



Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

EDITORIAL

Can saliva-based HPV tests establish cancer risk and guide patient management?

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignancy in the world today.¹ Despite numerous advances in treatment, the 5-year survival rate has remained modest. This poor outcome is due to several factors, including delayed diagnosis. Therefore, improved early detection and effective prevention strategies are critical components for management of this malignancy. The etiology of classical HNSCC has been attributed to chronic exposure to tobacco and alcohol.² In addition, there is now sufficient evidence to support the contention that high-risk forms of the human papillomavirus (HPV) are a major causative factor for HNSCC of the tonsil, base of tongue, and oropharynx.³⁻⁸ The increasing importance of HPV in oropharyngeal HNSCC has raised considerable concern and uncertainty among healthcare professionals and patients. For example, I am often asked to describe the clinical features of HPV-associated premalignant lesions. Unfortunately, to my knowledge, the clinical spectrum of HPV-associated premalignant disease has not been adequately described. Furthermore, because this subset of HNSCC often develops in hard-to-examine locations, such as tonsillar crypts, it can be exceedingly difficult to even identify the carcinomas. In the absence of such information, how can clinicians identify patients that are at increased risk for harboring an HPV-associated premalignant lesions or HNSCC?

Recently, a large commercial diagnostic lab began offering a saliva-based test for the identification of oral HPV infections. As a result of this new offering, I have been bombarded with queries from dentists who have two recurring questions: (1) Will my patient develop HNSCC if they have a positive test? (2) What should I do for my patient if they have a positive test? The company's website states that their test provides the dentist with information that will "establish risk for HPV-related cancer and determine appropriate referral and monitoring conditions." Unfortunately, given what we know, or more appropriately what we don't know, it is unclear how this test

will provide answers to the real-world patient management questions that confront dentists.

The Centers for Disease Control and Prevention (CDC) estimates that 20 million Americans are currently infected with HPV and that 6 million new individuals are infected each year.⁹ In addition, they estimate that at least 50% of sexually active adults will be infected with HPV in their lifetime.⁹ Further, the CDC estimates that 33,000 men and women will develop an HPV-associated malignancy this year, and that 12,000 of these cancers will be HNSCC.⁹ Why is there a considerable difference between rates of HPV infection and the incidence of HPV-associated cancers? In general, the HPV DNA must become integrated into the host genome (rather than remaining episomal) to be oncogenic. Fortunately, this integration occurs at a fairly low frequency. Therefore, the mere presence of HPV in a saliva test does not necessarily establish a patient as being at higher risk place for developing cancer. The company has also suggested that repeated oral HPV testing is an effective monitoring tool because serial tests will identify patients with persistent infections, which are more likely to undergo malignant transformation. While persistence of HPV infection may increase cancer risk, what is the evidence that serial HPV tests will specifically identify only those patients with persistent oral HPV infections? The natural history of cervical HPV infections is well documented. Surprisingly, there is very little known about the natural history of oral infections. However, the available data suggests that the natural history of oral and cervical HPV infections may be very different.¹⁰ For example, we do not know the clearance rates of oral infections versus cervical infections. Given the robust lymphoid tissue present in Waldeyer's ring, one could hypothesize that oral HPV infections may be cleared at a faster rate. Given these and other uncertainties, the clinical relevance and management implications of a positive repeat monitoring test are unclear. On the one

hand, a positive test may indicate that an individual has a persistent HPV infection, thus placing them at higher risk for developing HNSCC. Alternatively, a positive repeat test may simply reflect a scenario of multiple independent infections in which each viral infection was cleared prior to the subsequent re-infection. Therefore, if we do not fully understand the natural history of oral HPV infections, how will the oral HPV test aid clinicians in establishing appropriate management protocols?

The era of molecular diagnostics is upon us, with new tests introduced daily. Some of these tests may aid clinicians in their quest to improve the diagnosis, prevention, and treatment of many different diseases. However, at this time, the current saliva-based HPV test would appear to be a “test looking for a disease,” with limited clinical utility. I would respectfully urge clinicians to consider the fact that just because we *can* perform a test does not mean that we *should*. To be of true clinical benefit, a diagnostic test should have clear scientific evidence that it will aid in the treatment decision making process.

In support of this concept, I would encourage readers to review the article by Jaeschke et al.¹¹ This seminal article provides an appropriate discussion and clinical decision making framework for clinicians when considering whether or not to perform a particular test.

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