

adenocarcinoma in situ related to vaccine HPV types was reported in both trials. However, it would be important to know the overall rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ regardless of HPV types. Without these data, it is difficult to infer both the effectiveness of vaccination and the role of nonvaccine HPV types in overall rates of preinvasive lesions.

What do these results mean for cervical-cancer screening? Screening should continue in all vaccinated women, given the cumulative lifetime risk of exposure to other oncogenic HPV types and the unknown duration of anti-HPV immunity. The effect of vaccination on cervical cytologic findings was not reported in either trial, but if vaccination reduces the rates of abnormal findings, this benefit would be important. Of note, a trial of a monovalent HPV-16 vaccine reported no effect on cytologic abnormalities.¹²

Policymakers, clinicians, and parents have a keen sense of urgency about HPV vaccination. On one hand, the vaccine has high efficacy against certain HPV types that cause life-threatening disease, and it appears to be safe; delaying vaccination may mean that many women will miss an opportunity for long-lasting protection. On the other hand, a cautious approach may be warranted in light of important unanswered questions about overall vaccine effectiveness, duration of protection, and adverse effects that may emerge over time. HPV vaccination has the potential for profound public health benefit if the most optimistic scenario of effectiveness is realized.

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Human Papillomaviruses in Head and Neck Carcinomas

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Each year, almost 650,000 patients worldwide receive the diagnosis of head and neck cancer and some 350,000 die from this disease.¹ Nearly 90% of these cancers are squamous-cell carcinomas. The two main causative factors in approximately 80% of oral, oropharyngeal, and laryngeal carcinomas are smoking and alcohol use. Consumption of vegetables and fruit may modulate the carcinogenic effects of tobacco and alcohol,

whereas low body-mass index increases the risk of oral cancer.² The idea that human papillomavirus (HPV) plays a role in these cancers has been under investigation for at least 20 years.

It is widely accepted that HPV causes cervical cancer.³ HPV has also been associated with several other types of squamous-cell carcinoma and their precursors at different sites — skin, vulva, vagina, penis, esophagus, conjunctiva, paranasal

sinuses, and bronchus — but the role of HPV in the pathogenesis of the lesions is less clear than it is in cervical cancer.⁴ The similarity of the morphologic features of genital and oral HPV-associated lesions was one of the early findings that raised the possibility that HPV might be involved in oral and laryngeal squamous-cell carcinomas.^{5,6} Until recently, however, the role of HPV in the pathogenesis of head and neck squamous-cell carcinoma has been uncertain, mainly because detection of HPV DNA has been highly variable, with rates ranging from 0 to 100%.⁴

New data from case-control studies suggest that HPV is an independent risk factor for oral and oropharyngeal squamous-cell carcinomas.⁷⁻⁹ Moreover, a systematic review showed an overall prevalence of HPV infection of 25.9% in specimens obtained from 5046 patients with head and neck squamous-cell carcinoma that had been analyzed in 60 separate studies.¹⁰ This review found that the prevalence of HPV infection was significantly higher among patients with oropharyngeal squamous-cell carcinoma (35.6%) than among those with oral (23.5%) or laryngeal (24.0%) squamous-cell carcinoma. A review of more than 5000 cases of head and neck squamous-cell cancers showed that, as in cases of anogenital squamous-cell carcinoma, HPV type 16 (HPV-16) was the most prevalent genotype, accounting for 86.7% of cases of oropharyngeal squamous-cell carcinoma, 68.2% of oral squamous-cell carcinoma, and 69.2% of laryngeal squamous-cell carcinoma.¹⁰ Key unresolved questions concern where latent HPV resides in the head and neck region and whether HPV is transmitted through sexual contact into these regions.

In this issue of the *Journal*, D'Souza and colleagues report further evidence of the association between HPV and oropharyngeal cancer.¹¹ Their study involved 100 patients with newly diagnosed oropharyngeal cancer and 200 control subjects who did not have cancer. Sampling for HPV testing was performed with the use of a saline oral rinse and 5 to 10 strokes of a cytology brush on the posterior oropharyngeal wall. Serum antibodies against the HPV-16 proteins L1, E6, and E7 were also studied. Both a prevalent oral infection with HPV-16 and an oral infection with any of 37 other HPV types were significantly associated with oropharyngeal cancer. Moreover, on pathological examination of paraffin-embedded specimens

with the use of in situ hybridization, HPV-16 was found in 72% of 100 oropharyngeal cancers sampled.¹¹

One of the shortcomings of the study is the use of rinsing of the oral cavity as the sampling method. Where HPV resides in the oropharynx is not known — whether in the oral mucosa, in the tonsils, or in the anterior or posterior part of the tongue or both. There is evidence that tonsillar carcinomas have a stronger association with HPV than does any other HPV-associated extragenital tumor. It is unclear, however, whether HPV-associated cancer of the tonsils originates from crypt or surface epithelium, although data suggest that HPV inhabits the normal crypt epithelia.^{12,13} The possibility that tonsillar tissue in Waldayer's ring, which surrounds the oropharynx and is important as an antigen-presenting site, is the reservoir of HPV cannot be excluded.

Data presented by D'Souza and colleagues¹¹ suggest that sexual behavior is associated with oropharyngeal cancer, as has been suggested previously.^{7,9} In their study, a high lifetime number of vaginal- or oral-sex partners was associated with the presence of oropharyngeal cancer, and the degree of association increased with an increasing number of vaginal- or oral-sex partners. Transmission of the virus by direct oral contact or by other means could not be excluded, however. In a study that my colleagues and I performed, involving married couples with healthy oral mucosa (sampling at baseline and at months 2, 6, 12, 24, and 36), the results suggested that the oral route is an important means of HPV transmission between partners: one spouse had a 10-fold risk of acquiring persistent oral HPV infection if the other spouse had persistent oral HPV infection.¹⁴ Oral sex was not associated with oral or genital HPV infection in these studies, and oral HPV infection in one spouse was unrelated to genital HPV infection in the other spouse.¹⁴ In our study and in the study by D'Souza and colleagues, however, the patients were different: the couples we studied were younger and had no evidence of clinical lesions in the oropharynx, whereas those in the study by D'Souza and colleagues were older patients who had oropharyngeal cancer.¹¹

Mork and colleagues found a 14-fold increase in the risk of oropharyngeal cancer among patients seropositive for HPV-16 L1 protein and sug-

gested that exposure to HPV can precede the appearance of oropharyngeal cancer by 10 or more years.¹⁵ Their observation is supported by the results of D'Souza and colleagues,¹¹ who found a significant association between head and neck squamous-cell carcinoma (odds ratio, 32; 95% confidence interval, 15 to 71) and seropositivity for the HPV-16 L1 capsid protein, which is a measure of lifetime exposure to HPV-16. Nevertheless, whether persistent HPV infection in the head and neck region is a risk factor for oropharyngeal cancer has not been rigorously demonstrated.

It is possible that HPV-associated head and neck squamous-cell carcinoma arises by a different mechanism from that involved in the pathogenesis of HPV-associated cervical carcinoma. D'Souza and colleagues present data suggesting that smoking and alcohol use, which are important risk factors for oropharyngeal cancer, may not act as cofactors in HPV-mediated carcinogenesis in the oropharynx. Whether smoking is an independent or synergistic component of the mechanism of HPV-associated squamous-cell carcinoma in the oral and oropharyngeal region requires further study.

Now that the association between some cases of oropharyngeal cancer and HPV infection appears to be firmly established, the question that arises is whether there is any need for screening for persistent oral or oropharyngeal HPV infection in high-risk groups (smokers and drinkers). Moreover, we need to examine how to treat HPV-positive intraepithelial neoplastic lesions, which are cancer precursor lesions, in the head and neck region. Should HPV-associated oral and oropharyngeal carcinomas be treated in the same way that their HPV-negative counterparts associated with heavy smoking and drinking are treated? And finally, it is worth considering the possibility that some oral, oropharyngeal, and laryngeal cancers might be prevented by HPV vaccination.

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CORRECTION

HPV in Head and Neck Carcinomas

HPV in Head and Neck Carcinomas . The last sentence of the fourth paragraph should have read “Moreover, on pathological examination of paraffin-embedded specimens with the use of in situ hybridization, HPV-16 was found in 72% of 100 oropharyngeal cancers sampled,” rather than “HPV-16 was found in 72% of 60 oropharyngeal cancers sampled.” The text has been corrected on the *Journal's* Web site at www.nejm.org.