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Adults With Oral High-risk Human Papillomavirus (HPV) and/or Smoking History Have a Higher Risk for Clinically Diagnosed Oral Premalignant Lesions

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Subjects

Case and control patients were clinic-based at the Department of Craniomaxillofacial and Oral Surgery of the Medical University of Innsbruck, Austria. Between March and September 2013, 218 consecutive patients were categorized as either case patients (n = 118) by having a referral to the clinic for histopathologic determination of a clinically diagnosed leukoplakia or erythroplakia, or control patients (n = 100) by having a clinic visit for a reason other than a histopathologic determination of or the presence of clinically diagnosed leukoplakia or erythroplakia. The cases were 47% women, and the unmatched controls were 55% women. The age range was 19 to 50 years with a mean (± standard deviation) age of 29.7±6.9 years for cases and 28.2 ± 5.1 years for controls. Case patients were further categorized by biopsy results as having hyperkeratosis, mild dysplasia, moderate dysplasia, severe dysplasia, or carcinoma in situ. A study questionnaire was used to collect information on tobacco and alcohol consumption, sexual behavior, and family history of head and neck tumors.

Key Risk/Study Factor

The suspected etiologic factor was oral HPV infection. The oral specimen for HPV testing was made by brushing the left and right buccal mucosa, and also the lesion for case patients, using the Digene Cervical Sampler HC2 Hybrid Capture procedure. HPV testing was done using a nucleic acid hybridization assay with signal amplification that utilized microplate chemiluminescent detection (HC2-HPV-DNA-testing [Qiagen, NL]). Test results for HPV infection were categorized as ‘‘no infection,’’ ‘‘low-risk infection (HPV 6/11/42/43/44),’’ or ‘‘high-risk infection (HPV 16/18/31/33/35/39/45/51/56/58/59/68).’’

Main Outcome Measure

The primary outcome was being clinically diagnosed with potentially premalignant oral lesions (i.e., leukoplakia or erythroplakia).

Main Results

The risk for oral leukoplakia or erythroplakia was just over three times higher in patients with oral high-risk HPV (unadjusted odds ratio [OR] = 3.2; 95% confidence interval [CI] 1.6–6.2; $p < 0.001$) using logistic regression analysis with p-values for a two-tailed test. Also significant was a smoking history of either <10 pack years (unadjusted OR = 3.5; 95% CI 1.7–7.2; $p < 0.001$) or >10 pack years (unadjusted OR = 5.4; 95% CI 2.4– 12.3; $p < 0.001$).

After adjustment for other variables (not specified), the strength of association was slightly higher for patients with lesions and high-risk HPV infection (OR = 4.0; 95% CI 1.8–8.8; $p = 0.001$), and smoking history of either <10 pack years (OR = 4.4; 95% CI 2.0–9.5; $p < 0.001$) or >10 pack years (OR = 6.2; 95% CI 2.5–15.1; $p < 0.001$). If only dysplastic and carcinoma in situ lesions from histopathologic examination (hematoxylin and eosin stain) were considered (98/118), the OR was 4.3 ($p = 0.001$) for patients with lesions and high-risk HPV infection.

The presence of high-risk HPV varied over lesion grades with the highest proportion 63.3% (7/11) in the group with severe dysplasia, 50.0% (2/4) of those with carcinoma in situ, 35.7% (15/42) of those with moderate dysplasia, 29.3% (12/41) of those with mild dysplasia, and 20% (4/20) of those with hyperkeratosis. Detection of low-risk HPV and the presence of oral lesions was not statistically significant.

The brush specimens (3 separate brush collections for the cases – left and right buccal mucosa, and lesion – and 2 for controls) showed concordant results for 95% of the patients (n = 207). Eleven patients (5 cases and 6 controls) had a positive brush result in only one of the 3- or 2-brush specimens.

Conclusions

Results suggest that the risk of having an oral leukoplakia or erythroplakia is 3 to 4 times higher in patients with oral high-risk HPV infection. Additional study and analyses are needed to disentangle the effect of smoking from the effect of oral HPV infection.

COMMENTARY AND ANALYSIS

We agree with the conclusion of the authors that the study results demonstrated that oral HPV infections may play a role in the pathogenesis of premalignant oral lesions. Their findings are similar to those of a systematic review of studies from 1966–2010 to calculate pooled risk estimates for the association of HPV with oral squamous cell carcinoma and with oral premalignant lesions when compared with healthy oral mucosa as controls.[1]

There were a few items of information that would have made the interpretation of the results more straightforward, such as expanded details on the methods used in the analysis and

stating which variables were included in the adjusted results. Also, we would have liked to know the number of people excluded from the sample and the generalizability of the results to a specific population. The authors did discuss the limitations in quantifying the effects of smoking in the relatively young population.

This study calls attention to the importance of clinical examination for oral leukoplakia and erythroplakia and follow-up with biopsy for histopathologic determination of the oral lesion. In this study, the histologic diagnoses for the 118 case patients were 16.9% (n = 20) as hyperkeratosis, 34.7% (n = 41) as mild dysplasia, 35.6% (n = 42) as moderate dysplasia, 9.3% (n = 11) as severe dysplasia, and 3.4% (n = 4) as carcinoma in situ. Early detection and treatment for patients with oral squamous cell carcinoma greatly reduces the morbidity and mortality of this cancer.[2] Less is currently known about detection, specific malignant transformation rates, and treatment outcomes for potentially premalignant oral leukoplakia and erythroplakia.[3] As demonstrated by this study, general dentists should have established referral relationships with dental and medical specialists to pursue histopathologic diagnosis of oral lesions.

A second consideration proposed by the authors is HPV vaccination as an option for the prevention of oral cancer. As the health care specialists for the oral cavity, dental practitioners are expected to be the most educated resources for their patients. Dental practitioners are ideally positioned to discuss HPV vaccination and the potential prevention of high-risk HPV-associated oral and oropharyngeal cancer with the parents of their patients.[4–7] In 2008, Harald zur Hausen received the Nobel Prize for his 1983 discovery of HPV causing cervical cancer.[8] Vaccines are available today to prevent HPV-associated cervical cancer. This article is an example of the growing body of literature to use the knowledge from HPV-associated cervical cancer research to investigate the role of HPV in the etiology of oral cavity and oropharyngeal pre-malignancy and malignancy.[9–11]

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