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Sex, human papilloma virus infection, and head and neck cancer

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Over 100 human papillomavirus (HPV) types have been identified, with many linked to cancer. The burden of head and neck cancers is relatively small; it is estimated that 34,360 new cases of head and neck cancer will have been diagnosed in 2007 in the United States, and 7,550 deaths associated with head and neck cancers will occur.[1] Head and neck cancers account for less than 3% of new cancer diagnoses and 1.3% of cancer-related mortality.[1] Although molecular evidence supports the causal role of HPV in squamous-cell carcinomas of the head and neck, epidemiologic data showing an association between HPV and those cancers are lacking. A recent case-control study by D'Souza, et al,[2] adds an epidemiologic perspective to the growing body of scientific literature supporting the role of HPV infection in head and neck cancers.

In D'Souza, et al's, study, characteristics of patients with head-and-neck squamous-cell carcinoma diagnosed in the Johns Hopkins Hospital otolaryngology clinic between 2000 and 2005 were compared with those without a history of cancer seen at the same clinic during the same period. Enrolled patients submitted oral saline rinse, oral mucosal brush, and serum specimens. Researchers used multiplex polymerase chain reaction (PCR) assays targeting the L1 region of HPV to determine the HPV type(s) in tumor specimens, when available. Additionally, they used an enzyme-linked immunosorbent assay (ELISA) to measure serum antibodies to HPV-16 (the HPV subtype most commonly associated with head and neck cancers) L1 protein, and E6 and E7 proteins. The authors use multivariable regression to adjust for age, sex, smoking, alcohol use, dentition, dental-hygiene practices, and family history of head and neck cancers. To elucidate possible pathways in the etiology of head and neck cancers, various statistical interactions among smoking, alcohol use, and HPV infection were explored.

Enrolled cases (n=100) and controls (n=200) were primarily male (86%), less than 65 years old (85%) and white (86%). **The authors found increasing numbers of vaginal and oral sex partners, having had a casual sex partner and never or rarely using condoms, were significantly associated with an increased likelihood of head and neck cancer.** When analysis of sexual behaviors was restricted to only head and neck cancers that harbored HPV-16, those associations were strengthened. Having had a same-gender sex partner or a sex partner with a history of an HPV-related cancer was not associated with head and neck cancer.

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Participants who smoked or drank alcohol were more likely to have head and neck cancer. This increased risk from tobacco and alcohol use existed when the analyses were restricted to those who had no evidence of HPV-16 infection. The associations between alcohol use and smoking, and head and neck cancer, however, were no longer found among participants who had HPV-16 infection, suggesting that tobacco and alcohol use may be important factors in head-and-neck-cancer development in the absence of HPV-16 infection but may be less important among those who have been infected with HPV-16.

Head and neck cancers were also strongly associated with HPV-16 L1 seropositivity, HPV-16 E6 or E7 seropositivity, oral HPV-16 infection, and any oral HPV infection. **HPV-16 DNA was recovered from 72% of the paraffin-embedded head-and-neck-cancer specimens.**

This study is important for several reasons. It confirms the findings of other observational studies providing important epidemiologic evidence to complement the basic science data suggesting an association between HPV (and more specifically HPV-16) in head-and-neck carcinogenesis. Additionally, the findings of this study suggest that oral HPV infections may be sexually acquired. A strong and consistent dose response was seen with increasing numbers of oral sex partners and increased likelihood of head and neck cancer. Associations between oral sexual activity and cancer were only strengthened when the analysis was limited to HPV-16-positive head and neck cancers. **Given the relative rarity of head and neck cancer, and the high frequency of oral sex — from a public-health standpoint — curtailing the frequency of oral sex is not likely a practical strategy to reduce the risk of head and neck cancer.**

The authors reported an independent association between having a family history of head and neck cancer, and a new diagnosis of head and neck cancer. Family clustering of cancer has been reported by others, and similar findings have been noted with respect to cervical cancer. It remains unclear whether that finding reflects a genetic component to HPV-associated cancers and/or shared environmental exposures, or whether it is spurious. Furthermore, this case-control study found associations between poor oral hygiene and head and neck cancers. Given that many dental problems are a result of bacterial infections, the authors suggest that bacterial co-infection may play a role in the development of head and neck cancers, similar to the relationship between *Chlamydia trachomatis* and cervical cancers. Finally, D'Souza, et al, reported that while tobacco and alcohol use may be important risk factors for head and neck cancers, their data suggested no synergistic effect with HPV infection. In short, two pathways may be involved in the development of head and neck cancer — one driven by HPV infection and one by tobacco and/or alcohol use.

As with any study, its limitations must be considered. Since this was a case-control study, no claims can be made regarding causality. Moreover, the cases and controls were selected from the patient population of the Johns Hopkins University otolaryngology clinic, a tertiary-care specialty clinic that draws its patient population from many states and countries. As a result, the patients enrolled may not represent the "typical" head-and-neck-cancer patient who may have been seen at his local otolaryngology clinic, and the controls may also represent patients with atypical complaints and characteristics.

This study by D'Souza, et al, adds to the growing body of literature highlighting the importance of HPV infection in cancers other than cervical. These data also suggest the potentially limited effect of factors, such as alcohol and smoking, in head-and-neck-cancer development, in the absence of HPV infection. Although multitudinous authorities encourage condoms and other barriers for oral sex, data suggest that few use them. Therefore, developing behavioral interventions for head and neck cancer may not be feasible. Compared to other HPV types, HPV-16 is disproportionately associated with head and neck cancers, and is one of the four types of HPV included in the recently licensed Gardasil HPV vaccine. Yet, the potential effectiveness of Gardasil for prevention of oral HPV infection and subsequent cancer development will not be well characterized for many years. □

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