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Summers: Association between Human Papillomavirus Infection and Oral Carci

# ASSOCIATION BETWEEN HUMAN PAPILLOMAVIRUS INFECTION AND ORAL CARCINOMAS

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## INTRODUCTION

There are over 100 different types of Human Papillomavirus, also known as HPV<sup>4</sup>. It is a group of DNA viruses that can infect various parts of the body by changing normal cells into abnormal cells. HPV types are divided into high-risk and low-risk types. HPV types that are considered high-risk types have the potential to cause cancer. The low-risk HPV types may cause visible cell abnormalities, like skin warts. It is approximated that 20 million Americans are currently infected with some strain of Human Papillomavirus and another 6.2 million people are newly infected each year<sup>5</sup>. Oral squamous cell carcinomas develop from the mucosa of the oral cavity and oropharynx, and affect approximately 30,000 Americans per year<sup>9</sup>. The two main causative agents are smoking (especially more than two packs a day) and alcohol consumption. Interestingly enough, the role of high-risk HPV in the pathogenesis of these squamous cell carcinomas has been under investigation for several years now, and has recently become one of the leading causes of oral cancer, particularly in men<sup>9</sup>. The purpose of this paper is to review multiple literary sources on the epidemiologic relationship between Human Papillomavirus infection and oral squamous cell carcinomas. The significance of this association is that high-risk HPV strains are now one of the leading causative agents of oral squamous cell carcinomas. This shows that smoking and alcohol are not the only causative agents of oral cancers, and also introduces oral cancer as the first cancer associated with HPV infection that is not located in the genital area, but may be transmitted by sexual contact.

## LITERATURE REVIEW

The case-control study done by Bladstrom et al investigated the presence of Human Papillomavirus DNA of both high and low risk mucosal/genital types in patients diagnosed with oral and oropharyngeal squamous cell carcinoma (OOSCC) compared to population-based, matched healthy controls. Each patient gave samples from three different locations: the site of the tumor, the tonsillar fossa, and a mouthwash sample. Forty-seven (36%) of the 131 patients tested positive for a high-risk type of HPV, while seven (5.3%) patients tested positive for a low-risk type of HPV. Of the healthy controls, only 3 out of 320 (0.94%) tested positive for a high-risk type of HPV, while 13 (4.1%) tested positive for a low-risk type of HPV. The most common type identified was HPV 16, which was found in 61 out of 75 (81%) of the high-risk HPV positive samples. HPV 16 was also identified in two samples from the control group. The prevalence of HPV infection did not differ significantly between sexes. This investigation showed that HPV DNA of specified high-risk types was found to be a risk factor for OOSCC of all tumor sites. HPV DNA of low-risk types did not constitute a risk factor for OOSCC. The results of the study show strong evidence of a link between infection with high-risk HPV

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involves the same types that have been proven to be the cause of most anogenital cancers, and with multiple cases of OOSCC. As with cervical cancer, co-factors are probably also involved in the carcinogenesis<sup>1</sup>.

Overall, this study appears to have been conducted well. The possibility of different collection techniques was diminished by the fact that one qualified person handled the collection of specimens from all of the patients and controls. Furthermore, all samples were evaluated by the same technician, which also helped to eliminate observation bias. The investigators in this study chose to maximize sensitivity of the testing, allowing for more accurate positive results when the patients and controls tested actually had HPV. This decision could have overestimated the number of actual HPV positive cases and controls, which would cause the results to be skewed.

Seth Schwartz et al performed a population-based study, with the aim to determine the relationship of HPV DNA status to patient survival. Information was gathered about the subjects' age, gender, date of diagnosis, vital status, stage of disease, tumor site, extent of disease, and treatments received. Data was also collected via interviews on the highest level of school attended, socioeconomic status, specific comorbid illnesses (hepatitis, diabetes, kidney disease), lifetime smoking history, and lifetime alcohol consumption. Potential confounding factors included surgery, stage of disease, alcohol consumption, history of smoking, and radiation<sup>7</sup>.

Of the total sample, 40 (15.7%) of the tumors analyzed were HPV type 16 positive, 22 (8.7%) of the tumors contained other types of HPV, and 192 (75.6%) of the tumors contained no HPV DNA. The study found that subjects with HPV type 16 had better survival rates, even though they experienced more advanced disease. This result was independent of any known or unknown confounding factors<sup>7</sup>. Although the study found that subjects who were positive for HPV type 16 were younger, less likely to smoke, and less likely to have a comorbid illness, the authors dismiss the idea that these findings alone could enhance survival. Although an association was determined between HPV type 16 positivity and increased survival, the link between the two is still unknown<sup>7</sup>.

Stephen Schwartz et al performed a population-based case-control study that studied the association between oral cancer risk and sexual history in relation to HPV infection. It evaluated 284 subjects between the ages of 18-65 years. All case and control subjects participated in structured interviews where information on demographics, histories of tobacco and alcohol use, history of sexually transmitted diseases, and histories of sexual activity and practices was obtained. Venous blood samples and exfoliated oral tissue samples were taken at the time of the interview. While analyzing the samples from the cases and controls, the authors took great care in trying to prevent any biases by blinding the samples themselves (no samples were distinguished by any demographic markers), as well as blinding the laboratory technicians who were performing the analyses.

Of the 64 tumors that tested positive for HPV DNA, 43 (67.2%) of them tested contained a high risk HPV type; 41 (95.3%) of those 43 tumors contained HPV DNA type 16 either alone or in combination with another HPV DNA type. The overall prevalence of HPV DNA type 16 was 16.5% (41 out of 248 tested) and was similar in males and females<sup>8</sup>. When age, smoking, and alcohol consumption were adjusted for, the

Summers: Association between Human Papillomavirus Infection and Oral Carcinoma risk of oral cancer increased among males with decreasing age at first regular intercourse and increased with increasing number of opposite sex partners. These patterns were not seen in women. Odds ratios were not increased in either sex who reported ever performing oral sex on an opposite sex partner. Although not statistically significant, odds ratios were slightly elevated when the number of oral sex partners was equal to or greater than five. For both sexes, the associations with sexual histories were strongest for samples containing HPV DNA type 16. For those case subjects who reported having 15 or more sexual partners, the odds ratio for case subjects whose tumors contained HPV DNA type 16 was 2.5 (95% CI). The odds ratios were considerably smaller for those case subjects whose tumors contained other HPV DNA types, but still reported having 15 or more sexual partners. Similarly, for a history of greater than or equal to five oral sex partners, the odds ratio for case subjects with HPV DNA type 16 in tumors was 2.1 (95% CI). The findings of the study did not provide strong evidence of a sexually transmitted route underlying oral HPV infections associated with oral cancer risk.

Herrero et al performed a multicenter case-control study that took place in nine different countries. Specially trained interviewers administered a questionnaire to all subjects regarding demographic information, education, history of alcohol or tobacco usage, and sexual history. All case and control subjects gave a blood sample and an exfoliated oral tissue sample. The results showed two clear dose-response relationships between the risk of oral cancer and the number of cigarettes smoked, as well as the risk of oral cancer and the number of years smoked. Also, the number of drinks per day and the duration of drinking were also found to have a dose-dependent increase on the risk of oral cancer. No associations could be found between sexual behavior indicators and the risk of developing oral cancer. In 89.3% of HPV DNA positive samples, HPV DNA type 16 was the only type present. The overall results indicated that HPV seemed to play a definite etiologic role in a large fraction of cancers of the oral cavity. A large majority of the HPV DNA positive cases in the study (95%) had HPV DNA type 16<sup>3</sup>.

One of the limitations of the study is the location and lack of advancement in some of the participating countries. Improper or inadequate storage of the specimens and shipping them long distances to laboratories had the potential of degrading the samples. This could have led to inadequate samples for analysis, which could have caused improper analysis or loss of the sample entirely. Also, because the controls were often chosen from the same hospitals as the cases, it is very possible that the controls share similar exposures with the cases.

## SUMMARY & CONCLUSIONS

Based on these studies, the evidence seems to suggest an increased association between high-risk HPV infection, specifically HPV type 16, and the risk of oral squamous cell carcinoma. When the risk factors for oral cancer were analyzed, the literature seemed to be mixed. Some study results found an increase in the risk of squamous cell carcinoma with a history of alcohol and/or tobacco consumption, while others did not. There is no doubt that both alcohol and tobacco are major risk factors for the development of oral cancer, but it seems that these risk factors may act independently of HPV exposure. This was evident in the Seth Schwartz et al study that

subjects whose tumor samples tested positive for HPV DNA type 16 were less likely to have a history of smoking. This is an interesting finding considering that oral cancer is such a rare occurrence and that a majority of the cases are linked to tobacco and alcohol use. To find that these major risk factors may not play a role in the development of certain strains of oral cancers highlights the idea that there must be other etiological causes that need to be researched further, and could suggest the idea of two different pathways for the development of oral carcinomas; one of them being the carcinogenic effects of tobacco and alcohol and the other being HPV exposure<sup>2</sup>.

The association between HPV DNA positive oral tumors and their link to sexual behavior is just starting to become apparent and more research needs to be done on the topic. Those studies that have been done have found an increased risk of HPV positive, specifically HPV type 16, tumor samples with increasing number of heterosexual vaginal sex partners and heterosexual oral sex partners. It is interesting in the Stephen Schwartz et al study that this association was only observed in males. This could be explained by the fact that HPV type 16 is the predominate strain associated with anogenital cancers, specifically cervical cancer, and with the increasing popularity of oral sex, especially among the nation's youth, it makes sense that an HPV infection in a woman's genitals can be spread to a man's oral cavity by means of sexual contact. Unfortunately, none of the results of the two studies could confirm a sexual transmission route. It is highly likely that the healthcare community will be hearing much more about this topic in the near future because this is really the first time that a disease has been identified with a potentially sexually transmitted route that is not located in the genital region. Also, with the prevalence of HPV infection among sexually active individuals, a possible sexual transmission route of HPV infection to the oral cavity could greatly increase the occurrence of oral cancer. The recent development and usage of a vaccine for certain strains of HPV that cause cervical cancer also brings up the question of whether or not it may be effective against oral cancers that also contain the same types of HPV.

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