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More testing, more questions:

Screening tests for oral human papillomavirus infection

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In early 2014, a 48-year-old man visited his dentist for a routine visit. After the dental examination, his dentist offered him a new “3-in-1 swish and gargle” test to see if he might have, or be at risk of developing, oropharyngeal cancer. The only information the dentist provided was that the human papillomavirus (HPV) subtype polymerase chain reaction test would help evaluate for the presence of HPV infection, an emerging cause of throat cancer. The patient agreed to the test, and the result was positive for HPV-16. Cytologic examination of his specimen demonstrated no pathological changes. Fluorescence in situ hybridization results showed normal copy numbers of chromosomes and did not detect amplification of the genes *TERC*, *TERT*, or *CCND1*. The dentist charged the patient approximately $100 for the test; when the patient’s insurance denied the claim, the test manufacturer waived the charges.

Because of the positive HPV test result, the dentist referred the patient to an otolaryngologist, who performed nasopharyngolaryngoscopy (NPL); examination findings were unremarkable. The cost of this visit, including the NPL, was approximately $2,000. The patient’s otolaryngologist recommended quarterly follow-up visits with NPL. The patient later discovered that his health insurer did not agree with the indication for his visit to the otolaryngologist, so he paid much of the cost of the visit out of pocket.

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For screening to be effective, several criteria need to be met, including the following: a disease that is an important health problem; a disease that has a long precancerous phase (oropharyngeal cancer has no precancerous phase) for which the natural history of the condition is well known; a screening test that is accurate, affordable, and acceptable; and a disease for which treatment is available to treat the precancerous phase before it progresses to cancer.[1] For cervical cancer, the long-term experience of the Papanicolaou test fulfills many of the criteria of screening.[1] Ever since investigators found HPV infection to be a necessary condition for developing cervical cancer, testing for the oncogenic HPV types has received much attention. Results from several large-scale randomized trials in which the investigators used high-grade cervical cancer as an endpoint support initiation of HPV-based screening for cervical cancer as a more effective form of screening than is cytologic examination. Since 2012, the US Preventive Services Task Force (USPSTF) recommended the HPV test to be used with the Papanicolaou test for screening.[2] In 2014, the US Food and Drug Administration (FDA) approved an HPV test for primary cervical cancer screening,[3] and the USPSTF is reviewing the evidence for this indication. For oropharyngeal cancer and HPV-based screening, we are not there yet.

Clinicians diagnose approximately 11,000 HPV-attributable oropharyngeal cancers each year, and most of these are caused by HPV-16.[4] Testing samples from tissue registries, Chaturvedi and colleagues[2] demonstrated that HPV prevalence in oropharyngeal cancers in the United States increased from 16% in the 1980s to 72% during the 2000s. From 1988 to 2004, population-level incidence of HPV-positive oropharyngeal cancers more than doubled, and HPV-negative cancers decreased by 50%.[2]

The natural history of HPV and oropharyngeal cancers has not been well characterized; notably, investigators have determined no detectable precancerous phase.[3] Among US men and women aged 14 to 69 years, the prevalences of any oral HPV and of HPV-16 infection were 6.9% and 1.0%, respectively.[5] Oral HPVs, including type 16 and other oncogenic types, likely clear within 18 months after an infection.[3] In contrast to our understanding regarding HPV and cervical cancer, we have much less information about the natural history of HPV and oropharyngeal cancer.[3,6]

With the increased awareness and publicity that HPV infection can cause oropharyngeal cancer, manufacturers[7] have developed oral HPV tests and marketed them to health care providers, including dentists, dental hygienists, and primary care physicians. The test kits recommend testing annually, although there are no data to support that testing once, or more often, will decrease the risk of developing or dying from oropharyngeal cancer. More importantly, the FDA has not approved these tests, nor have the USPSTF or the American Dental Association recommended them.[8,9] These oral HPV tests are considered laboratory-developed tests (LDTs). LDTs historically included low-risk simple diagnostics run in a single institution, but LDTs have become more complex; they may use components that are not FDA regulated, and institutions and private companies are using them increasingly.[10]

In our vignette, the positive HPV test result from the dental visit created substantial anxiety and led to many questions. Was it safe for the patient to kiss other people (could he pass on the virus and cause cancer in someone else)? How likely was it he would develop cancer?

Would the results of the test and subsequent NPL reduce his likelihood of developing cancer and improve his chances of survival should he develop cancer? Since the original test, he has undergone 4 additional quarterly NPLs and is in discussion with his otolaryngologist about the frequency of the examinations.

Although HPV may be transmitted via oral sex or deep kissing, there are no data to support oral HPV transmission through casual social contact. Little is known about the risk of developing oropharyngeal cancer associated with an oral HPV infection, which has a high likelihood of clearing, and whether an invasive procedure such as NPL reduces the likelihood of developing cancer. Rigorous prospective studies characterizing the likelihood of and preventable risk factors for developing oropharyngeal cancer are lacking, and we are unaware of any data supporting the use of tests that are not FDA approved to reduce morbidity or mortality from oropharyngeal cancer.

There is no recommended clinical indication for oral HPV screening to evaluate the risk of developing oropharyngeal cancer, and there is no FDA-approved test. Oral HPV infection prevalence may be common, but its precise role in the pathogenesis of oropharyngeal cancer has not been defined. The use of unapproved oral HPV tests could result in harm without any proven benefit. Detection of HPV (not cancer) through oral screening may result in invasive procedures of uncertain value, the potential for provoking patient anxiety, and extra costs, as our vignette demonstrated. Oral HPV tests add to the growing number of available oral cancer tests that are marketed to dentists or primary care physicians for routine screening of patients without symptoms but that have not been shown to improve outcomes.[9] Understanding of the risk and potential consequences of overdiagnosis is especially important for health care providers in an environment in which patients often rely on social media or the Internet as their source of information.[11] Primary prevention through widespread HPV vaccination, which is recommended for use in both boys and girls aged 11 or 12 years, is likely the best strategy for reducing HPV-attributable oropharyngeal cancers.[12]

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