail notification is sent to the clinician when the comprehensive, HIPAA-compliant result report is available.

Patient education and communication

The test results are a valuable asset to share with the patient, as they demonstrate that these are definitive and objective results from a state-of-the-art diagnostic laboratory. The clinical laboratory report should be read, shown to, and discussed with the patient, since the results serve to help make the condition “real” (i.e., “seeing is believing”) to the patient.

The report further serves to define risk for oral HPV-related diseases and/or disease progression. It thereby serves as a persuasive means to instill the need for regularly

scheduled and judicious monitoring of the oropharyngeal complex for signs and symptoms of disease.

Summary

Human papillomavirus is a ubiquitous infectious disease, and substantial molecular evidence suggests a role for HPV (particularly HPV-16) in the pathogenesis of oropharyngeal squamous cell carcinoma.

Dental professionals are on the front lines of screening and detecting oral HPV. Dentistry that is centered on the concept of overall wellness is one where dentists use information that is only available through saliva testing in conjunction with the more traditional clinical exam to help clinicians identify the underlying causes of disease unique to each individual. Now, all dental clinicians can definitively determine if true causative agents (such as oral HPV) exist in the patient, as well as determine appropriate referral and monitoring conditions.

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