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Considerations in Human Papillomavirus–Associated Oropharyngeal Cancer Screening
A Review

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IMPORTANCE The incidence of human papillomavirus (HPV)–positive oropharyngeal cancer (OPC) is anticipated to rise over the next few decades until the effects of prophylactic vaccination are realized, which highlights the potential importance of secondary prevention. The objective of this review is to evaluate the evidence associated with screening for HPV-positive OPC.

OBSERVATIONS Evaluation of a potential clinical preventive screening service requires characterization of the disease burden, the at-risk target screening population, screening tests, treatment, and screening benefits and harms. The lifetime risk of OPC is 0.7% for men and 0.2% for women and is expected to increase. The disease burden of HPV-positive OPC is substantial; most patients undergo morbid multimodality treatment and incur high costs in the process. Middle-aged and older adult men with elevated number of lifetime vaginal or oral sex partners are at highest risk. Patients may benefit from early detection of the disease—the 4-year overall survival of patients with stage I HPV-positive OPC is 87%, a considerable portion of whom are eligible for less morbid single-modality therapy. However, available screening tests are insufficiently sensitive and specific considering the current HPV-positive OPC incidence rates in the most at-risk patients. Further, the benefits and harms of screening for HPV-positive OPC are unknown.

CONCLUSIONS AND RELEVANCE The current and projected future population-level burden of HPV-positive OPC supports further exploration of secondary preventive interventions. However, screening for HPV-positive OPC is not currently justified. Advances in biomarker discovery and improved characterization of (1) a highly at-risk, target screening population and (2) the benefits and harms of screening will be necessary. Large-scale clinical trials and rigorous evaluation of how to best implement this service into clinical practice will also be needed.

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The incidence of human papillomavirus (HPV)–associated oropharyngeal cancer (OPC) is rising with notable associated morbidity, mortality, and cost, yet current preventive interventions are inadequate. In the US, HPV-positive OPC has surpassed cervical cancer as the most common HPV-associated cancer, with more than 13 000 new diagnoses annually.[1] Treatment may result in substantial morbidity, including death,[2-4] and is costly; the economic burden of OPC in the US is estimated to be much greater than $300 million annually.[1,5] Despite current prophylactic vaccination efforts, the incidence of OPC is projected to double in middle-aged and older adult men over the next decade.[6] The absence of secondary prevention or screening for HPV-positive OPC represents a gap in care and a potential opportunity to reduce the burden of this disease.

This article will explore the evidence associated with screening for HPV-positive OPC. Mucosal types of HPV are typically sexually transmitted and are detected in 80% of US adults at some point in their lifetime.[7] The prevalence of high-risk oral HPV-16 infections—1 of 13 high-risk types of HPV—is 1.8% in men and 0.3% in women.[8] Because approximately 82% of HPV-positive OPC is attributable to HPV-16,[9] the US Preventive Services Task Force (USPSTF) announced in 2014 that "future assessment of…the health effect of screening persons who are [oral] HPV-16–positive" may be warranted.[10] However, to our knowledge, there is only 1 ongoing clinical trial (ClinicalTrials.gov Identifier: NCT02897427) evaluating the secondary prevention of HPV-positive OPC—a single-institution trial evaluating a blood-based HPV-16 antibody test in men aged 50 to 64 years.

The objective of this narrative review is to evaluate considerations in screening for HPV-positive OPC in the context of the methods applied by the USPSTF.[11,12] We will use the 8 key questions identified in the USPSTF analytic framework (**Box**; **Figure 1**) to assess the effectiveness and safety of the potential preventive service.[11,12] Following this, we will discuss HPV vaccination, which provides an important backdrop for secondary prevention of HPV-positive OPC.

Box. US Preventive Services Task Force Key Questions for Evaluating a Potential Clinical Preventive Screening Service

1. Is there direct evidence that screening reduces morbidity and/or mortality?
2. What is the prevalence of disease in the target group? Can a high-risk group be reliably identified?
3. Can the screening test accurately detect the target condition?
   A. What is the sensitivity and specificity of the test?
   B. Is there significant variation among examiners in how the test is performed?
   C. In actual screening programs, how much earlier are patients identified and treated?
4. Does treatment reduce the incidence of the intermediate outcome?
   A. Does treatment work in ideal, clinical trial conditions?
   B. How do the efficacy and effectiveness of treatments compare in the community settings?
5. Does treatment improve health outcomes for people diagnosed clinically?
   A. How similar are people diagnosed clinically to those diagnosed by screening?
   B. Are there reasons to expect people diagnosed by screening to have even better health outcomes than those diagnosed clinically?
6. Is the intermediate outcome reliably associated with reduced morbidity and/or mortality?
7. Does screening result in adverse effects?
   A. Is the test acceptable to patients?
   B. What are the potential harms, and how often do they occur?
8. Does treatment result in adverse effects?

Discussion

Key Question No. 1: Is There Direct Evidence That Screening Reduces Morbidity and/or Mortality?

To our knowledge, no studies have been performed in which a population at risk for HPV-positive OPC was randomized to screening vs no screening and health outcomes were evaluated. Therefore, there is currently no direct evidence that screening reduces morbidity and/or mortality.

Key Question No. 2: What Is the Prevalence of the Disease in the Target Group? Can a High-risk Group Be Reliably Identified?

Given the limitations of available candidate screening tests, an ideal target group has not been identified. Hence, the prevalence of disease in this group is unknown. Whether an ideal high-risk group can be reliably identified is also currently unknown.

Overview

Patients with HPV-positive OPC often exhibit characteristic sociodemographic and behavioral exposures. However, given the absence of population-based HPV-positive OPC data collectively describing age, sex, sexual history, and tobacco use, disease prevalence in an ideal target group is unknown. Indeed, best estimates account for only 2 risk factors: age and sex. Using modeling techniques combining institutional and population-based case and control data, Tota et al[13] creatively developed a risk-prediction model for incident OPC that incorporated age, sex, race/ethnicity, history (pack-years) of smoking, alcohol use, lifetime number of sex partners, and high-risk HPV status as determined by oral rinse and gargle testing. In the validation cohort, patients in the highest risk decile accounted for 62% and 100% of all incident OPCs and HPV-positive OPCs, respectively.[13] Large-scale, multi-institutional, retrospective case-control studies will be needed to further validate this model or independently define an ideal target group. Here, we briefly summarize cohort and case-control studies that have evaluated specific sociodemographic and behavioral risk factors for HPV-positive OPC.

Sex

Worldwide, HPV accounts for 9% of cancers in women and less than 1% of cancers in men, which reflects the high incidence of cervical cancer in developing countries.[14] Conversely, in the US in 2015, the incidence of OPC (18 917 cases) and HPV-positive OPC (approximately 13 320 cases) eclipsed the incidence of cervical carcinoma (11 788 cases).[1] Among women and men, the incidence rate of OPC is 1.7 and 8.0 per 100 000 person-years, respectively.[15]

Age

Among 14 805 patients with HPV-positive OPC in the US, the mean age at presentation was 58.4 years.[16] Approximately 41% of individuals with HPV-positive OPC are diagnosed between ages 55 and 64 years.[17] According to 1992 to 2015 Surveillance, Epidemiology, and End Results data,[18] OPC incidence rates per 100 000 person-years were highest (36.0-37.0) among white men aged 55 to 74 years (**Figure 2**). For perspective, the 2012 to 2016 US incidence rates in men of all ages were 44.4 per 100 000 person-years for colon and rectum cancer, 69.1 per 100 000 person-years for lung and bronchus cancer, and 104.1 per 100 000 person-years for prostate cancer.[19]

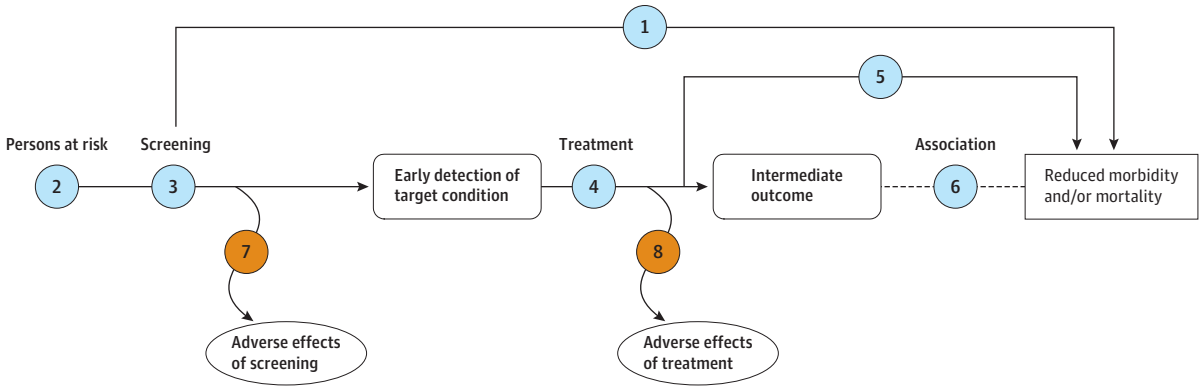
Sexual Behavior

Human papillomavirus–positive OPC, like oral oncogenic HPV infection,[20] has been strongly linked to sexual behavior. A case-control study[21] of 92 patients with HPV-16–positive head and neck cancer and 184 control participants demonstrated that patients with HPV-16–positive head and neck cancer had higher odds of having 11 or more lifetime vaginal sex partners (odds ratio [OR], 6.4; 95% CI, 1.9-22.0) and 6 or more lifetime oral sex partners (OR, 4.3; 95% CI, 1.4-14.0) after adjusting for race/ethnicity and tobacco, alcohol, and marijuana use. Other case-control and case-case studies have confirmed associations of higher lifetime number of vaginal and oral sex partners with OPC.[22-25]

Tobacco Use and Other Risk Factors

Population-based National Health and Nutrition Examination Survey data have clearly demonstrated an association of tobacco use with increased prevalence of oral oncogenic HPV infection.[8,20] Further, tobacco use portends a worse prognosis among patients with HPV-positive OPC.[26] Despite this, there is limited evidence that tobacco use is a risk factor for the development of HPV-positive OPC.[21,27-31] A 2016 population-based cohort modeling study[32] estimated that current smokers (relative risk, 2.26; 95% CI, 1.60-3.21) and former smokers (relative risk, 1.38; 95% CI, 1.02-1.85) exhibited a significantly higher risk of HPV-positive OPC compared with

Figure 1. US Preventive Services Task Force Analytic Framework for Evaluating a Potential Clinical Preventive Screening Service



This generic analytic framework is used by the US Preventive Services Task Force to evaluate potential topics in screening. The numbers refer to the key questions listed in the Box.

Reprinted from US Preventive Services Task Force.[11]

never smokers. Associations of HPV-positive OPC with various other sociodemographic and behavioral variables, including race/ethnicity, alcohol use, and marijuana use, have not been firmly established.[21,22,33,34]

Key Question No. 3: Can the Screening Test Accurately Detect the Target Condition?

Overview

A screening test that accurately detects HPV-positive OPC has not been developed. There are several candidate screening tests for HPV-positive OPC that collectively exhibit important limitations—inadequate test specificity (owing to insufficient differentiation among prevalent infection, cleared infection, and malignant neoplasm) and inability to localize or lateralize (ie, determine the side of) the malignant neoplasm. Advances in screening test discovery and validation and improved understanding of the natural history of oral oncogenic HPV infections will be needed to develop a screening program for HPV-positive OPC.

Specific Background

Human papillomaviruses, which belong to the Papillomaviridae family, contain a circular, double-stranded, 7000- to 8000–base-pair DNA genome. This encodes for viral capsid proteins (late proteins L1 and L2), regulatory proteins (early proteins E1, E2, and E4), and oncoproteins (E5, E6, and E7).[35] The L1 protein self-assembles into viruslike particles, which are the basis for prophylactic HPV vaccines. Virus types of the *Alphapapillomavirus* genus primarily infect the mucosa, and a portion (13) of these are oncogenic (α-HPV species 5 type 51; α-HPV species 6 types 56 and 66; α-HPV species 7 types 18, 39, 45, and 59; α-HPV species 9 types 16, 31, 33, 35, 52, and 58).[35] Transmission of HPV is thought to occur through direct skin/mucosa-to-skin/mucosa contact, primarily via sexual contact, although nonsexual routes have been described.[35,36] Worldwide, HPV-16 accounts for 82% of all HPV-associated head and neck squamous cell carcinomas.[9] In the US, HPV-16 and HPV-18 together are responsible for 86% of HPV-positive OPCs.[37] Types 31, 33, 45, 52, and 58 account for 8% of HPV-positive OPCs, and other oncogenic HPV types account for the remaining 6% of HPV-positive OPCs.[37]

Current candidate screening assays and the relevant epidemiologic characteristics of HPV infections are discussed below.

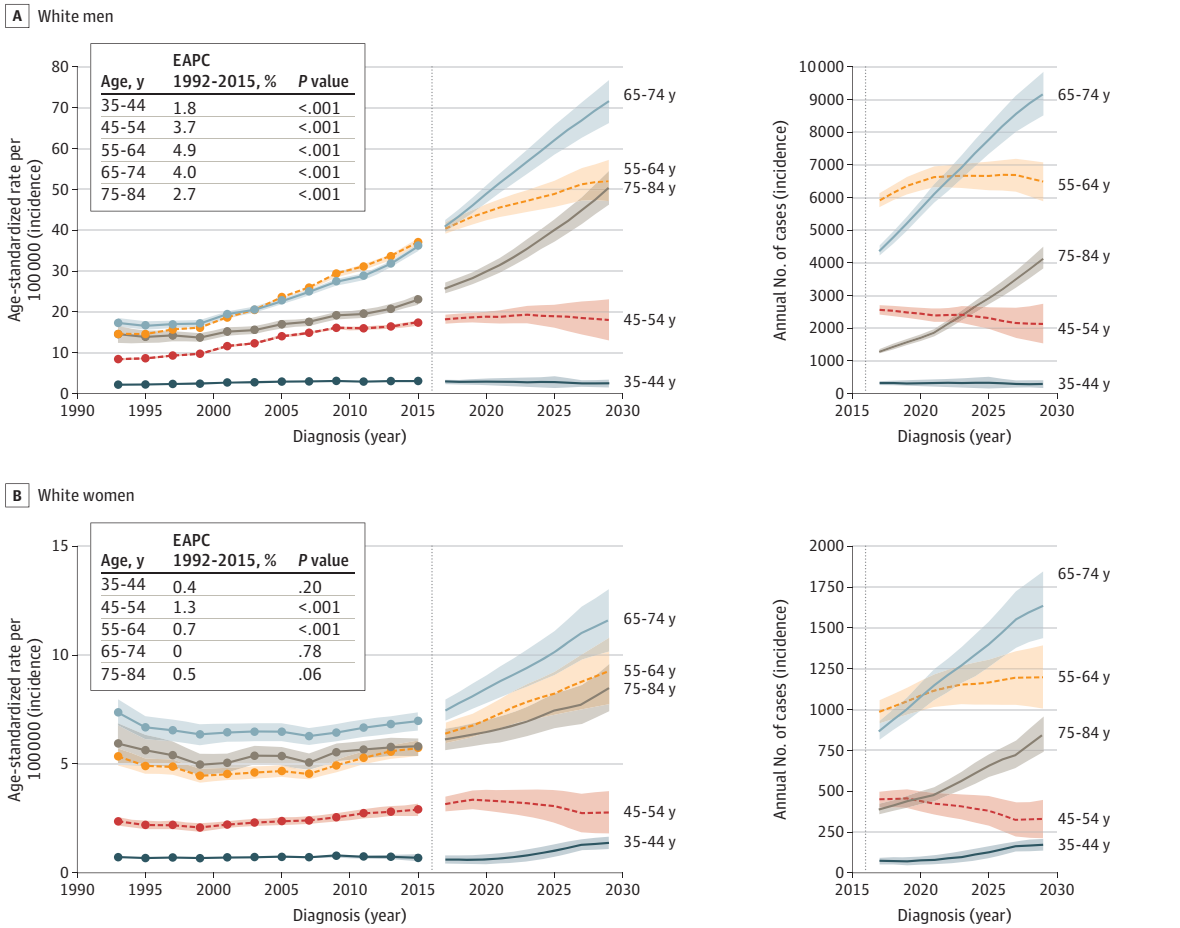
Candidate Screening Tests

Testing of Oral Rinse and Gargle Specimens to Detect Oral/Oropharyngeal HPV DNA Infection | In the US, oral and oral oncogenic HPV infection prevalence rates are 12% and 7%, respectively, in men and 3% and 1% in women.[38] According to the HPV Infection in Men study[39] among 1626 men, the annual incidence rates of oral HPV, oral oncogenic HPV, and oral HPV-16 infections are 4.4%, 1.7%, and 0.6%, respectively. The median duration of infection for all HPV types was 6.9 months.[39] Data describing the clearance of prevalent infections are more limited.[39-41]

According to a 2018 meta-analysis,[42] oral HPV-16 detection via oral rinse and gargle or swab testing was 72% sensitive (95% CI, 45-89) and 92% specific (95% CI, 82-97) for HPV-positive head and neck squamous cell carcinoma. A nested case-control study using pooled Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial cohort and American Cancer Society Cancer Prevention Study II Nutrition Cohort data[43] demonstrated for the first time that oral HPV infection may precede diagnosis of OPC; patients with oral HPV-16 DNA exhibited 22-fold (95% CI, 2-277) greater odds of developing OPC. However, given the high prevalence rates of oral oncogenic HPV infections relative to HPV-positive OPCs, the positive predictive value of the test in the context of screening is very low.

Testing of Oropharyngeal Cytologic Specimens Collected via Brush Biopsy to Detect Cellular Atypia | A 2015 single-institution case study[44] reported that intraoperative brush cytologic results identified dysplastic cells in 43 of 49 patients (88%) with OPC, 27 of 41 (66%) of whom exhibited HPV-positive OPC. In another study of HIV-positive patients without squamous cell carcinoma,[45] cytologic results were similar for those with detectable oral HPV-16 DNA (6 of 126) and without oral HPV-16 DNA (6 of 70) (OR, 1.9; 95% CI, 0.5-7.3). Given the paucity of detectable premalignant or malignant changes in patients with known oral HPV-16 DNA, to our knowledge, this study was the first to question the potential efficacy of oropharyngeal brush cytologic testing, or a Papanicolaou test equiva-

Figure 2. Recent and Projected Rates of Oropharyngeal Cancer Among White Men and Women According to Age Group Using Surveillance, Epidemiology, and End Results Data



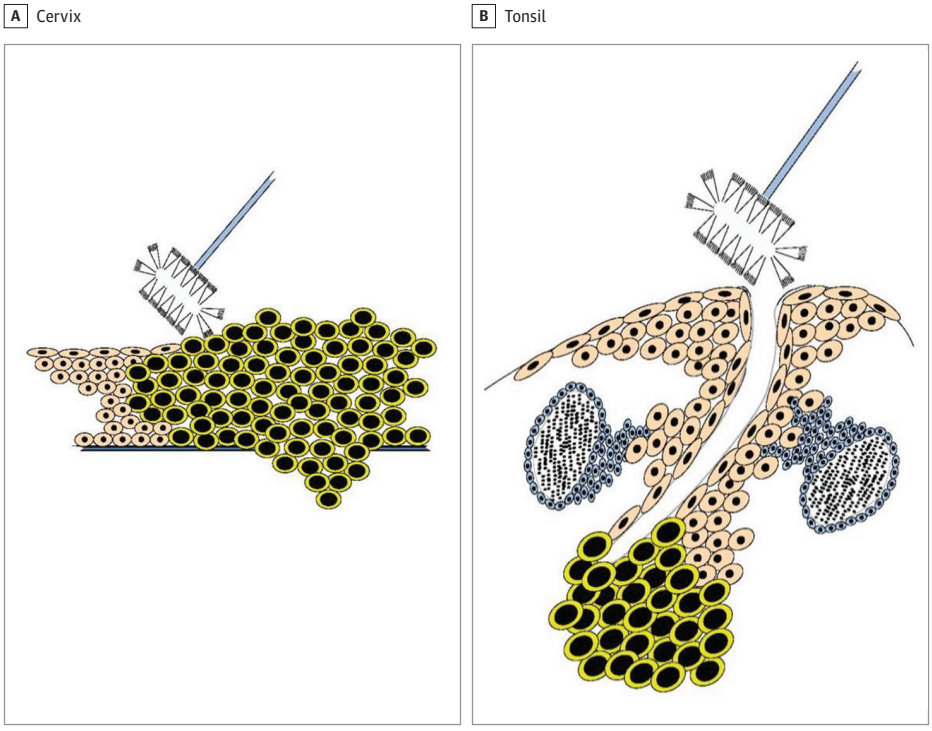
Surveillance, Epidemiology, and End Results data from 18 registries tracked from 1992 to 2015. Log-linear joinpoint regression and age-period-cohort models were used to evaluate trends and forecast the burden of oropharyngeal cancers (OPCs) through 2029 by projecting cohort-specific, age-specific incidence rates in non-Hispanic white men and women in the US. Incidence of OPCs increased significantly among men of all ages and women aged 45 to 64 years. The incidence and number of OPCs are projected to increase among older white men and women. EAPC indicates estimated annual percent change. Reprinted with permission from Tota et al.[13]

lent, in screening for OPC.[45] It was posited that this was because of the brush's inability to access the tonsillar crypts—the presumed location of early tumor origin (**Figure 3**).[46]

Testing of Blood Specimens to Detect HPV-16 E Antibodies | Strong associations of HPV-16 E6 seropositivity with OPC have been demonstrated in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort (OR, 274; 95% CI, 110-681),[47] the PLCO Cancer Screening Trial cohort (OR, 140; 95% CI, 40-491),[48] and the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) case-control study (OR, 132; 95% CI, 65-267).[49] Indeed, HPV-16 E6 antibodies were present in 35%, 42%, and 30% of patients with OPC in each study, respectively, and in 1% of control patients.[47-49] In the EPIC cohort, 23% and 44% of patients with blood samples collected less than 2 years and 2 to 5 years prior to OPC diagnosis, respectively, were HPV-16 E6 seropositive, and 1 patient was seropositive 13.7 years prior to OPC diagnosis.[47] However, these studies were limited by absent or limited stratification of OPC according to p16-positive or HPV-positive status and thus underestimated the true significance of the association. Of note, p16 protein is "markedly overexpressed in tumor cells with transcriptionally active [high-risk] HPV" and is therefore "an excellent surrogate marker of viral infection in the correct context."[50]

In a 2017 case-control study of 348 patients with p16-positive OPC and 782 healthy age-matched and sex-matched control participants,[51] patients with a positive HPV-16 E antibody panel test (83% sensitive; 99% specific) exhibited 453-fold (95% CI, 199-1030) greater odds of p16-positive OPC compared with patients without p16-positive OPC after adjusting for smoking and alcohol status. Validation of the assay in the Janus Serum Bank cohort in Norway (39 patients with HPV-16–positive OPC and 460 matched controls) using serum samples collected up to 15 years prior to diagnosis revealed lower test sensitivity of 21% and stable specificity of 99%.[52] However, even if we were to screen highly at-risk patients (at a generous incidence rate of 20 HPV-16–positive OPCs per 100 000 middle-aged or older adult men per year) using a hypo-

Figure 3. Collection of Squamous Cells at Oropharyngeal and Cervical Sites



A, The Cytobrush (CooperSurgical) is able to obtain an adequate and representative collection of atypical or cancer cells from a relatively flat and uniform cervical mucosa. B, The Cytobrush has difficulty in obtaining an adequate and representative sample of dysplastic or malignant tonsillar mucosa, particularly when these lesions are lurking deep within a tonsillar crypt (running diagonally from top of tonsil to lower left), which would not be sampled using a conventional Cytobrush. The large, oval structures to the left or right of the crypt are lymphoid follicles, with lymphoid cells (blue) emanating from them. Reprinted with permission from Lingen et al.[46]

thetical 100% sensitive, 99.5% specific HPV-16 test, the positive predictive value would be 3.8% and the number needed to screen would be 5000 to identify 1 person with HPV-16–positive OPC.[6] Further, other studies have reported the number needed to screen to prevent 1 cancer-related death as 1140 in cervical cancer, 588 to 1000 in colorectal cancer, and 543 to 3125 in breast cancer.[53]

Hence, at this time, HPV-16 antibody testing appears insufficiently specific as a screening assay if used in isolation. Further, because HPV-16 seropositivity does not localize or even lateralize the site of disease, screening of HPV-16–seropositive patients would require evaluation of the oropharynx, genitals, and anus.

Testing of Blood Specimens to Detect Circulating HPV DNA | A case-case study of 27 patients with HPV-16 DNA-negative OPC and 114 patients with HPV-16 DNA-positive OPC[54] demonstrated that pretreatment serum HPV-16 E6 and/or E7 DNA (detected using real-time polymerase chain reaction) testing was 61% sensitive and 68% specific for HPV-16 DNA-positive OPC. More recent single-institution data using a digital droplet polymerase chain reaction assay to detect plasma-circulating HPV DNA types 16, 18, 31, 33, and 35 exhibited 88% sensitivity among patients with p16-positive OPC (51 of 58).[55]

Other Tests | Discussion of the myriad other candidate screening modalities for HPV-positive OPC is beyond the scope of this review. These include other biomarkers (eg, DNA methylation, messenger RNA, microRNA, and protein signatures)[56,57] and imaging to identify the primary tumor or evidence of nodal metastases (eg, transcervical oropharyngeal or neck ultrasonography).[58]

Key Question No. 4: Does Treatment Reduce the Incidence of the Intermediate Outcome?

Treatments for candidate intermediate outcomes, such as oral oncogenic HPV infection, HPV-16 E6 antibody seropositivity, and circulating oncogenic HPV DNA, are in development and not clinically available (see the Therapeutic Vaccination section). Furthermore, to our knowledge, a precancerous state—another potential intermediate outcome—has not been identified to date for HPV-positive OPC. Human papillomavirus–associated cervical cancer is characterized by progression from cervical infection to intraepithelial neoplasia or from precancer to invasive carcinoma. Conversely, the porous nature of the oropharyngeal basement membrane may facilitate rapid progression of infection to invasive cancer.

Key Question No. 5: Does Treatment Improve Health Outcomes for People Diagnosed Clinically?

Yes, treatment reduces mortality in patients with clinically diagnosed HPV-positive OPC; however, the adverse effects of treatment on health outcomes are considerable, as discussed in key question No. 8. Traditional treatment options include primary surgery, adjuvant radiotherapy, and/or chemotherapy or definitive radiotherapy and/or chemotherapy. Prognosis is favorable compared with HPV-negative OPC,[59] which is reflected in the creation in 2017 of a unique American Joint Committee on Cancer staging system for HPV-positive OPC.[60] An estimated 64% of patients in the US present with stage I disease, which has 4-year overall survival rates of 87%.[17] Four-year overall survival progressively decreases for patients with stage II (77%), stage III (63%), and stage IV (21%) HPV-positive OPC.[17]

We do not know whether people diagnosed by screening would have better health outcomes than those diagnosed clinically. Conceivably, screening might identify a greater proportion of patients with early-stage disease compared with usual care. Because 84% of patients present with regional metastases (N+ disease) at diagnosis, 87% of all patients with HPV-positive OPC undergoing curative treatment require morbid bimodality therapy and 25% receive trimodality therapy.[17] Up to 20% of patients with stage I disease require only single-modality therapy—surgery alone or radiotherapy alone.[17] Therefore, screening may be effective if it detected a greater proportion of patients with early stage I HPV-positive OPC amenable to single-modality therapy or other de-escalation therapies. Large-scale, prospective clinical trial data will be needed to define the stage distribution of screened patients with newly diagnosed HPV-positive OPC.

Key Question No. 6: Is the Intermediate Outcome Reliably Associated With Reduced Morbidity and/or Mortality?

As discussed previously in key question No. 4, treatments for candidate intermediate outcomes (eg, oral oncogenic HPV infection, HPV-16 E6 antibody seropositivity, circulating oncogenic HPV DNA) are in development and not clinically available. A precancerous state, another potential intermediate outcome, has not yet been identified for HPV-positive OPC.

Key Question No. 7: Does Screening Result in Adverse Effects?

Because of the lack of prospective randomized clinical trial data, the discrete harms of screening for HPV-positive OPC are unknown. The moderate harms of screening for cervical cancer,[61] a sister disease, may provide some insight into the potential harms of screening for HPV-positive OPC. These include psychological harms, frequent follow-up testing, invasive diagnostic procedures, overdiagnosis, unnecessary treatment of patients with false-positive results, and potential treatment of patients with lesions that may regress on their own.[61]

Key Question No. 8: Does Treatment Result in Adverse Effects?

Treatment of clinically detected disease results in substantial adverse effects. Whether treatment of disease detected by screening reduces these effects is unknown.

Overview

Most patients with HPV-positive OPC will require multimodality therapy, which is both morbid and costly. As previously described, if a screened population exhibits a greater proportion of early-stage disease amenable to treatment de-escalation, a screened population may experience reduced adverse effects.

Toxic Effects of Treatment

According to Radiation Therapy Oncology Group 1016 trial data,[62] among 398 patients with HPV-positive OPC receiving treatment with concurrent intensity-modulated radiotherapy plus cisplatin, 325 patients (81.7%) experienced at least 1 grade 3 to 4 adverse event, 6 patients (1.5%) died owing to treatment, 243 of 395 patients (61.5%) were gastrostomy tube dependent at the end of treatment, and 34 of 368 patients (9.2%) were gastrostomy tube dependent 1 year after treatment. Prospectively collected single-institution data identified a 7% five-year prevalence rate of mandibular osteoradionecrosis among 1196 patients with OPC undergoing intensity-modulated radiotherapy with or without chemotherapy.[63] According to recent systematic reviews of transoral surgical management of OPC, the prevalence rates of adverse events and ostomy dependence were as follows: postoperative hemorrhage, 0% to 13%; percutaneous gastrostomy tube dependence, 20% to 39%; and tracheostomy, 0% to 31%.[2,3] Favorable survival rates in the setting of marked toxic effects of treatment have prompted a shift toward the evaluation of treatment de-escalation, as evidenced by the recent proliferation of surgical (eg, Eastern Cooperative Oncology Group 3311, PATHOS, ADEPT) and nonsurgical (eg, Radiation Therapy Oncology Group 1016,[62] NRG HN002) de-escalation trials.[64] Therefore, it is expected that treatment toxic effect profiles for patients with HPV-positive OPC may modestly improve over time.

Quality of Life and Patient Preference

Quality of life is also compromised by OPC and its treatment. Many patients with HPV-positive OPC report minimal symptoms at diagnosis. Among 71 patients with primary HPV-positive OPC at 1 institution, 36 patients (51%) reported a neck mass; 20 patients (28%) reported a sore throat; less than 10% reported globus sensation, otalgia, nonspecific pain, or voice change; and 1% reported bleeding, weight loss, or fatigue.[65] According to meta-analytic data of patient-reported outcomes compared with normative references, patients who received OPC treatment at least 12 months prior reported clinically significant deterioration in physical function, fatigue, appetite loss, appearance, activity, recreation, dysphagia, chewing, speech, shoulder, taste, and saliva quality-of-life domains.[66] Patient preference studies also reflect the negative effect of treatment. In a study of 51 patients with OPC surveyed a median of 1 year after treatment,[67] 25 patients (49%) would have chosen a 5% decrease in cure rate to avoid chemotherapy.

Cost

Using 2004 to 2007 OPC incidence data (n = 11 242), Chesson et al[5] estimated the economic burden of OPC was $306 million (range, $113 million to $516 million) (in 2010 US dollars). Since this time, the incidence of OPC has risen approximately 70%, incurring an estimated $515 million in treatment costs alone.[15] Escalating treatment costs of single-modality, bimodality, and trimodality therapy are reported in bi-institutional data from 2009 to 2010.[68] The mean reported reimbursements for 3-month episodes of OPC treatment according to private vs government payer status were $37 435 vs $15 664 for transoral surgery alone, $74 484 vs $34 343 for transoral surgery plus adjuvant radiotherapy, $191 780 vs $53 245 for transoral surgery plus adjuvant chemoradiation therapy, and $198 285 vs $57 429 for definitive chemoradiation therapy.[68]

Other Screening Considerations—HPV Vaccination

Prophylactic Vaccination

Gardasil-9 (Merck & Co) is a commercially available prophylactic HPV vaccine that comprises recombinant HPV L1 major capsid proteins of 9 HPV strains.[69] It promotes the production of antibodies that bind to viral particles and block entry into host cells but does not eliminate preexisting infections because HPV-infected basal epithelial cells do not express L1 capsid proteins.[70] While HPV vaccina-

tion prevents 93% of oral HPV infections,[71] full series uptake is less than 50% in US adolescents.[72] Moreover, HPV-positive OPC presents in older individuals (median age, 58 years),[16] but until 2018, the HPV vaccine had only been approved by the US Food and Drug Administration for patients 26 years or younger. These restrictions were based on presumptions that oral HPV infection latency may last decades, infection-to-cancer progression is prolonged, and vaccination of patients older than 26 years with potential prior exposure or prevalent infections was unlikely to be cost-effective. Although expansion of the indications for prophylactic HPV vaccination to adults aged 27 to 45 years may help prevent new infections in previously unexposed patients, patients with prevalent high-risk HPV infections will likely not receive benefit.

Therapeutic Vaccination

Therapeutic HPV vaccination is a nascent field of study that aims to eliminate preexisting HPV infections and HPV-associated cancers in patients via a T-cell–mediated immune response.[73] There are a wide variety of vaccine types in phase 1 through phase 3 clinical trials.[70,74] Many therapeutic HPV vaccines being developed present E6 and/or E7 DNA-based, RNA-based, peptide-based, or protein-based antigens of HPV-16 or HPV-18.[70,74] Some therapeutic HPV vaccines use bacterial or viral vectors to improve immunogenicity, whereas others are delivered in combination with other therapies. These vaccines are being tested for (1) HPV-16/HPV-18 infection alone or precancer (ie, ProCervix [Genticel] plus topical imiquimod cream in a phase 2 trial) and (2) HPV-positive OPC and cervical cancer treatment (ie, ADXS11-001 and MEDI0457 in phase 2 and 3 trials).[73] According to a 2018 systematic review,[74] while preliminary data demonstrate that therapeutic HPV vaccines collectively exhibit minimal toxic effects and were immunogenic in 25 of 34 patients (74%), clinical outcome data are lacking to date.

Conclusions

Because prophylactic vaccination is not expected to curb the HPV-positive OPC epidemic for decades, novel preventive interventions are needed. Further evaluation of screening for HPV-positive OPC is warranted given the substantial disease burden, potential for early treatment benefit, and early progress in biomarker development. However, advances in secondary prevention are profoundly impeded by the lack of a clear target screening population at high risk for HPV-positive OPC, sufficiently valid screening tests or other technologies capable of detecting early OPC, and prospective trial data that evaluate the benefits and harms of screening.

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Study concept and design: Day, Fakhry, Sturgis.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Day, Fakhry.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Day, Sturgis.
Administrative, technical, or material support: Sturgis.
Study supervision: Fakhry, Sturgis.

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REFERENCES

1. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers—United States, 1999-2015. *MMWR Morb Mortal Wkly Rep*. 2018;67(33):918-924. doi:10.15585/mmwr.mm6733a2

2. Hutcheson KA, Holsinger FC, Kupferman ME, Lewin JS. Functional outcomes after TORS for oropharyngeal cancer: a systematic review. *Eur Arch Otorhinolaryngol*. 2015;272(2):463-471. doi:10.1007/s00405-014-2985-7

3. de Almeida JR, Byrd JK, Wu R, et al. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. *Laryngoscope*. 2014;124(9):2096-2102. doi:10.1002/lary.24712

4. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol*. 2014;32(34):3858-3866. doi:10.1200/JCO.2014.55.3925

5. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine*. 2012;30(42):6016-6019. doi:10.1016/j.vaccine.2012.07.056

6. Kreimer AR, Shiels MS, Fakhry C, et al. Screening for human papillomavirus-driven oropharyngeal cancer: considerations for feasibility and strategies for research. *Cancer*. 2018;124(9):1859-1866. doi:10.1002/cncr.31256

7. Centers for Disease Control & Prevention. Human papillomavirus (HPV): reasons to get vaccinated. Accessed March 30, 2019. https://www.cdc.gov/hpv/parents/vaccine/six-reasons.html

8. Sonawane K, Suk R, Chiao EY, et al. Oral human papillomavirus infection: differences in prevalence between sexes and concordance with genital human papillomavirus infection, NHANES 2011 to 2014. *Ann Intern Med*. 2017;167(10):714-724. doi:10.7326/M17-1363

9. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. *Lancet Oncol*. 2014;15(12):1319-1331. doi:10.1016/S1470-2045(14)70471-1

10. Moyer VA; US Preventive Services Task Force. Screening for oral cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(1):55-60. doi:10.7326/M13-2568

11. US Preventive Services Task Force. Procedure manual. Accessed January 15, 2020. https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual

12. Harris RP, Helfand M, Woolf SH, et al; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3, suppl 1):21-35. doi:10.1016/S0749-3797(01)00261-6

13. Tota JE, Gillison ML, Katki HA, et al. Development and validation of an individualized risk prediction model for oropharynx cancer in the US population. *Cancer*. 2019;125(24):4407-4416. doi:10.1002/cncr.32412

14. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664-670. doi:10.1002/ijc.30716

15. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2010-2014 [US Cancer Statistics Data Brief No. 1]. Accessed January 15, 2020. https://www.cdc.gov/cancer/uscs/about/data-briefs/no1-hpv-assoc-cancers-UnitedStates-2010-2014.htm

16. Liederbach E, Kyrillos A, Wang CH, Liu JC, Sturgis EM, Bhayani MK. The national landscape of human papillomavirus-associated oropharynx squamous cell carcinoma. *Int J Cancer*. 2017;140(3):504-512. doi:10.1002/ijc.30442

17. Cramer JD, Hicks KE, Rademaker AW, Patel UA, Samant S. Validation of the eighth edition American Joint Committee on Cancer staging system for human papillomavirus-associated oropharyngeal

cancer. *Head Neck*. 2018;40(3):457-466. doi:10.1002/hed.24974

18. Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK. Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. *J Clin Oncol*. 2019;37(18):1538-1546. doi:10.1200/JCO.19.00370

19. US Cancer Statistics Working Group. Leading cancer cases and deaths, male and female, 2016. Accessed April 3, 2020. https://www.cdc.gov/cancer/dataviz

20. Chaturvedi AK, Graubard BI, Broutian T, et al. NHANES 2009-2012 findings: association of sexual behaviors with higher prevalence of oral oncogenic human papillomavirus infections in US men. *Cancer Res*. 2015;75(12):2468-2477. doi:10.1158/0008-5472.CAN-14-2843

21. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst*. 2008;100(6):407-420. doi:10.1093/jnci/djn025

22. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956. doi:10.1056/NEJMoa065497

23. Dahlstrom KR, Li G, Tortolero-Luna G, Wei Q, Sturgis EM. Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites. *Head Neck*. 2011;33(6):847-855. doi:10.1002/hed.21550

24. Schnelle C, Whiteman DC, Porceddu SV, Panizza BJ, Antonsson A. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. *Int J Cancer*. 2017;140(5):1027-1034. doi:10.1002/ijc.30519

25. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol*. 2010;39(1):166-181. doi:10.1093/ije/dyp350

26. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. doi:10.1056/NEJMoa0912217

27. Applebaum KM, Furniss CS, Zeka A, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst*. 2007;99(23):1801-1810. doi:10.1093/jnci/djm233

28. Herrero R, Castellsagué X, Pawlita M, et al; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst*. 2003;95(23):1772-1783. doi:10.1093/jnci/djg107

29. Schwartz SM, Daling JR, Doody DR, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst*. 1998;90(21):1626-1636. doi:10.1093/jnci/90.21.1626

30. Smith EM, Ritchie JM, Summersgill KF, et al. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst*. 2004;96(6):449-455. doi:10.1093/jnci/djh074

31. Smith EM, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Tobacco and alcohol use increases the risk of both HPV-associated and HPV-independent head and neck cancers. *Cancer Causes Control*. 2010;21(9):1369-1378. doi:10.1007/s10552-010-9564-z

32. Chaturvedi AK, D'Souza G, Gillison ML, Katki HA. Burden of HPV-positive oropharynx cancers among ever and never smokers in the US population. *Oral Oncol*. 2016;60:61-67. doi:10.1016/j.oraloncology.2016.06.006

33. Fakhry C, Krapcho M, Eisele DW, D'Souza G. Head and neck squamous cell cancers in the United States are rare and the risk now is higher among white individuals compared with black individuals. *Cancer*. 2018;124(10):2125-2133. doi:10.1002/cncr.31322

34. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin*. 2012;62(2):118-128. doi:10.3322/caac.20141

35. International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*. 2007;90:1-636.

36. Liu Z, Nyitray AG, Hwang LY, et al. Human papillomavirus prevalence among 88 male virgins residing in Brazil, Mexico, and the United States. *J Infect Dis*. 2016;214(8):1188-1191. doi:10.1093/infdis/jiw353

37. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2011–2015 [US Cancer Statistics Data Brief No. 4]. Accessed February 5, 2020. https://www.cdc.gov/cancer/hpv/pdf/USCS-DataBrief-No4-August2018-508.pdf

38. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in adults aged 18-69: United States, 2011-2014. *NCHS Data Brief*. 2017;(280):1-8.

39. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. *Lancet*. 2013;382(9895):877-887. doi:10.1016/S0140-6736(13)60809-0

40. Pierce Campbell CM, Kreimer AR, Lin HY, et al. Long-term persistence of oral human papillomavirus type 16: the HPV Infection in Men (HIM) study. *Cancer Prev Res (Phila)*. 2015;8(3):190-196. doi:10.1158/1940-6207.CAPR-14-0296

41. Tam S, Fu S, Xu L, et al. The epidemiology of oral human papillomavirus infection in healthy populations: a systematic review and meta-analysis. *Oral Oncol*. 2018;82:91-99. doi:10.1016/j.oraloncology.2018.04.005

42. Gipson BJ, Robbins HA, Fakhry C, D'Souza G. Sensitivity and specificity of oral HPV detection for HPV-positive head and neck cancer. *Oral Oncol*. 2018;77:52-56. doi:10.1016/j.oraloncology.2017.12.008

43. Agalliu I, Gapstur S, Chen Z, et al. Associations of oral α-, β-, and γ-human papillomavirus types with risk of incident head and neck cancer. *JAMA Oncol*. 2016;2(5):599-606. doi:10.1001/jamaoncol.2015.5504

44. Broglie MA, Jochum W, Förbs D, Schönegg R, Stoeckli SJ. Brush cytology for the detection of high-risk HPV infection in oropharyngeal squamous cell carcinoma. *Cancer Cytopathol*. 2015;123(12):732-738. doi:10.1002/cncy.21606

45. Fakhry C, Rosenthal BT, Clark DP, Gillison ML. Associations between oral HPV16 infection and cytopathology: evaluation of an oropharyngeal "pap-test equivalent" in high-risk populations. *Cancer Prev Res (Phila)*. 2011;4(9):1378-1384. doi:10.1158/1940-6207.CAPR-11-0284

46. Lingen MW. Brush-based cytology screening in the tonsils and cervix: there is a difference! *Cancer Prev Res (Phila)*. 2011;4(9):1350-1352. doi:10.1158/1940-6207.CAPR-11-0373

47. Kreimer AR, Johansson M, Waterboer T, et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. *J Clin Oncol*. 2013;31(21):2708-2715. doi:10.1200/JCO.2012.47.2738

48. Kreimer AR, Johansson M, Yanik EL, et al. Kinetics of the human papillomavirus type 16 E6 antibody response prior to oropharyngeal cancer. *J Natl Cancer Inst*. 2017;109(8):djx005. doi:10.1093/jnci/djx005

49. Anantharaman D, Gheit T, Waterboer T, et al. Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. *J Natl Cancer Inst*. 2013;105(8):536-545. doi:10.1093/jnci/djt053

50. Lewis JS Jr, Beadle B, Bishop JA, et al. Human papillomavirus testing in head and neck carcinomas: guideline from the College of American Pathologists. *Arch Pathol Lab Med*. 2018;142(5):559-597. doi:10.5858/arpa.2017-0286-CP

51. Dahlstrom KR, Anderson KS, Field MS, et al. Diagnostic accuracy of serum antibodies to human papillomavirus type 16 early antigens in the detection of human papillomavirus-related oropharyngeal cancer. *Cancer*. 2017;123(24):4886-4894. doi:10.1002/cncr.30955

52. Anderson KS, Wallstrom G, Langseth H, et al. Pre-diagnostic dynamic HPV16 IgG seropositivity and risk of oropharyngeal cancer. *Oral Oncol*. 2017;73:132-137. doi:10.1016/j.oraloncology.2017.08.014

53. Gates TJ. Screening for cancer: evaluating the evidence. *Am Fam Physician*. 2001;63(3):513-522.

54. Dahlstrom KR, Li G, Hussey CS, et al. Circulating human papillomavirus DNA as a marker for disease extent and recurrence among patients with oropharyngeal cancer. *Cancer*. 2015;121(19):3455-3464. doi:10.1002/cncr.29538

55. Chera BS, Kumar S, Shen C, et al. Plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2018;102(5):1605-1606. doi:10.1016/j.ijrobp.2018.08.053

56. Boda D, Docea AO, Calina D, et al. Human papilloma virus: apprehending the link with carcinogenesis and unveiling new research avenues (review). *Int J Oncol*. 2018;52(3):637-655. doi:10.3892/ijo.2018.4256

57. Clarke MA, Wentzensen N. Strategies for screening and early detection of anal cancers: a narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers. *Cancer Cytopathol*. 2018;126(7):447-460. doi:10.1002/cncy.22018

58. Fakhry C, Agrawal N, Califano J, et al. The use of ultrasound in the search for the primary site of unknown primary head and neck squamous cell

cancers. *Oral Oncol*. 2014;50(7):640-645. doi:10.1016/j.oraloncology.2014.03.015

59. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2014;32(30):3365-3373. doi:10.1200/JCO.2014.55.1937

60. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(2):122-137. doi:10.3322/caac.21389

61. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686. doi:10.1001/jama.2018.10897

62. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393(10166):40-50. doi:10.1016/S0140-6736(18)32779-X

63. Caparrotti F, Huang SH, Lu L, et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. *Cancer*. 2017;123(19):3691-3700. doi:10.1002/cncr.30803

64. Fung N, Faraji F, Kang H, Fakhry C. The role of human papillomavirus on the prognosis and treatment of oropharyngeal carcinoma. *Cancer Metastasis Rev*. 2017;36(3):449-461. doi:10.1007/s10555-017-9686-9

65. McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2014;140(5):441-447. doi:10.1001/jamaoto.2014.141

66. Høxbroe Michaelsen S, Grønhøj C, Høxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: a systematic review and meta-analysis of 1366 patients. *Eur J Cancer*. 2017;78:91-102. doi:10.1016/j.ejca.2017.03.006

67. Brotherston DC, Poon I, Le T, et al. Patient preferences for oropharyngeal cancer treatment de-escalation. *Head Neck*. 2013;35(2):151-159. doi:10.1002/hed.22930

68. Moore EJ, Hinni ML, Olsen KD, Price DL, Laborde RR, Inman JC. Cost considerations in the treatment of oropharyngeal squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 2012;146(6):946-951. doi:10.1177/0194599812437534

69. Huh WK, Joura EA, Giuliano AR, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet*. 2017;390(10108):2143-2159. doi:10.1016/S0140-6736(17)31821-4

70. Hung CF, Ma B, Monie A, Tsen SW, Wu TC. Therapeutic human papillomavirus vaccines: current clinical trials and future directions. *Expert Opin Biol Ther*. 2008;8(4):421-439. doi:10.1517/14712598.8.4.421

71. Chaturvedi AK, Graubard BI, Broutian T, et al. Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States. *J Clin Oncol*. 2018;36(3):262-267. doi:10.1200/JCO.2017.75.0141

72. Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(33):909-917. doi:10.15585/mmwr.mm6733a1

73. Chabeda A, Yanez RJR, Lamprecht R, Meyers AE, Rybicki EP, Hitzeroth II. Therapeutic vaccines for high-risk HPV-associated diseases. *Papillomavirus Res*. 2018;5:46-58. doi:10.1016/j.pvr.2017.12.006

74. Schneider K, Grønhøj C, Hahn CH, von Buchwald C. Therapeutic human papillomavirus vaccines in head and neck cancer: a systematic review of current clinical trials. *Vaccine*. 2018;36(45):6594-6605. doi:10.1016/j.vaccine.2018.09.027