The incidence of human papillomavirus (HPV)-associated tumors of the head and neck has increased substantially in the past 30 years. These tumors are differentiated clinically from their non-HPV counterparts by affecting younger patients who do not have such traditional risk factors as smoke and alcohol exposure.

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There also are distinct molecular genetic differences between the 2 entities, including their effects on the retinoblastoma and p53 tumor suppressor pathways. All of these factors seem to play a role in the improved mortality associated with HPV-positive tumors of the head and neck. They also might mean that less-intensive therapies and a greater emphasis on prevention may be needed in the future to halt this relative cancer epidemic.

Recent changes in the epidemiology of cancers of the head and neck have revealed that HPV is a common etiologic agent. The epidemiology and clinical characteristics of HPV-associated head and neck tumors differ from our previous understanding of cancers not associated with HPV, which has implications in the counseling and prevention of HPV transmission. This article reviews the differences in epidemiology and clinical presentation of HPV-associated oropharyngeal cancers, and discusses important concepts in prognosis, management, and prevention.

**Epidemiology**

The gradual decline in smoking tobacco over the past 3 decades has led to a commensurate decline in head and neck squamous cell carcinoma (HNSCC). Unfortunately, it appears that the incidence of a subset of HNSCC, oropharyngeal squamous cell carcinomas (OSCC), has increased over the past half century. Studies suggest that this increase is due to HPV-associated tumors of the palatine tonsils and base of the tongue, which account for 90% of all OSCCs. Chaturvedi et al report a decrease of 50% in the incidence of HPV-negative OSCC from 1988 to 2004. Over that same time, HPV-positive OSCC increased by 225%, from an incidence of 0.8 per 100,000 to 2.6 per 100,000. HPV type 16 is identified in approximately 90% of OSCCs.

The prevalence of oral HPV infection in adults aged 14-69 years is about 7%—and 1% for HPV type 16, specifically. Due to the ubiquitous nature of HPV, it is reasonable to question whether it is truly causative of OSCC. However, strong molecular pathologic evidence exists to support the causal role of HPV in OSCC. This includes observation that suppression of the oncogenes E6 and E7, produced by
HPV 16, reactivates the p53 and retino-blastoma (pRb) tumor suppressor pathways. This, in turn, leads to apoptosis of HPV-positive OSCC cell lines. This observation is facilitated by the understanding that HPV exerts its oncogenic influence by E6 and E7 binding and degrading p53 and pRb tumor suppressor proteins, respectively. In contrast, HPV-negative tumor OSCC cells demonstrate mutations in the underlying p53 and pRb gene pathways. Other molecular genetic differences have been described between HPV-positive and HPV-negative OSCCs. These differences demonstrate how presence of HPV is most likely contributing causally to the surge in OSCC incidence. It is nonetheless important to determine that HPV is the biological cause of individual cancers and not a coincidental finding for epidemiologic purposes as well as for potential issues with management.

There are strong epidemiologic factors that suggest a causative role of HPV in the recent increase in OSCC. HPV-positive OSCCs tend to occur in younger patients who lacked the traditional risk factors of alcohol and tobacco consumption. Instead, they show positive correlations with number of lifetime vaginal and oral sex partners. There is even evidence to suggest possible HPV transmission via open-mouthed kissing. Further studies correlating these behaviors with increased OSCC incidence are ongoing but almost certainly have potential significance to management and prevention of HPV transmission. The epidemiologic differences
between HPV-positive and HPV-negative OSCCs also strongly suggest that the observed increase in incidence of the former is not simply due to better detection methods. The actual reasons for increases in oral HPV infection and malignancy remain unclear.

**Clinical manifestations and diagnosis**

Most HPV-associated OSCC originate near the tonsils and base of the tongue. The primary tumors tend to present at a relatively early stage, with relatively advanced regional lymph node involvement but with less risk of distant metastasis. Non-Hispanic black and white males tend to be most commonly affected, at a rate of 6.3 and 6.4 per 100,000 men in these categories, respectively. Both non-Hispanic black and non-Hispanic white females are affected at a rate of about 1.4 per 100,000 women. Median age at onset is 58 years among males and 61 years among females.

Presenting symptoms of HPV-positive OSCC are similar to those of other oral cavity cancers and can include painful ulcerations, changes in the fit of dentures, sore throat, and otalgia. More advanced disease may present with trismus, dysphagia, odynophagia, limited movement of the tongue, fistula development, and massive lymphadenopathy.

With the troublesome rise in HPV-associated OSCC, it is conceivable that routine screening for HPV infection of the mucosal epithelium may be recommended for high-risk individuals or the population in general. All individuals at risk should undergo examination of the oral cavity and bimanual palpation of the neck; however, at this time what constitutes an individual “at risk” has not been clearly defined and should remain in the judgment of the health care provider. At this time, no evidence suggests routine laboratory or radiographic screening would reduce the mortality from OSCC. As previously mentioned, the ubiquitous nature of HPV means that polymerase chain reaction (PCR) may not be the optimal method of assessing the association of HPV with OSCC. Studies are ongoing to demonstrate the best method for establishing HPV’s role in the pathology of individual OSCCs. Detection of p16 (a protein up-regulated by HPV’s inhibition of the pRb pathway) expression by immunohistochemistry and HPV-16 by in situ hybridization appear to have promising sensitivity and specificity, respectively. The former may be able to determine oncogenic potential in premalignant oral HPV lesions. The role of these tests in screening for oncogenic HPV activity will take some time to truly elucidate. Additionally, screening the oral cavity may prove to be more difficult than a more localized area, such as the cervix.

For the time being, all lesions suspicious for OSCC should be biopsied (usually via direct examination under anesthesia), and all head and neck cancers should be assayed for HPV using available techniques. Computed tomography of the head and neck should be performed to assess the extent of disease. Patients with lymph node involvement should undergo evaluation for distant metastases with either chest radiography and bone scanning or positron emission tomography. Occasionally, a patient may present with lymphadenopathy without evidence of a primary tumor. If results of lymph node biopsy are consistent with squamous cell carcinoma, the patient should undergo extensive endoscopy and biopsy of any suspicious lesions.

### Prognosis

The body’s immune system resolves about 90% of all lesions that are caused by HPV within 2 years. This is true for both “low-risk” (wart-causing) and “high-risk” (cancer-causing) HPV types. It is only when HPV stays in the body for a number of years that cancer develops. It is still unknown why HPV goes away in most people, but not all, and thus it is impossible to predict which patients will develop HPV-related cancers. It has been shown that OSCCs caused by HPV tend to respond better to treatment than HNSCCs caused by alcohol or tobacco. Cancers of the head and neck typically remain confined locally for months to years. The first sign of spread is local tissue invasion, which is eventually followed

### Table 1. Staging of head and neck cancers

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Regional Lymph Node Metastasis</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>≤ 2 cm</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>2-4 cm, or affects 2 areas within a specific site</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>&gt;4 cm, or affects 3 areas within a specific site</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Any of the above</td>
<td>One node ≤ 3 cm</td>
<td>None</td>
</tr>
<tr>
<td>IV A</td>
<td>Any of the above</td>
<td>One node 3-6 cm, or multiple nodes</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Resectable tumor that invades specific structures</td>
<td>Any of the above</td>
<td>None</td>
</tr>
<tr>
<td>IV B</td>
<td>Resectable tumor that invades specific structures</td>
<td>Any of the above</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Any of the above</td>
<td>Node &gt; 6 cm</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Any of the above</td>
<td>Any of the above</td>
<td>Present</td>
</tr>
</tbody>
</table>
Head and neck tumor prognosis is best when the diagnosis is made early and appropriate treatment is initiated quickly. ... Survival rates are decreased by about 50% with local invasion, regional nodal spread, and distant metastases.

by metastasis to regional lymph nodes. Staging of head and neck cancers is dependent on the size and site of the primary lesion, the number and size of cervical lymph node metastases, and evidence of distant metastases (see Table 1). Complete staging usually requires computed tomography and/or magnetic resonance imaging, and frequently positron emission tomography as well.

In general, head and neck tumor prognosis is best when the diagnosis is made early and appropriate treatment is initiated quickly. Better-differentiated cancers have less chance for metastasis and, consequently, a better prognosis. Survival rates are decreased by about 50% with local invasion, regional nodal spread, and distant metastases. Five-year survival for appropriately treated head and neck tumors can be as high as 90% for stage I tumors and up to 40% for stage IV tumors (see Table 2 on p. 20). These rates vary greatly depending on the location of the primary lesion.

Management
HPV-infected patients generally receive the same treatment as other cancer patients who do not have HPV-related tumors. This is done based on the type, location, and stage of the cancerous tumors. Treatment can involve a combination of surgery, radiation therapy, and occasionally chemotherapy. Although there is no consensus on how best to determine if the presence of HPV has caused the malignancy, there is good reason to know...
whether an OSCC harbors HPV. HPV-positive OSCC may be treated differently.\textsuperscript{22}

Recent research also suggests that patients with HPV-positive oropharyngeal tumors may do just as well with less-intense treatment.\textsuperscript{22} Traditional chemotherapy for OSCC is associated with significant morbidity that affects patients’ quality of life. Because HPV-positive OSCC is generally detected at a younger age it tends to have improved mortality, patients may suffer treatment-related morbidity for many years. Some burgeoning new treatments and ongoing clinical trials involving less-intensive therapies are available to patients who have HPV-positive OSCCs that may confer a better quality of life. These treatment modalities include vaccine clinical trials and deintensification chemoradiation.\textsuperscript{21}

Prevention
HPV is found in saliva, semen, and genital secretions. Because it is sexually transmitted, one method of prevention is use of barrier-method, safer-sex practices, such as condoms. This may greatly decrease the risk of transmission of some types of HPV, but areas not covered by the condom may be infected. For this reason, condoms cannot completely protect against the spread of virus.\textsuperscript{22} For sexually active persons, a mutually monogamous relationship with an uninfected partner is the most effective way to prevent infection.\textsuperscript{22}

Certain types of HPV, like those found in benign skin warts, are transmitted via skin-to-skin contact.\textsuperscript{22} Avoiding direct contact with affected skin is the only way of truly avoiding this type of transmission. These types of prevention strategies are difficult because most people who are sexually active have had HPV at one point in their lives, and many never know they are infected and spreading the virus.

There are 2 vaccines currently available that protect against infection by certain types of HPV. Cervarix protects against HPV types 16 and 18 and is available for females aged 9-26 years.\textsuperscript{24} Gardasil protects against HPV types 6, 11, 16, and 18 and is available for both males and females aged 9-26 years.\textsuperscript{24} These vaccines protect against new HPV infections only and are not considered curative or protective against HPV infections that occurred prior to vaccination. For the vaccines to be most beneficial, it is important that the patient receive all 3 doses before any sexual activity begins. For this reason, it is recommended that males and females receive these vaccines routinely at age 11. It is important to note that, although it is most beneficial for patients to receive all 3 doses before any sexual activity begins, all patients in the proper age range should receive the vaccine irrespective of sexual activity.

According to the US Centers for Disease Control and Prevention (CDC), these vaccines may prevent about 15,000 HPV-associated cancers in women in the United States annually. These cancers include cervical, vaginal, anal, vulvar, and oropharyngeal cancers.\textsuperscript{25} Similarly, the CDC estimates that vaccines may prevent about 7000 HPV-associated cancers in men in the United States annually, with oropharyngeal cancers being the most common in this group.\textsuperscript{25} Further research needs to be done, but evidence of HPV transmission due to open-mouth kissing may suggest that vaccines should be administered at an earlier age.

Although it is most beneficial for patients to receive all 3 doses of the vaccine prior to any sexual activity, all patients in the proper age range should receive the vaccine irrespective of sexual activity.

| Table 2. Five-year survival rate with appropriate treatment based on stage of head and neck cancer |
|--------------------------------------------------|--------------------------------------------------|
| Stage of Head and Neck Tumor | 5-year Survival Rate with Appropriate Treatment |
| I | Up to 90% |
| II | 75-80% |
| III | 45-75% |
| IV | Up to 40% |

Current research and investigation
One of the current studies in this area is called the HPV Oral Transmission Study in Partners Over Time (HOTSPOT), and is led by Dr. Gypsyamber D’Souza at the Johns Hopkins Bloomberg School of Public Health. Enrollment for this study is ongoing at 4 institutions—Dana-Farber Cancer Institute in Boston, Mount Sinai Medical Center in New York City, Oregon Health...
and Science University in Portland, and Johns Hopkins University in Baltimore. Researchers are evaluating HPV infection and certain lifestyle activities in HPV-positive OSCC patients and their sexual partners. One of the goals of the study is to better understand the risk of oral HPV infection in high-risk partners. Participants of this study must be newly diagnosed with head and neck cancer that is suspected to be HPV-positive, and they must be enrolled before initiating treatment. Johns Hopkins also lists a number of ongoing clinical trials for both newly diagnosed, locally advanced head and neck squamous cell cancers and metastatic or recurrent head and neck squamous cell cancers. The principal contact for each trial is listed on their website (http://www.hopkinsmedicine.org) and may be contacted for additional information.

**Final notes**

As the incidence of HPV-associated tumors of the head and neck continues to rise, it is very important for physicians to be familiar with the details of such cancers. Knowing the epidemiologic and clinical presentation can help physicians with early detection of these diseases. Adequate knowledge of the prognosis and management will help physicians to sufficiently counsel their affected patients. Knowledge of the different preventative strategies and vaccines can protect at-risk individuals. Ongoing studies and clinical trials will bring much-needed information about this ubiquitous virus and the increasing incidence of HPV-related head and neck cancers.

**References**


