2016 Head and Neck Cancer Symposium: Study Maps Distinct Molecular Signatures of HPV-Positive Throat Cancer by Smoking Status

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Key Points

- Overall mutation rates were higher for HPV-positive oropharyngeal squamous cell carcinoma patients in the > 10 pack year group than those in the < 10 pack year group.
- *HLA-A* mutations occurred more often in the heavy smoking group, and mutations associated with tobacco exposure and poor survival occurred almost exclusively within the heavy smoker group, including those in *TP53*, *CDKN2A*, *FAT1*, *CASP8*, *NOTCH1*, *FGFR3*, and *KRAS*.
- Patients who smoked and had a history of fewer than 10 pack years had significantly better disease-free and overall survival rates than the heavier smoking group.

Patients with throat cancer exposed to both human papillomavirus (HPV) and tobacco smoke demonstrate a pattern of mutations along several key cancer genes, according to research presented by Zevallos et al at the 2016 Multidisciplinary Head and Neck Cancer Symposium (Abstract 1). These distinct molecular profiles of heavy and light smokers who develop HPV-positive oropharyngeal squamous cell carcinoma may inform decisions related to treatment intensity by establishing additional prognostic criteria for this subset of patients.

Rates of Tobacco Usage

Researchers examined the molecular characteristics of oropharyngeal squamous cell carcinoma caused by HPV in an effort to determine which DNA mutations predict lower disease free and survival rates among HPV-positive throat cancer patients who smoke. Whereas most patients with oropharyngeal squamous cell carcinoma caused by HPV have an excellent prognosis for disease free survival, those who also smoke generally face more dire prognoses.

The 66 cases of HPV-positive oropharyngeal squamous cell carcinoma in this study were split into heavy and light smoking behavior groups based on pack years. Forty of the 66 patients reported more than 10 pack years (eg, more than one pack per day for 10 years or two packs per day for 5 years), and 26 patients reported fewer than 10 pack years.

"Throat cancer patients who smoked and had a history of fewer than 10 pack years had significantly

better disease-free and overall survival rates than the heavier smoking group," said **Jose P. Zevallos, MD, MPH, FACS**, Assistant Professor and Director of Oncologic Research in the Division of Head and Neck Surgical Oncology at the University of North Carolina, Chapel Hill and member of the Lineberger Comprehensive Cancer Center. "Our analyses identified several key differences in molecular mutational profiles of the two groups that may shape these outcomes."

Molecular Differences

Overall mutation rates were higher for HPV-positive OPSCC patients in the > 10 pack year group than those in the < 10 pack year group. *HLA-A* mutations occurred more often in the heavy smoking group, and mutations associated with tobacco exposure and poor survival occurred almost exclusively within the heavy smoker group, including those in *TP53* (6% vs 0%, $P = .428$), *CDKN2A* (2% vs 0%, $P = .758$), *FAT1* (14% vs 6%, $P = .688$), *CASP8* (8% vs 0%, $P = .565$), *NOTCH1* (18% vs 0%, $P = .092$), *FGFR3* (10% vs 0%, $P = .325$), and *KRAS* (4% vs 0%, $P = .232$). Researchers on the study note that these are preliminary data and that they are currently recruiting additional participants to add to the small sample size and fully power the between-group tests.

"I think what is most striking is that these genes are mutated almost exclusively in smokers," said Dr. Zevallos. "This molecular profile suggests that while HPV-positive oropharyngeal squamous cell carcinoma carcinogenesis initiates similarly, tumors in patients who smoke acquire novel mutations not traditionally associated with HPV-associated cancers." Analyses indicated that the molecular profile of HPV-positive smokers bears similarities to the profile for HPV-negative head and neck cancer, although the profile does maintain several important molecular characteristics of HPV-positive cancer, including frequent *PIK3CA* and *MLL-3* mutations.

Differences in immune-related and tobacco-related gene mutations by smoking status identified in this study may explain why HPV-positive cancer in smokers may be more aggressive. Findings could impact which treatment options are recommended to patients with HPV-positive oropharyngeal squamous cell carcinoma by informing clinical trials to establish new molecular parameters to guide determinations of treatment intensity.

"Because HPV-positive throat cancers respond well to treatment, patients often are given the option of choosing less aggressive treatment with fewer side effects," explained Dr. Zevallos. "Our study begins to set criteria-based changes in tumor DNA that can be used to predict more aggressive cases that should be given more intense treatment. We hope that this information will one day help to guide more personalized treatments for HPV-positive throat cancers."