EPIDEMIOLOGY

Human papillomavirus—a powerful predictor of survival in patients with oropharyngeal cancer

Patients with oropharyngeal squamous-cell carcinoma caused by human papillomavirus (HPV) infection have been reported to have a more favorable chance of survival than patients with HPV-negative tumors. However, the prognostic value and clinical significance of this association has, to date, remained undetermined. Now, a study published in the *New England Journal of Medicine* has demonstrated that "tumor HPV status is the single greatest predictor of survival in patients with head and neck cancer," reports lead investigator Maura Gillison, of the Ohio State University, Columbus, USA.

HPV-positive and HPV-negative oropharyngeal squamous-cell carcinomas are distinct subtypes and have different causes, risk profiles, and survival outcomes. For example, HPV-positive carcinomas are associated with sex-related risk factors, whereas alcohol and tobacco consumption are the key risk factors for HPV-negative carcinomas. Previous studies have indicated that patients with HPV-positive tumors have a better prognosis than those with HPV-negative tumors, but these studies have been limited by small patient numbers. Thus, other favorable prognostic factors, such as young age or early tumor stage, could not be discounted as being involved in the observed improved survival.

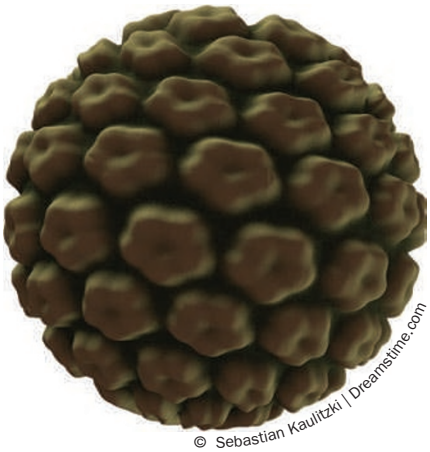
In the present investigation, Gillison's team sought to evaluate the effect of tumor HPV status in a study of sufficient size to allow other prognostic variables to be accounted for in a uniformly treated population of patients with similar stages of cancer receiving standard-of-care therapy. The analysis was performed using data from patients with oropharyngeal squamous-cell carcinoma enrolled in the Radiation Therapy Oncology Group (RTOG) 0129 study.

In the RTOG 0129 randomized clinical trial, the outcomes of cisplatin therapy combined with either accelerated-fractionation radiotherapy or standard-fractionation radiotherapy in patients with locally advanced squamous-cell carcinoma of the head and neck were evaluated. In the study, HPV status was only assessed in patients with oropharyngeal squamous-cell carcinoma. HPV status was determined by means of *in situ* hybridization detection of HPV DNA and p16 expression (evaluated by immunohistochemistry).

"Our *in situ* hybridization assay for determination of tumor HPV status has single copy sensitivity for HPV type 16 per tumor cell, which provides specificity of HPV presence to the tumor cell," describes Gillison. HPV type 16 is the most predominant type in oropharyngeal squamous-cell carcinoma. Expression of p16 is an established biomarker for the HPV-oncoprotein function and, in contrast to HPV DNA, is not specific for HPV type.

Gillison's group assessed 721 patients (360 received accelerated-fractionation radiotherapy and 361 received standard-fractionation radiotherapy), and the 3-year overall survival rate was similar between the two treatment groups. A total of 433 patients had oropharyngeal squamous-cell carcinoma; HPV status was determined in 323 (74.6%) of these patients, of whom 206 had HPV-positive tumors (96.1% of which were positive for HPV type 16 DNA). The 3-year overall survival rates were substantially better in patients who had HPV-positive tumors than in those who had HPV-negative tumors (82.4% versus 57.1%).

After adjustment for known prognostic factors—including tumor and nodal stage, age, and tobacco consumption—patients with HPV-positive carcinomas had a 58% reduction in the risk of death relative to patients with HPV-negative tumors. Of note, the risk of cancer relapse and/or death increased by 1% for every pack-year of tobacco exposure.



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In light of these results, Gillison's team propose that therapeutic decisions should be made on the basis of a combination of factors, rather than just tumor stage, which is currently the principal determinant in decision making. Indeed, risk factors, such as HPV infection and tobacco use, are also major determinants of the biological behavior of the tumor in response to therapy. "If our findings are confirmed in other study populations it will be important to incorporate tumor HPV status and tobacco-pack years as nonanatomic determinants of risk classification for patients with head and neck cancer," Gillison comments.

A strong agreement was observed between tumor HPV status as determined by the presence of HPV DNA and expression of p16. As p16 expression status is not specific for HPV type, the researchers suggest that this biomarker is best for determining HPV status until a validated multiplex assay for HPV *in situ* hybridization is available.

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Original article Ang, K. K. *et al.* Human papillomavirus and survival of patients with oropharyngeal cancer. *N. Engl. J. Med.* **363**, 24–35 (2010)

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