

cited unanswered questions argue for a cautious approach to vaccination policy until trials have been completed and fully reported.

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**DRS. AGOSTI AND GOLDIE REPLY:** As we noted, the need for long-term follow-up data are important, which Suba and Raab emphasize. Furthermore, it is imperative that momentum behind efforts in the past decade to develop feasible options for cervical-cancer screening in low-resource settings continues to build. The Bill and Melinda Gates Foundation provided \$55.6 million to the Alliance for Cervical Cancer Prevention to promote screening and \$13 million toward the development of low-cost HPV DNA tests and other tests. We believe it is inequitable to exclude women in developing

countries from the potential benefits of vaccination, new technology, and screening approaches that appear to be promising.<sup>1</sup>

We emphasized that an integrated approach that includes screening and vaccination is likely to prevent the greatest number of deaths from cervical cancer. However, countries will make their own decisions about the best strategic approach to cervical-cancer prevention, accounting for local epidemiologic factors and disease burden,<sup>2</sup> competing priorities, and the cost-effectiveness, affordability, and feasibility of vaccination programs targeting adolescents and the screening of adult women. We urge that attention be given to real-world solutions for preventing death from cervical cancer in women living in poverty.

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## Human Papillomavirus and Oropharyngeal Cancer

**TO THE EDITOR:** The study by D'Souza et al. (May 10 issue)<sup>1</sup> on oropharyngeal squamous-cell carcinomas associated with human papillomavirus (HPV) provides important epidemiologic insights into a cancer that is becoming increasingly common in the United States.<sup>2</sup> However, the molecular mechanisms of carcinogenesis in HPV-associated oropharyngeal squamous-cell carcinomas remain unclear.

The integration of HPV type 16 (HPV-16) into the host genome is an important mechanism in cervical carcinogenesis,<sup>3</sup> but there is no direct evidence that this process occurs in oropharyngeal squamous-cell carcinomas. The authors state that Southern blot, real-time polymerase-chain-reaction (PCR), and fluorescence in situ hybridization analyses<sup>4</sup> have established integration sites but that these methods provide only indirect evidence. Direct evidence would require observation of the viral DNA sequence either flanked or attached to

one end of human DNA (junction sequences). Melin et al.<sup>5</sup> did not observe this finding in HPV-16-positive tonsillar carcinomas. We previously used restriction-site PCR in more than 100 HPV-16 and HPV-18 cervical cancers to identify many of these junction sequences.<sup>6</sup> However, when we used this same technique in 40 oropharyngeal squamous-cell carcinomas that were positive for HPV-16, we did not detect junction sequences (unpublished data). This finding, which suggests a mechanism of carcinogenesis that is distinct from that in cervical cancer, warrants further investigation.

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**TO THE EDITOR:** Little is known about the natural history of oral HPV infection.<sup>1</sup> In a cohort of 360 healthy students (mean age, 18.7 years), 69% of whom were female,<sup>2</sup> we tested oral cytobrush samples for HPV DNA by means of multiplex PCR. Of these students, 20 (5.6%) were positive for HPV. Three years later, 8 of 183 students who were retested (4.4%) were positive, and 1 had persistent infection. Oral HPV infection was unusual, and the persistence of infection was rare.

Of the 183 students who were retested, 28 were sexually inactive, and all these students were HPV-negative. Of the sexually active students, 100% of those who were HPV-positive had had both penetrative and oral-genital sex in the previous 3 years; of those sexually active students who were HPV-negative, 88% had had only penetrative sex and 86% had had only oral-genital sex. These findings support the hypothesis that oral HPV is transmitted through sexual contact and that oral-genital contact is the likely mechanism.

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**TO THE EDITOR:** D'Souza et al. report a very high prevalence of HPV involving 72% of oropharyngeal

squamous-cell carcinomas. This finding is unlikely to be related to the detection method,<sup>1</sup> since in situ hybridization was used, a reliable technique with a test outcome that is often similar to that of viral oncogene transcript analysis.<sup>2</sup> We previously reported that in a Dutch cohort, 6 of 37 oropharyngeal carcinomas (16%) contained transcriptionally active HPV.<sup>3</sup> This prevalence differs significantly ( $P < 0.001$ ) from that reported by D'Souza et al. A review article also reported a prevalence of HPV in oropharyngeal carcinomas that was much lower than 72%.<sup>4</sup> We wonder whether the associations reported by DeSouza et al. can be extrapolated to other populations.

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**THE AUTHOR REPLIES:** The results of in situ hybridization correlate with viral oncogene expression in our laboratory (unpublished data). Therefore, it is unlikely that the high prevalence of HPV in oropharyngeal cancers that we found can be explained by false positive misclassification. However, our study was performed in a hospital and was not population-based. We cannot exclude the possibility that subjects who did not have traditional risk factors were more likely to participate in the study. The HPV prevalence of 72% was similar to the 63% prevalence in cancers of the oropharynx that were collected throughout the United States in a clinical trial conducted by the Eastern Cooperative Oncology Group.<sup>1</sup>

We acknowledge that the fraction of oropharyngeal cancers caused by HPV in the United States may differ from that in other geographic regions. Cross-sectional prevalence in a population would largely be driven by incidence rates for HPV-positive and HPV-negative squamous-cell cancers of

the head and neck. One might reasonably expect that the relative incidence of these two cancers would be driven by local societal mores — for example, the prevalence of alcohol and tobacco use, sexual behaviors, and other cofactors (including diet and oral hygiene) in a population. Incidence rates may also be quite dynamic, because behaviors may change considerably over time. For instance, a significant increase in the prevalence of HPV-associated tonsillar cancer from about 23% in the 1970s to 68% in the period from 2000 through 2002 was reported in Sweden.<sup>2</sup> Therefore, geographic variation in the prevalence of HPV in oropharyngeal cancers may be strongly influenced by the region and calendar period sampled.

Although viral integration occurs in the majority of cervical cancers, it is neither necessary nor specific to invasive carcinoma.<sup>3</sup> Increased expression and stability of viral oncogene transcripts occur as a consequence of viral integration. Analogous deregulation of viral oncogene expression may occur in episomal virus through methylation or mutation of the viral upstream regulatory region.<sup>3</sup> Although we agree with Ukpo et al. that patterns of in situ hybridization and RT-PCR are indirect measures of integration, analysis of restriction-fragment-length polymorphisms by Southern blot hybridization is a direct measure. Viral integration into the genome of head-and-neck squa-

mous-cell carcinoma has been demonstrated by this method<sup>4</sup> and through the cloning of viral-cell genome fusion sites,<sup>5</sup> albeit in few cases.

Although oral HPV infection is now recognized as a causative factor for a subgroup of head-and-neck squamous-cell carcinomas, little is known about the natural history of oral HPV infection. Natural-history studies are needed to gain a better understanding of the risk factors for acquisition of oral HPV infection and the factors that affect the duration of infection.

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## Bariatric Surgery for Morbid Obesity

**TO THE EDITOR:** In his review of the surgical treatment of morbid obesity, DeMaria (May 24 issue)<sup>1</sup> lists key components of the preoperative medical evaluation; these components include screening for diabetes, hypertension, coronary artery disease, sleep apnea, pulmonary hypertension, and musculoskeletal disease. However, the role of esophagogastroduodenoscopy in this evaluation should also be mentioned. Although its routine use remains controversial,<sup>2,3</sup> there is evidence for recommending esophagogastroduodenoscopy with biopsy and assessment of samples for *Helicobacter pylori* in all patients planning to undergo bariatric surgery, even if they are asymptomatic.<sup>4-6</sup> Several arguments provide support for this statement. First, there is a lack of correlation between symptoms and endoscopic findings.<sup>4,5</sup> Second, in patients who undergo Roux-en-Y gastric bypass, the bypassed gastric and duodenal mucosa may no lon-

ger be within the reach of the endoscope postoperatively, making it more difficult to treat lesions that could have been diagnosed preoperatively.<sup>5</sup> Finally, routine esophagogastroduodenoscopy has been shown to have a high diagnostic yield and a relatively low cost.<sup>5</sup>

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