HPV-associated Oropharyngeal Cancers—Are They Preventable?

Aimé R. Kreimer and Anil K. Chaturvedi

Abstract

It is not known whether a human papillomavirus (HPV)-induced oropharyngeal precancerous lesion could be identified by screening with a pap test equivalent or whether one even exists. In this issue of the journal (beginning on page 1378), Fakhry and colleagues report their results showing that cytologic evaluation of the oropharynx, although useful in detecting invasive oropharyngeal cancers, may have limited utility as a screening modality for detecting precancer. These findings argue against the potential for secondary prevention of HPV-associated oropharyngeal cancers through screening for and preventing the progression of precancer and highlight the opportunity for primary prevention through prophylactic HPV vaccination, if proven efficacious and cost-effective. Cancer Prev Res; 4(9); 1346–9. © 2011 AACR.

More than 5% of cancers worldwide are caused by human papillomavirus (HPV; ref. 1). HPV causes all cervical cancers and thus is necessary to carcinogenesis in this site. It also causes a large proportion of other anogenital cancers, including cancers of the vagina, vulva, penis, and anus, and some head and neck cancers occurring in the oropharynx, for which the proportion differs by geographic region (Table 1; ref. 1). In the United States and other countries with organized screening programs for cervical cancer, the incidence of cervical squamous cell carcinomas has dramatically declined since the 1960s (2): its current U.S. annual age-standardized rate is approximately 6.5 per 100,000 women aged 25 years and older. In contrast, the incidences of cervical adenocarcinomas and anal, vulvar, and oropharyngeal cancers have significantly increased over the last couple of decades, underscoring increased HPV exposure among recent birth cohorts (2–5). Noncervical HPV-associated cancers, which individually are relatively rare, now collectively parallel the burden of cervical cancers in the United States (6). Of note, the annual number of HPV-associated oropharyngeal cancers is projected to exceed the annual number of cervical cancers over the next decade in the United States (7), highlighting the need for early detection and prevention.

The multistep nature of HPV-induced carcinogenesis in cancers of the cervix, anus, penis, vagina, and vulva provides a possible opportunity for secondary prevention via screening to detect precancers that are amenable to treatment with the goal of preventing progression to cancer. At these anogenital sites, HPV persistence precedes the development of histologic precancerous lesions, or intraepithelial neoplasias, a proportion of which progresses to invasive cancers if left untreated (8). Of importance, studies in each of these sites have shown the feasibility of visual inspection and specimen collection for cytologic and histologic examination of the presence of dysplasia, as well as the ability to treat precursor lesions (Table 1). Analogous studies of the presence of an HPV-induced oropharyngeal precancerous lesion, or a method to collect specimens for identifying such a lesion, have been lacking.

In this issue of the Journal, Fakhry and colleagues report on the question of whether a "Pap test equivalent," which involves collecting cell samples via a cytology brush, would be useful for screening and early detection of HPV-associated oropharyngeal cancer; the oropharynx includes the tonsil, base of tongue, and other parts of the pharynx (9). The authors investigated associations between HPV16 infection and cytologic abnormalities in cell samples from 2 groups of patients at high risk for oropharyngeal cancer—patients with oropharyngeal abnormalities, of whom 70% had been diagnosed with invasive oropharyngeal cancer, and patients infected with the human immunodeficiency virus (HIV) and with no clinical symptoms of oropharyngeal disease. Results in the first patient group showed that HPV16 infection and abnormal cytology, individually and combined, were strongly associated with the presence of oropharyngeal cancer, indicating that cytologic evaluation of visible lesions in the oropharyngeal region (tonsil, base of tongue, and other parts of the pharynx) could detect invasive oropharyngeal cancer.

Yet, detecting cancer is only the first step in a screening process, which includes a screening test with acceptable sensitivity and specificity, diagnostic work-up, and treatment, all with the goal of prolonging disease-free survival and reducing cancer-specific mortality. As such, it is ideal to detect not frank cancer but precancer instead. The results in the nonasymptomatic HIV-infected patients under study, however, showed that the presence of tonsillar cytologic abnormalities (atypical squamous cells of unknown significance) was rare and not associated with either tonsillar...
or oral HPV16 infection. It is unclear whether this lack of association between oropharyngeal cytologic abnormalities and HPV16 infection arose from the absence of an HPV-induced precancerous lesion or from the inability to adequately sample the most relevant sites of a precancerous lesion—the lower part of deep tonsillar crypts. The authors postulate the latter as a potential explanation. Whatever the reason or reasons, the overall results in the 2 high-risk patient groups indicate that cytologic evaluation of the tonsil and other parts of the oropharyngeal region, although useful in detecting invasive oropharyngeal cancer in the presence of accessible lesions, has limited utility as a screening modality for populations without visible lesions or clinical disease.

The present results of Fakhry and colleagues (9) have important implications for secondary prevention of HPV-associated oropharyngeal cancers. The success of a secondary prevention strategy depends on the presence of a precancerous stage in the pathogenesis of the cancer, the availability of a screening modality with adequate sensitivity and specificity to detect the precancer, and the ability to treat the precancer such that progression to cancer can be interrupted. In the case of HPV-induced oropharyngeal cancer, the question still remains whether there is an identifiable precancerous lesion akin to lesions at other HPV-associated cancer sites. The present results indicate that cytologic evaluation of the tonsil and other oropharyngeal sites cannot be used as a screening modality for populations at a high risk of HPV-associated oropharyngeal cancers, such as HIV-infected individuals. Analogous studies in high-risk populations without HIV infection, such as cancer-free individuals with persistent oral HPV infection, have not yet been conducted. Last, even if an identifiable precancer and an appropriate screening modality were available, the sites at which HPV causes cancer in the head and neck region—tonsil, base of tongue, and other parts of the pharynx—would be less amenable than are anogenital sites for treatment of such precancerous lesions. These observations argue against secondary prevention through screening as a viable strategy to reduce the burden of HPV-associated oropharyngeal cancers.

Given that an HPV-induced oropharyngeal precancerous lesion has not yet been identified, the presence of oral HPV infection remains the only currently available indicator of future oropharyngeal cancer risk. Few prospective studies, however, have addressed the natural history of oral HPV infections. Consequently, there are few stable estimates of oral HPV incidence, clearance, or persistence. At present, it seems that acquisition of oral HPV infection is rare among healthy individuals (data indicate that <3% acquire a new oral HPV infection in a 6-month time period; ref. 10) and more frequent among high-risk, HIV-positive individuals (in which 10% to 20% acquire a new oral HPV infection in a 6-month time period; ref. 11). Rates of HPV persistence may be comparable with or higher than that observed at anogenital sites, although more data are needed (10–12). In view of the lack of data on the natural history of oral HPV infection, the utility of identifying populations at a high risk of oropharyngeal cancer through detection of oral HPV infection is currently unclear. The absolute risk of oropharyngeal cancer among individuals with oral HPV16 infection is unknown. Likewise, little is currently known about modifiable risk factors for preventing oral HPV persistence, which is believed to be a prerequisite for HPV-induced cancer.

**Table 1. Sites of HPV-associated cancers: Proportion of cancer due to HPV, presence of HPV-induced precancer, screening modality, and HPV vaccine efficacy**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>% attributable to HPV infection</th>
<th>HPV-induced premalignant lesion</th>
<th>Screening modality</th>
<th>Vaccine efficacy against persistent HPV16/18 infection</th>
<th>Vaccine efficacy against HPV16/18-associated premalignant lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>100</td>
<td>Cervical intraepithelial neoplasia (CIN)</td>
<td>Cytology, colposcopy, primary screening through HPV cotesting</td>
<td>91%–94%</td>
<td>93%–98%</td>
</tr>
<tr>
<td>Anus</td>
<td>90</td>
<td>Anal intraepithelial neoplasia (AIN)</td>
<td>Cytology, high-resolution anoscopy</td>
<td>95%</td>
<td>78%</td>
</tr>
<tr>
<td>Penis</td>
<td>40</td>
<td>Penile intraepithelial neoplasia (PIN)</td>
<td>Cytology/histology</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Vagina</td>
<td>40</td>
<td>Vaginal intraepithelial neoplasia (VIN)</td>
<td>Cytology/histology</td>
<td>?</td>
<td>100%</td>
</tr>
<tr>
<td>Vulva</td>
<td>40</td>
<td>Vulvar intraepithelial neoplasia (VIN)</td>
<td>Cytology/histology</td>
<td>?</td>
<td>100%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>12–72</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*In an according-to-protocol or per-protocol susceptible analytic cohort, which is typically restricted to individuals who were HPV DNA negative and seronegative at baseline and through the vaccination phase.

**Against a composite endpoint of penile, perianal, or perineal intraepithelial neoplasia.**
Current epidemiologic knowledge of oral HPV comes predominantly from cross-sectional studies. In a recent systematic review of the literature (13), HPV16, the most commonly detected HPV genotype in HPV-associated oropharyngeal cancers (14), was present in 1.3% of 3,977 healthy individuals from 13 studies. In an assessment of all genotypes considered to be carcinogenic, 3.5% of 4,441 healthy individuals from 17 studies had a carcinogenic HPV genotype in the oral region. Last, 4.5% of healthy individuals had any HPV of any genotype (carcinogenic or noncarcinogenic) in the oral region. Generally, the prevalence of oral HPV infection is low among healthy, cancer-free individuals, especially compared with anogenital HPV infections among similar-age populations, in which prevalence at the cervix (15), penis (16), and anus (17, 18) often may be one order of magnitude higher than in the oral region. Other differences exist between the natural histories of oral and cervical HPV. For example, oral HPV prevalence seems to be stable across age strata (19), whereas it has often been observed that cervical HPV prevalence is highest in the few years after sexual debut and then declines (20). Known factors that increase the risk for anogenital HPV infection similarly increase the risk of oral HPV infection and include sexual behavior (including oral sex for oral HPV; ref. 21), current tobacco use (21), and HIV infection (22). It is uncertain whether the prevalence of oral HPV is comparable among men and women.

The current challenges in secondary prevention of HPV-associated oropharyngeal cancers, coupled with the rapidly growing burden of HPV-positive oropharyngeal cancers in several parts of the world, bring to the fore the prospect of primary prevention through prophylactic HPV vaccination. HPV16 and -18 cause approximately 70% of cervical cancers and an even higher proportion (range = 75%–95%) of HPV-associated cancers at extracervical sites (anus, oropharynx, penis, vagina, and vulva). This high prevalence at extracervical sites is relevant to the 2 currently available HPV vaccines that prevent HPV16 and -18 infections: Bivalent HPV16/18 vaccine (Cervarix; GlaxoSmithKline Biologicals; ref. 23) and quadrivalent HPV6/11/16/18 vaccine (Gardasil; Merck and Co, Inc; ref. 24). There is published evidence for vaccine efficacy (VE) against persistent infections at the cervix, vagina, vulva, penis, and anus (23–26); at many of these anatomic sites, the HPV vaccine has been shown to prevent HPV-associated precancers as well (Table 1).

No study to date has addressed the efficacy of HPV vaccination in preventing oral HPV infection. The low prevalence of oral HPV16 infections and the absence of a recognized precursor lesion have hampered studies of VE for oral HPV infections. Nonetheless, vaccination is anticipated to have equivalent efficacy in preventing oral HPV persistence. In the United States, routine HPV vaccination is currently recommended only for females, given the high burden of cervical precancers. Although the predominant and growing burden of HPV-associated oropharyngeal cancers among men (7) argues for gender-neutral HPV vaccination strategies, it remains to be seen whether vaccination will be efficacious against oral HPV infection and subsequent oropharyngeal cancers, and if so, will prove to be cost-effective for males as it is for females.

In conclusion, several key questions remain with regard to HPV-associated head and neck cancers, including the natural history of oral HPV infections, the existence of an HPV-related oropharyngeal precursor, the multistep progression of infection to cancer, and opportunities for preventing HPV-induced oropharyngeal cancer. In addition to targeting HPV infection, prevention strategies also need to focus on tobacco and alcohol use, which remain major risk factors for oropharyngeal as well as other head and neck cancers worldwide (27).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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