

## EDITORIAL



## Prognostic Implications of HPV in Oropharyngeal Cancer

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Identification of human papillomavirus (HPV) as the etiologic agent of cervical cancer has led to its identification in other cancers, with oropharyngeal squamous-cell carcinoma the most common of these.<sup>1,2</sup> In this issue of the *Journal*, Ang and colleagues<sup>3</sup> report findings from their study (ClinicalTrials.gov number, NCT00047008) that contribute to the growing body of evidence that HPV-positive oropharyngeal squamous-cell carcinoma represents a distinct clinicopathological entity associated with a better prognosis than HPV-negative oropharyngeal squamous-cell carcinoma.<sup>4,5</sup> In a randomized trial of patients with oropharyngeal squamous-cell carcinoma, the overall survival was substantially better among patients with HPV-positive cancer than among patients with HPV-negative cancer. The size of the sample — 323 patients with oropharyngeal squamous-cell carcinoma and known HPV status, of whom 64% had HPV-positive tumors — enabled the authors to control for many variables and to conclude that HPV status was a critical independent prognostic determinant.

The two classes of oropharyngeal squamous-cell carcinoma appear to have distinct causes. HPV-positive cases are associated with sex-related risk factors that have also been linked to cervical cancer and an increased likelihood of orogenital activity, whereas tobacco and alcohol consumption are the key risk factors for HPV-negative cases. Epidemiologic studies suggest little interaction between the two sets of risk factors, suggesting that HPV-positive cancer and HPV-negative cancer may each have a distinct pathogenesis. However, the data reported by Ang and colleagues suggest that smoking has an adverse effect on prognosis in both HPV-positive and HPV-negative cases. The incidence of oropharyn-

geal squamous-cell carcinoma is increasing in industrialized countries, because the substantial rise in HPV-positive cases is greater than the decrease in HPV-negative cases, which has paralleled decreases in other cancers associated with tobacco use.

Clear-cut molecular differences between HPV-positive and HPV-negative oropharyngeal squamous-cell carcinoma have been identified.<sup>5,6</sup> Nearly all HPV-positive cases express the viral E6 and E7 oncoproteins. Each of these proteins subverts a variety of cellular regulatory mechanisms that are predominantly antiproliferative, of which the best known are the p53 and retinoblastoma (pRb) tumor suppressors.<sup>7</sup> The gene encoding p53, which is inactivated at the protein level by E6, remains the wild type in almost all HPV-positive tumors, whereas it is frequently mutated in HPV-negative tumors. In HPV-positive cases, the pRb protein is inactivated by E7; in HPV-negative cases, the p16 tumor suppressor, a component of the pRb tumor-suppressor network, is frequently inactivated. Most HPV-positive tumors, including HPV-positive oropharyngeal squamous-cell carcinoma, express p16, although its tumor-suppressor activity is lost because that function is mediated by pRb, which is inactivated by E7. Other molecular differences between HPV-positive and HPV-negative oropharyngeal squamous-cell carcinoma have also been described.<sup>8</sup>

The viral proteins E6 and E7 may render the HPV-positive tumors more immunogenic than the HPV-negative tumors. Serologic assays can detect anti-E6 or anti-E7 antibodies in many patients with HPV-positive tumors. A higher proportion of patients with HPV-positive tumors have partial or complete responses to therapy, even after adjustment for differences in tumor stage. In ad-

dition, patients with HPV-positive oropharyngeal squamous-cell carcinoma are younger, often have less-advanced disease, and are less likely to have serious concomitant disease than patients with HPV-negative cancer. However, Ang and colleagues estimate that these factors account for only about one tenth of the prognostic difference between the two groups.

Given this background, how might we understand the relative contributions of differences in inherent malignancy, immunogenicity, and treatment response to the prognosis for patients with HPV-positive oropharyngeal squamous-cell carcinoma? It is plausible that HPV-positive cancer is inherently less malignant than HPV-negative cancer. Consistent with this speculation, when surgery is the only treatment provided for oropharyngeal squamous-cell carcinoma, patients with p16-positive tumors have a better prognosis than those with p16-negative tumors, after adjustment for tumor stage.<sup>9</sup> Mechanistically, although expression of the HPV E6 and E7 oncogenes markedly dampens the activity of certain tumor suppressors, these suppressor pathways are often inactivated to a greater degree in HPV-negative tumors, by genetic or epigenetic mechanisms. For example, HPV E6 expression causes accelerated degradation of the p53 protein, resulting in a dramatic reduction of p53 levels. In contrast, p53 mutation in an HPV-negative tumor may result in the synthesis of a p53 protein that not only is inactive as a tumor suppressor but also can bind and inactivate any remaining wild-type p53 in a tumor cell and that may be associated with a gain of oncogenic activity. Other differences in gene expression may also contribute to a more severe, malignant phenotype in HPV-negative tumors than in HPV-positive ones.<sup>8</sup>

The immunogenicity of viral proteins could partially restrict the malignant behavior of HPV-positive cancers. The presence of antibodies against E6 and E7 or tumor-infiltrating lymphocytes may be associated with a better prognosis.<sup>10,11</sup> Murine models suggest that treatment might enhance the immunogenicity of HPV-positive tumors, thus contributing to the superior treatment response.<sup>12</sup> However, the extent to which the clinical outcome is attributable to the immune response is unclear.

Biologic and immunologic properties of HPV-

positive tumors may contribute to their better response to treatment with radiation and chemotherapy. Critical factors may include differences in the degree to which various growth-regulatory pathways are altered in HPV-positive tumors as compared with HPV-negative tumors, together with the mechanisms by which the pathways have been perturbed. For example, since the p53 and pRb pathways are merely rendered dormant by expression of the HPV E6 and E7 oncogenes, these pathways can be reactivated under conditions that reduce this expression.<sup>13</sup> Laboratory evidence suggests that treatment of HPV-positive cells with standard chemotherapeutic agents causes down-regulation of HPV E6 and E7 expression and reactivation of tumor-suppressor pathways, including that of p53.<sup>14</sup> On the other hand, mutant p53, frequently present in HPV-negative tumors, is associated with treatment resistance.

The conclusion that HPV-positive and HPV-negative oropharyngeal squamous-cell carcinomas are distinct entities implies that their treatment or prevention might benefit from different approaches. For example, in HPV-positive cancers, efforts to inhibit the expression or activity of E6 and E7 might result in effective treatment.<sup>13</sup> For HPV-negative cancers, the targeting of pathogenetically relevant biomarkers associated with a poor prognosis, such as BCL2, might improve the therapeutic response.<sup>15</sup> For prevention, risk reduction through modification of exposure to the various etiologic factors is one approach, and the development of screening methods is another. Vaccination against HPV also may be a way to prevent HPV-positive oropharyngeal squamous-cell carcinoma.<sup>6</sup> Approximately 90% of HPV-positive cancers contain HPV type 16, and another 5% have HPV type 18. Both HPV types are targeted by the two preventive HPV vaccines approved by the Food and Drug Administration. Vaccination, if performed before exposure to the virus, might prevent a large number of HPV-positive cases of oropharyngeal squamous-cell carcinoma. The vaccines can prevent persistent genital infection with these types of HPV and the consequent precancerous lesions, but it is not known whether they can prevent oropharyngeal HPV infection.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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