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Epidemiology of HPV-associated oropharyngeal cancer

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Abstract

Squamous cell carcinoma of the oropharynx is increasing in incidence in epidemic proportion. This site specific increase in incidence is due to an increase in human papillomavirus (HPV)-related squamous cell carcinoma, while the incidence of tobacco related squamous cell carcinoma is decreasing. In particular, the incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) is increased among middle aged white men, and sexual behavior is a risk factor. HPV-related oropharyngeal squamous cell carcinoma represents a growing etiologically distinct subset of head and neck cancers with unique epidemiological, clinical, and molecular characteristics that differ from those of HPV-unassociated cancers. In this review, we discuss the epidemiology of HPV-related OPSCC, the prevalence of oral/oropharyngeal HPV infection, and efforts aimed at reducing the incidence of HPV-related OPSCC.

Keywords

human papillomavirus; oropharyngeal cancer; epidemiology

Introduction

Squamous cell carcinoma of the upper aerodigestive tract has traditionally been strongly associated with tobacco and alcohol exposure. However, over the past three decades, despite decreasing smoking rates, there has been a stagnation followed by an increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC). This site-specific increase has been noted particularly among middle-aged white men (often nonsmokers or former/light smokers in studies with tobacco data) compared with traditional patients with OPSCC (as well as other squamous cell carcinomas of the upper aerodigestive tract), i.e., older men

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with a significant smoking and drinking history. This increasing incidence of OPSCC is now attributed to human papillomavirus (HPV), the virus essential to the etiology of cervical cancer. Transmission of HPV is primarily through sexual contact, and oral-genital contact can lead to oral/oropharyngeal HPV infection. There are many types of HPV, and the overwhelming majority of HPV-related OPSCC cases are caused by HPV16. In this review, we discuss the epidemiology of HPV-related OPSCC, the prevalence of oral/oropharyngeal HPV infection, and efforts aimed at reducing HPV-related OPSCC.

Human Papillomavirus

First discovered in skin cells in the 1950s, HPV is now understood to infect basal keratinocytes in the skin or mucosal membranes. The role of HPV in carcinogenesis of the cervix was elucidated by Harald zur Hausen, for which he received the 2008 Nobel Prize in Medicine.¹

Since its first implication in carcinogenesis, HPV has been found to cause cancer of the cervix, anus, penis, vulva, vagina, and oropharynx, as well as benign genital and cutaneous warts, respiratory papillomatosis, and nasal/oral papilloma. Testing has been developed to examine cervical cytologic samples for high-risk HPV DNA, allowing for more sensitive screening among women with an abnormal Pap test result, and HPV testing along with a PAP smear is the recommended screening every five years for low risk women over the age of 30 in the United States.² In 2006 in the United States the first vaccine directed against prevention of HPV infection was approved for widespread use.³ The vaccine is currently indicated for the prevention of cervical and vulvar intraepithelial neoplasia and cancer in females as well as genital warts and anal cancer in both males and females in the United States and Australia, and for females in the European Union.^{4, 5}

Exposure to HPV is very common, with an estimated point prevalence in genital samples of 43-62%, and the lifetime prevalence is certainly higher.^{6, 7} Although transmitted primarily via sexual contact, HPV can also be transmitted by less intimate skin-to-skin contact. High-risk HPV infections are asymptomatic, and the vast majority of persons exposed to HPV will clear the infection and never develop carcinoma. HPV DNA encodes for eight major proteins. Episomal expression of viral capsids L1 and L2 leads to viral proliferation, a hallmark of HPV infection but not sufficient for carcinogenesis. Some cases will progress to integration of viral DNA into the human keratinocyte nuclear DNA and expression of oncogenic proteins E6 and E7. This process of integration is central to carcinogenesis. E6 binds to the tumor-suppressor protein p53 and signals the cell to degrade p53. E7 binds to pRb (retinoblastoma protein), allowing unchecked cell division. An increase in p16 expression occurs as an attempt to control the unchecked cell division resulting from E7 protein disruption of the Rb pathway.^{8, 9} p16 expression appears to be a marker of HPV DNA integration into nuclear DNA, and immunohistochemical staining for p16 can be used as a predictor of HPV tumor status for OPSCC.¹⁰ HPV exposure is so common that the presence of HPV DNA in malignant tissues does not establish causality, but a cell that has become malignant due to HPV oncogenesis will typically overexpress p16. p53 is commonly mutated in tobacco-related cancers of the upper aerodigestive tract, but such mutations are not a common occurrence in HPV-related OPSCC. p16 staining, as well as

p53 mutation status, can therefore help distinguish HPV-driven cancers from mere detectable HPV DNA or a false positive result.

Cervical squamous cell carcinoma, the first cancer recognized as driven by HPV, has been widely studied. In the cervix, high-risk HPV is one necessary factor in the development of cervical squamous cell carcinoma but not the exclusive oncological event. Cervical cancer is caused chiefly by the high-risk subtypes of HPV: 16, 18, 31, and 45. While most exposures to high-risk HPV do not result in cervical cancer, the progression from cervical infection to carcinoma follows a predictable pattern. Viral infection in some cases leads to expression of HPV oncogenes, and basal cells become dysplastic. Dysplasia resolves in most patients, but some cases may progress over the course of a decade or more from mild to severe dysplasia to invasive carcinoma. It is unclear what factors lead to HPV-driven dysplasia as opposed to viral clearance. Because almost all cervical cancers are caused by HPV, it is thought that the elimination of cervical high-risk HPV infections could eradicate cervical squamous cell carcinoma.¹¹

The current literature shows that at any given time approximately 7% of the population has a prevalent oral/oropharyngeal HPV infection.^{12, 13} Most infections are cleared by the immune system, and only about half of patients with a known HPV infection at any site will develop antibodies to HPV. Therefore, seropositivity is not an accurate reflection of previous HPV exposure, as it has a high false negative rate, and in fact there is no reliable test for prior HPV infection if the virus has been cleared from the original site of infection. The lifetime oral exposure rate is unknown, but an estimated 65-100% of sexually active adults have been exposed to HPV at any anatomic site (oral, genital, or anal).^{6, 7}

Men are more likely than women to have an oral HPV infection.¹³

This may be due to the female genital mucosa having a higher HPV viral load than the male genital mucosa/skin, and thus men giving oral sex to women have higher viral dose exposures than vice versa. The past few decades have shown a decrease in the age of sexual debut and increase in the number of sexual partners, and these factors may have contributed to a rise in oral/oropharyngeal HPV exposures.¹⁴ The risk of oral HPV infection increases with the number of oral sexual partners.¹⁵ It is almost certain that oropharyngeal HPV infection is a necessary event in the development of HPV-related OPSCC.¹⁶ Given the high point prevalence of oral/oropharyngeal HPV infection (approximately 7%), most such HPV infections do not progress to cancer, and oral/oropharyngeal HPV infections (like genital infections) are usually cleared by the immune system. Delayed clearance of oral/oropharyngeal HPV infection may be a risk factor for development of OPSCC.

Oropharyngeal Squamous Cell Carcinoma

Squamous cell carcinoma of the upper aerodigestive tract is caused primarily by exposure to tobacco and alcohol. Public health efforts have reduced the smoking rate in the United States from 40% in 1965 to 20% currently, and this decrease in the smoking rate seems to have resulted in a dramatic decrease in the incidence of smoking-related cancers of the oral cavity, larynx, and hypopharynx.¹⁷ It was expected that OPSCC would also decrease in incidence in relation to decreasing smoking rates, but in fact there was only a plateau in

OPSCC incidence followed more recently by a dramatic increase.¹⁸⁻²⁰ As demonstrated in a large single-institution study with almost 4000 patients with newly diagnosed OPSCC, this increase in OPSCC incidence included a number of nonsmokers and nondrinkers – people who do not have traditional risk factors for OPSCC.²¹

Two molecularly and epidemiologically distinct types of OPSCC exist as classified according to HPV status. HPV-negative OPSCC is epidemiologically similar to the traditional type of squamous cell carcinoma of the upper aerodigestive tract, in which long-term exposure to tobacco and alcohol products leads to development of malignancy. HPV-positive OPSCC starts with exposure to high-risk HPV, most often HPV 16, and can develop independently of tobacco or alcohol exposure.^{16, 22} As discussed above, there are molecular markers that distinguish between HPV-positive OPSCC and HPV-negative OPSCC. HPV-positive OPSCC have wild-type p53 and high levels of p16. In contrast, HPV-negative OPSCC have (similar to other squamous cell carcinomas of the upper aerodigestive tract) mutations in p53 (as well as other somatic mutations), resulting in defective p53 and malignant transformation. Whereas HPV-positive OPSCC will typically overexpress p16 by immunohistochemical analysis, HPV-negative OPSCC will usually not stain or only weakly stain positive for p16. It has become apparent that the increase in OPSCC incidence is restricted to HPV-positive disease, while HPV-negative OPSCC is declining in incidence similar to other squamous cell carcinomas of the upper aerodigestive tract caused by tobacco and alcohol and not HPV (oral cavity, larynx, and hypopharynx).^{22, 23} In the oropharynx, HPV is most strongly associated with OPSCC found at the tonsil and base of tongue, and cancers at these subsites are an increasing proportion of all OPSCC.²¹ The association of HPV with oropharyngeal cancer was evidenced both by HPV DNA in OPSCC tumors as well as an increase of OPSCC in those patients seropositive for HPV antibodies. Gillison et al showed that oropharyngeal tumor specimens were 7.7 times as likely to be have HPV DNA (OR =7.7; 95% CI 4.0–15) compared to nonoropharyngeal sites.²² Mork et al. found that serologically HPV16-positive patients had more than 14 times the risk of oropharyngeal cancer compared to serologically HPV16-negative patients (OR, 14.4; 95% CI, 3.6-58.1).¹⁶

Likewise, Smith et al. found that positivity for HPV16 E6 and E7 antibodies was associated with 73 times the risk of an oropharyngeal tumor compared with seronegativity for these antibodies (OR, 72.8; 95% CI, 16.0-330).²⁴

While HPV DNA has been identified in squamous cell carcinomas at other subsites of the upper aerodigestive tract, the causal role of HPV in carcinogenesis at these subsites (other than the tonsil and base of tongue) has not been established, and the proportion of cancers at these other subsites attributable to HPV is likely small. Given the almost ubiquitous presence of HPV and the high exposure rates, the mere presence of HPV DNA does not imply causality. HPV-related oncogenic proteins and downstream events such as p16 overexpression must be detected as part of proving causality. Additionally, poor classification of the tumor subsite, as well as overlap of some subsites, may also lead to misclassification, particularly in the older literature. For instance, and consistent with a shift in quality of site classification in the literature whereby previously some oropharyngeal cancers (particularly those of the base of tongue, which are often coded as a generic site

“tongue”) were misclassified as oral cavity cancers, rates of HPV positivity among non-
oropharyngeal cancers of the upper aerodigestive tract have continued to drop over time,
while HPV positivity rates for oropharyngeal cancer have continued to rise.²⁵

Also, differences in testing methods for HPV may contribute to high rates of false positives.
Regardless, the rate of HPV-positive squamous cell carcinoma has consistently been the
highest in the oropharynx compared with the oral cavity, larynx, or hypopharynx.²⁰

While the precise mechanism of HPV carcinogenesis in the oropharynx is not well
documented, it is likely similar to the development of HPV-related carcinoma in the cervix,
in that exposure to the HPV virus is followed by viral DNA integration, activation of
oncogenes, and subsequent carcinogenesis.¹⁶ Oropharyngeal HPV exposure may not be
sufficient to cause carcinoma, and other factors are likely involved. There is evidence that
HPV infection likely precedes the development of OPSCC by many years if not decades.¹⁶
While there is likely a dysplastic phase, this has not been clearly demonstrated in the
oropharynx.^{26, 27} Other indicators of HPV carcinogenic process such as p16 overexpression
and lack of p53 somatic mutations are well documented.¹⁰ The role of other factors in the
development of HPV positive OPSCC is unclear. Smoking is a risk factor for reduced
clearance of oral HPV infection, as is HIV, and therefore tobacco exposure and immune
status may play a role in the development of HPV positive OPSCC.²⁸ Other known risk
factors for the development of OPSCC, such as genetic polymorphisms, may also predispose
patients to the development of HPV positive OPSCC as well as decrease survival.^{29, 30}
Further studies need to be completed to examine cofactors of malignant transformation in
patients with HPV positive OPSCC.

Incidence

The incidence of HPV-positive OPSCC is increasing markedly, and it is not hyperbole to
call this an epidemic. An estimated 85,000 cases of oropharyngeal cancer occurred
worldwide in 2008, and at least 22,000 of these were HPV positive.³¹ From 1988 to 2004,
there was a 225% population-level increase in HPV-positive OPSCC in the United States
(from 0.8 cases per 100,000 individuals in 1988 to 2.6 per 100,000 in 2004) and a
concomitant 50% decrease in HPV-negative OPSCC (from 2.0 cases per 100,000
individuals in 1988 to 1.0 per 100,000 in 2004). Figure 1²³ The percentage of OPSCC cases
that were HPV positive increased from 16.3% in the period 1984–1989 to over 70% in
2000–2004 in the United States. There has been a 5% annual percentage rate increase in the
incidence of OPSCC in the United States and a 6% increase in Finland.^{23, 32} Chaturvedi et al
estimated that by 2020 the incidence of HPV-positive OPSCC will be greater than the
incidence of cervical cancer, and by 2030 half of all head and neck cancers will be related to
HPV.²³ The increase in HPV-related OPSCC is well documented in North America as well
as in Europe and Australia.^{23, 33} Such a trend has not been well established in South
America, Africa, and Asia, but population-based studies with careful site classifications and
exposure data in these regions are limited or non-existent, and different cultural sexual
practices and continued increased smoking rates may also obscure these trends. In the
United States, the increase in HPV-positive OPSCC is highest among middle-aged white
men (40 to 59 years old).¹⁹

The typical patient with HPV-positive OPSCC is a middle-aged, nonsmoking white man from a higher socioeconomic status and with a history of multiple sexual partners and/or orogenital sexual partners.³⁴ In 2008, using the Surveillance Epidemiology and End Results (SEER) database (1973-2004), Chaturvedi et al demonstrated in a landmark study that the rise of OPSCC incidence was occurring among a specific age group in the United States, the middle aged. There were no significant changes in OPSCC incidence among those under 40 years or over 59 years of age, but among middle-aged white men a 10% annual increase in incidence was seen since 2000.¹⁹ Mehta et al also utilized the SEER database to compare the incidence of OPSCC in different age groups but from a more recent timeframe (1973-2006, United States); the proportion of patients aged 40-59 years increased from 35% to 45%, while the proportion of oropharyngeal cancer patients aged 60-79 years decreased from 52% to 40%.¹⁸ The increase in OPSCC incidence among Caucasian males is so dramatic as to nearly equalize the previous racial disparity in the incidence of squamous cell carcinoma of the upper aerodigestive tract.³⁵ In the late 1980s, African American males had more than twice the incidence of OPSCC of white American males; this has been completely eliminated by the increase in OPSCC among white men and continued declining OPSCC incidence among African American men.¹⁹

Patients with HPV-positive OPSCC are less likely to have a history of tobacco exposure, with most series of OPSCC patients consisting of about 30% nonsmokers in the HPV-positive group compared with less than 5% in the HPV-negative group.³⁶ Patients with HPV-positive OPSCC are also less likely to use alcohol compared with HPV-negative OPSCC patients or those with squamous cell carcinoma at other subsites of the head and neck.³⁷ The past few decades have shown a decrease in the age of sexual debut and an increase in the number of sexual partners, contributing to HPV exposure.¹⁴ The risk of oral/oropharyngeal HPV infection increases with the number of oral sexual partners.¹⁵ Patients with HPV-positive OPSCC are more likely to have an increased number of sexual partners (greater than 8-10) and more likely to have a history of more than four oral sexual partners.³⁸⁻⁴¹ However, demographic, exposure, and behavioral factors are only somewhat predictive of HPV status in patients with OPSCC and should not replace HPV testing.⁴²

Patients with HPV-positive OPSCC are more likely to present with small primary tumors and more extensive nodal disease.⁴³ Because small primary oropharyngeal tumors are unlikely to be symptomatic, most patients seek medical treatment due to symptomatic nodal disease.⁴⁴ Nodal disease may be cystic, which can make diagnosis difficult for medical practitioners unfamiliar with the disease process, and misdiagnosis as a benign cyst is not uncommon. It is important for the initial medical practitioner to recognize that not all squamous cell carcinomas of the upper aerodigestive tract occur in heavy smokers and drinkers and that patients with HPV-related OPSCC often lack a significant history of smoking and drinking. These patients may also present at a younger age than the typical head and neck cancer patient, and complaints of neck mass or other symptoms related to the upper aerodigestive tract should be carefully evaluated. The small primary may easily be overlooked on imaging, and the cystic nodal metastasis may be misdiagnosed as a branchial cleft cyst.⁴⁵ Finally, HPV-related OPSCC tumor histology is more likely to be basaloid, lymphoepithelial, or poorly differentiated.⁴⁴ While these clinical/pathologic characteristics

of HPV-related OPSCC are typical, they are not definitive of an individual's tumor HPV status and proper tumor testing is essential.

Despite presentation with advanced nodal disease, survival is improved in patients with HPV-positive OPSCC compared with patients with HPV-negative OPSCC.^{43, 46-48} As might be expected as a consequence of the epidemic of HPV-related OPSCC, this survival advantage has resulted in dramatic improvements in the 5-year survival rates for OPSCC patients on a national level and have transitioned OPSCC from one of the gravest diagnoses of carcinomas of the upper aerodigestive tract to the best.⁴⁹ The exact mechanism behind the improved survival is unclear; however, clinical trials are under way to determine whether de-escalation of therapy may maintain survival and decrease acute and long-term complications.⁵⁰ RTOG 1016 is a phase III trial open in the United States for patients with HPV-positive OPSCC, and this trial compares concurrent cetuximab to concurrent cisplatin for patients treated with definitive radiotherapy.⁵¹ ECOG 1308 is a phase II trial (accrual complete) for patients with HPV-positive OPSCC exploring the role of induction chemotherapy followed by reduced-dose radiotherapy in patients with complete response at the primary.⁵² ECOG 3311 is a pending phase II trial for patients with HPV-positive OPSCC utilizing transoral robotic surgery as a means of selecting patients for observation without radiotherapy in a low-risk category or reduced-dose postoperative radiotherapy in an intermediate-risk category.

While overall recurrence rates are lower for patients with HPV-positive OPSCC than for patients with HPV-negative OPSCC, the former have a higher proportion of their recurrences at distant sites and are more likely to develop these disseminated metastases in nontraditional sites (i.e., other than the lungs).⁵³⁻⁵⁵ These metastases may also develop more than 2 years after initial treatment for patients with HPV-positive OPSCC, in contrast to distant metastases in patients with HPV-negative OPSCC, which typically occur within 2 years.⁵⁶ This unusual pattern and timing of distant metastasis requires that physicians be vigilant about workup of any unusual complaints in patients with a history of HPV-positive OPSCC. However, patients who develop metastases may have a better response to treatment than previously reported for HPV-negative head and neck metastatic cancers.^{53, 54}

Patients with HPV-positive OPSCC are less likely to develop second primaries than those with HPV-negative OPSCC.^{57, 58} While population-based studies have demonstrated an excess of second primary malignancies at HPV-related sites (anogenital and oropharyngeal) for patients with an index cancer at an HPV-related site, there has not been an excess of second primaries related to HPV in recent large case series of patients with index HPV-related OPSCC.^{48, 55, 58-60} Hemminki et al reported a twofold increase in the development of OPSCC in partners of women with cervical cancer, although it is unclear whether partners develop HPV infections because of infection from their current partner or whether both partners shared similar exposures to HPV infection many years prior.⁶¹

Over 90% of HPV-positive OPSCC cases are caused by a single HPV type (HPV 16), and few OPSCC can be attributed to the other HPV types.⁶² In the United States, two current FDA-approved HPV vaccines provide strong protection against infection with HPV 16. These vaccines are directed towards the viral capsid L1, a late protein that is expressed

during initial infection and prior to carcinogenesis. The two vaccines differ in the number of HPV subtypes against which they are effective. Both vaccines are effective against HPV 16 and 18, and the quadrivalent vaccine is also effective against types 6 and 11, which cause benign genital warts and respiratory papilloma. Currently these HPV vaccines are approved in the United States for prevention of cervical cancer as well as genital warts and anal cancer in both men and women.⁶³ There is not currently an indication for prevention of HPV-positive OPSCC, as studies evaluating the vaccine effect on OPSCC development have not been conducted. Hererro et al showed that vaccination against high risk HPV decreases the prevalence of oral infection in those vaccinated, with an estimated vaccination efficiency of 93.3% (95%CI = 62.5% to 99.7%).⁶⁴ While the effect of the vaccine on HPV related OPSCC has not been studied, and likely will not be as the decades-long delay between HPV exposure and carcinoma detection make such a study difficult and costly, the results of vaccination effect on HPV oral/oropharyngeal infection are encouraging. Because HPV 16 is the cause of the majority of HPV-positive OPSCC, it is likely that the vaccine would help prevent HPV 16 infection and subsequent OPSCC development when given to individuals prior to HPV 16 exposure.

Cervical screening with the Pap smear has identified many women at risk for cervical cancer, and treatment of early disease is lifesaving. The Pap smear is effective because the transitional zone of the cervix has a small surface area and one swab can test most of the area at risk for cervical cancer. The predictable progression from cervical dysplasia to cervical carcinoma allows for medical intervention if moderate or severe dysplasia or cervical intraepithelial neoplasia is detected, and repeated testing increases Pap specificity. While it is suspected that oropharyngeal carcinoma also arises from a dysplastic lesion, this is not proven, and unfortunately there is no screening exam for the oropharynx equivalent to the cervical clinical exam and Pap smear. The tonsil and base of tongue differ histologically from other subsites in the upper aerodigestive tract in having substantial submucosal lymphoid tissue present, and this creates mucosal redundancy and crypts. Additionally, the large surface area of the tonsil and base of tongue, as well as the presence of crypts, prevents sampling of the entire mucosal surface, making sampling for dysplasia inadequate and not representative and of poor predictive value.^{26, 27} Random detection of HPV DNA in an oral/oropharyngeal swab or saliva sample has no known utility as a screening test, because most patients will clear the infection without long-term sequela and a positive saliva test is unlikely to anatomically direct a clinician to an early (silent) cancer.

Conclusion

The increase in incidence of HPV-positive OPSCC is epidemic, and OPSCC will likely soon be the most common cancer in the United States caused by HPV as well as the most common cancer of the upper aerodigestive tract. Patients with HPV-positive OPSCC are more likely to be white, middle-aged, of moderate to upper income, and to have had more oral sexual partners. Clinically, HPV-positive OPSCC behaves differently with a better prognosis but a different pattern of distant metastases and fewer second primary malignancies. Studies are under way to determine whether treatment intensity can be reduced without decreasing survival. Clinicians should be aware of the different epidemiologic factors and clinical behaviors associated with HPV-positive OPSCC in order

to efficiently diagnose and treat patients. Because the vast majority of HPV-positive OPSCC cases are caused by HPV16, vaccination against HPV 16 during childhood and prior to HPV exposure may prevent later development of HPV-positive OPSCC.

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Figure 1. Fig 4, Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruze S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011 Nov 10;29(32):4294-301. (A) Observed and projected incidence rates and bootstrap 95% CIs (ages 30 to 84 years) for oropharyngeal cancers overall (solid squares), oropharyngeal cancers among men (solid circles), oropharyngeal cancers among women (open circles), and cervical cancers (open squares). (B) Projected annual number of patients (ages 30 to 84 years) of oropharyngeal cancers overall, oropharyngeal cancers among men, oropharyngeal cancers among women,

and cervical cancers through the year 2030. (C) Observed and projected incidence rates for oropharyngeal (solid squares), oral cavity (open squares), larynx (solid circles), and other pharynx (open circles) cancers. (D) Projected annual number of patients with oropharyngeal, oral cavity, laryngeal, and other pharynx cancers through the year 2030. Observed incidence rates during 1973 to 2007 from nine registries within the Surveillance, Epidemiology, and End Results (SEER) program were used in age-period-cohort models to project expected incidence through the year 2030. Projected incidence rates were applied to the 2008 US population projections to calculate the annual number of patients. Oropharyngeal cancers included base of tongue (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3] topography code C019), lingual tonsil (C024), soft palate not otherwise specified (NOS; C051), uvula (C052), tonsil (C090-099), oropharynx (C100-109), and Waldeyer ring (C142). Oral cavity cancers included lip (C000-009), oral tongue (C020-23, C028, and C029), gum (C030-039), floor of mouth (C040-049), hard palate (C051, C058, and C059), and other and unspecified parts of the mouth (C060-069). Laryngeal cancers included glottis (C320), supraglottis (C321), subglottis (C322), laryngeal cartilage (C323), overlapping lesion of larynx (C328), and larynx NOS (C329). Other pharynx cancers included nasopharynx (C110-119), pyriform sinus (C129), postcricoid region (C130), hypopharynx (C130-139), and pharynx NOS (C140 and C148). Oropharyngeal cancers included both HPV-related and HPV-unrelated (soft palate NOS and uvula) anatomic subsites because projections were conducted for all head and neck cancer sites. Oropharyngeal, oral cavity, laryngeal, and other pharynx cancers were restricted to squamous cell histologies (ICD-O-3 codes 8050-8076, 8078, 8083, 8084, and 8094). Cervical cancers (C530-539) included all histologic subtypes.