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Human Papillomavirus and Oropharyngeal Cancer

TO THE EDITOR: The study by D’Souza et al. (May 10 issue) 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. 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, 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 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). Mellin et al. 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. 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in 40 oropharyngeal squamous-cell carcinomas that were positive for HPV-16, we did not detect junction sequences (unpublished data).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. In a cohort of 360 healthy students (mean age, 18.7 years), 69% of whom were female, 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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**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.

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

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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.¹ 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 for nor specific to invasive carcinoma.² 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.³ 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 squamous-cell carcinoma has been demonstrated by this method⁴ and through the cloning of viral-cell genome fusion sites,⁵ 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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