Head and Neck Cancer Screening

Current Status in Oral Cavity and Oropharyngeal Carcinomas

Hugh A.J. Kim, MD[a,1], Kristina Dahlstrom, PhD[d,1], Erich M. Sturgis, MD, MPH[b], Andrew Day, MD, MPH[c,2], Antoine Eskander, MD, ScM[a,2,*]

KEYWORDS

• Cancer screening • Oral cavity • Oropharynx • Human papillomavirus • Risk factors • Preventative care

KEY POINTS

- At present, the US Preventative Services Task Force does not recommend oral cavity or oropharyngeal cancer (OPC) screening in asymptomatic adults by primary care physicians.
- South and south-east Asians may represent a targetable population for oral cavity screening examinations given their proportionally higher prevalence of tobacco chewing.
- Otolaryngologists must be vigilant to identify human papillomavirus (HPV) + OPC, given the often-subtle signs and symptoms that precede a clinically detectable neck mass.
- HPV vaccination is the cornerstone of HPV-related cancer prevention, and otolaryngologists must support Center for Disease Control HPV vaccination recommendations.
- An HPV + OPC screening paradigm could screen high-risk subjects using biofluid-based biomarkers, followed by comprehensive head, neck, and anogenital examination, as well as imaging.

INTRODUCTION TO CANCER SCREENING

Cancer screening programs are used to identify asymptomatic individuals who have an occult premalignant or malignant disease. Two major objectives of a cancer

[a] Department of Otolaryngology–Head and Neck Surgery, University of Toronto, Canada; [b] Department of Otolaryngology–Head and Neck Surgery, Baylor College of Medicine, Houston, TX, USA; [c] Department of Otolaryngology–Head and Neck Surgery, UT Southwestern Medical Center; [d] Section of Epidemiology & Population Sciences–Medicine, Baylor College of Medicine, One Baylor Plaza, MS: 307, Houston, TX 77030, United States
[1] These authors contributed equally to this article, co-first authors.
[2] Indicates co-senior authors.
* Corresponding author.
E-mail address: Antoine.eskander@sunnybrook.ca

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Abbreviations	
HPV	human papillomavirus
USPSTF	United States Preventative Services Task Force
CDC	Center for Disease Control
HNC	head and neck cancer
OPC	oropharyngeal cancer
EBV	Ebstein-Barr Virus
NPC	nasopharyngeal carcinoma

screening program should be to detect disease at a pre-symptomatic stage with more effective treatment options, and to identify and modify risk factors for developing the disease.

To justify implementation of a cancer screening program, the disease should constitute an important public health issue associated with significant morbidity and mortality if not found in a detectable, asymptomatic stage. If premalignant disease is detected, effective treatment should be available to prevent progression. The screening test should be easy to use, minimally invasive, and yield valid, reproducible results. Sensitivity and specificity are intrinsic properties of a screening test that should be balanced. Highly sensitive tests limit missed cases, while highly specific tests limit false positives, which can cause distress and unnecessary procedures. Lastly for screening to be cost-effective, it should identify and target high-risk populations, using inexpensive, widely available tests and incorporating counseling on risk reduction (**Fig. 1**).[1]

INTRODUCTION TO SCREENING FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

Head and neck squamous cell carcinomas comprise multiple anatomic sites throughout the upper aerodigestive tract. Annually, there are 68,000 new diagnoses of head and neck squamous cell carcinomas in the United States, accounting for 4% of all cancers nationwide.[2] Human papillomavirus-mediated oropharyngeal cancer (HPV + OPC) constitutes ~15,000 of these cases, and most of the remaining cases are designated HPV-negative HNCs, which are largely caused by chemical carcinogens. Potential approaches to HNC screening vary according to HNC type. In this review, we first consider screening for HPV-negative HNCs and then consider screening for HPV + OPCs.

HUMAN PAPILLOMAVIRUS-NEGATIVE CANCER

Risk Factors

Several lifestyle factors are associated with HPV-negative HNC. Tobacco smoke and alcohol are associated with 70% to 80% of all new global cases (20% – 30% of oral cavity cancers), with a clear dose-response relationship with smoking intensity and duration.[3–5] Smokers have a tenfold increased risk compared to never-smokers. Alcohol independently doubles the risk in non-smokers, but only with high-frequency use.[4] Other oral cavity cancer risk factors include betel quid chewing, oral inflammatory disorders, and genetic syndromes.[3,6,7]

Oral Cavity Cancer

According to GLOBOCAN 2020 estimates by the International Agency for Research on Cancer, there were approximately 377,700 new global cases of lip and oral cavity cancer accounting for 177,800 deaths.[8] The survival rate for patients with early-stage oral

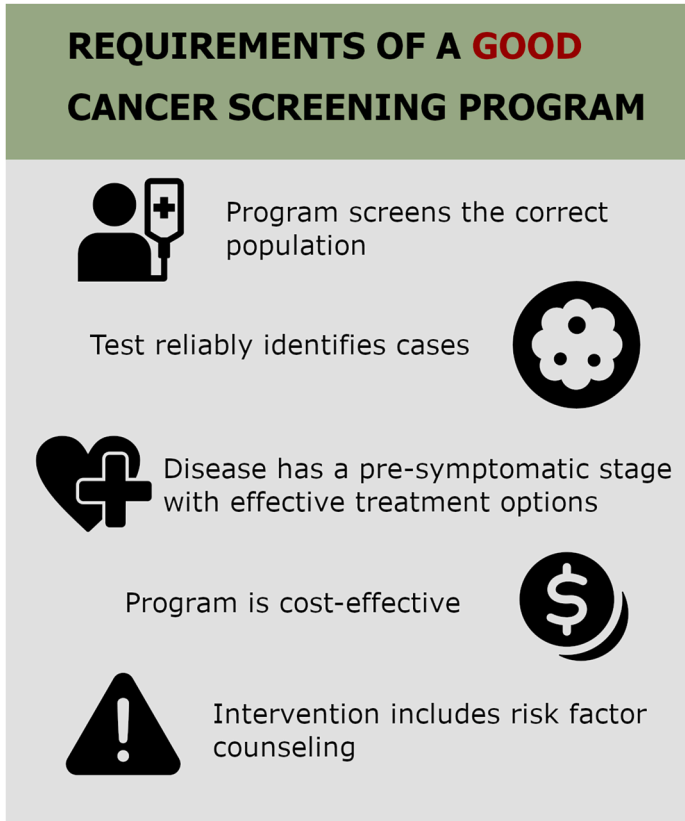

Fig. 1. Requirements of a good cancer screening program.

cavity cancer limited to the primary site is around 80%, but drops to 40% with late-stage metastases.[9] Therefore, early detection has the potential to reduce both mortality and treatment-related morbidity, which may impact speech and eating.[2] Primary surgery and primary radiation are first-line and second-line treatment options for oral cavity cancers, respectively. Stage I-II cancers may be eligible for primary surgery alone, whereas stage III or IV cancers generally require radical surgery followed by adjuvant radiation ± chemotherapy. Major ablative surgery may require reconstruction with free tissue transfer and lead to significant psychosocial and functional morbidity. Aesthetic outcomes can be varied, and possible functional outcomes include oral incompetence, feeding tube dependence, and speech difficulties.[10] Additionally, radiation to the oral cavity and neck can result in mucositis, xerostomia, infections, dental caries, osteoradionecrosis, and muscular dysfunction.[11]

Five-year survival rates of oral cavity cancer have not significantly improved in recent decades, largely due to delays in detection. Only 30% of oral cavity cancers are detected early, despite being often preceded by visible potentially malignant disorders, such as leukoplakia or erythroplakia.[12] Leukoplakia affects 2.6% of the global population with a 1.4% annual malignant transformation rate, while erythroplakia, present in 0.2% to 0.8%, has a malignant transformation rate exceeding 85%.[7,13,14] Oral lichen planus affects 2% of the world's population, more commonly women and older adults, and approximately two-thirds are symptomatic. Its malignant potential remains

debated, though a meta-analysis reported a 0.44% malignant transformation rate, higher in individuals who smoke, drink alcohol, have positive hepatitis C serology, or present with the red subtype.

LARYNGEAL AND HYPOPHARYNGEAL CANCER

Laryngeal cancer represents 19% of all head and neck squamous cell carcinomas and carries high morbidity and mortality. Although incidence has declined by 55% in recent decades, mortality has only dropped by 43%, resulting in a 25% increase in case fatality rate.[15] In includes cancers of the supraglottis, glottis, and subglottis, with supraglottic subsite associated with the highest mortality due to the lack of symptoms in early stages.[16] Early detection reduces mortality and treatment-related morbidity. Early-stage disease is highly curable with either limited surgery or radiation and has excellent voice outcomes.[17] In advanced stages, total laryngectomy may still be curative but with significant implications to voice and quality of life. In recent decades its use has declined from 24% to 12% in favor of definitive chemoradiation.[18,19]

Hypopharyngeal cancer is rare, representing only 0.4% of new cancers and cancer deaths globally. It is typically advanced at diagnosis due to minimal symptoms present in early stages. It includes cancers between the oropharynx and the esophageal inlet and is molecularly distinct from laryngeal cancer.[20] Common late-stage symptoms include pain, bleeding, and dysphagia. Overall 5-y survival is 60% in early stages and falls to 25% in late stages.[21]

Head and Neck Cancer Screening by Otolaryngologists

A free annual head and neck cancer (HNC) screening program was conducted by the University of Michigan, with data gathered over 14 y. Recruitment was carried out through various public online and print media. The screening visit included a medical history and examination, and patients were provided with counseling on risk factors and smoking cessation, or arranged for follow-up or referral when there were suspicious findings. Of 759 eligible subjects, the most common complaints were hoarseness and dysphagia. Only 41 patients had findings suspicious for cancer, and 7 ended up with a confirmed diagnosis of a malignant or premalignant lesion. Twelve of the 41 patients received benign diagnoses after further workup, while 25 were lost to follow-up. Significant predictors of finding a lesion suspicious for malignancy were history of chewing tobacco use (not smoking), male sex, and social determinants including lack of insurance and separated marital status. Oral pain and neck mass were presenting complaints significantly associated with higher risk of suspicious findings.[9] The study concluded that future screening clinics should focus on patients with identified demographic risk factors and emphasize education and prevention.

There is no evidence-based screening approach for asymptomatic cancers of the larynx and hypopharynx. The American Academy of Otolaryngology-Head and Neck Surgery recommends performing flexible nasolaryngoscopy for dysphonia lasting longer than 4 w or when malignancy is otherwise suspected.[15,22] In individuals with risk factors, such as tobacco and alcohol use, earlier laryngoscopic evaluation is advised for hoarseness lasting longer than 2 w.[23] While hoarseness alone has not been found to correlate with higher rates of suspicious lesions, screening clinics remain valuable for counseling on modifiable risk factors such as smoking.[9]

Oral Cavity Cancer Screening

The World Health Organization and the National Institute of Dental and Craniofacial Research recommend that an oral cavity cancer screening examination include

thorough visual inspection of the oral cavity and neck, in addition to palpation of the neck, tongue, and floor of mouth. A 2008 survey of American adults found that 29.4% reported ever having a screening examination that included palpation of the neck or tongue.[24] Warning signs of oral cavity cancer include a non-healing ulcer or persistent white or red lesion, bleeding, pain, and difficulty with tongue and jaw movements, such as chewing and swallowing. Incisional biopsy is the gold standard for diagnosis and should be considered for suspicious lesions persisting longer than 2 w, and suspected traumatic lesions should be referred to a dentist. Other diagnostic adjuncts, such as toluidine blue, diffused-white light, chemiluminescence, or loss of tissue autofluorescence, have been studied but exhibit limited validity.[25]

The US Preventative Services Task Force (USPSTF) concluded that there is insufficient evidence to support screening of asymptomatic adults aged 18 or older by primary care clinicians. This recommendation does not apply to dental providers or otolaryngologists, who regularly conduct comprehensive examinations of the oral cavity and neck as part of the clinical encounter. It is known that the accuracy of the oral cavity screening examination is highly heterogeneous depending on the performing provider and setting. Across 7 studies in India and Taiwan, sensitivity of oral screening examination for oral cavity cancer or potentially malignant disorders ranged from 18.0% to 94.3% and specificity from 54.0% to 99.9%. In studies of patients in the United Kingdom at high-risk and unknown risk for oral cavity cancer, dental examinations were found to have a sensitivity of 74% and 71%, and specificity of 99% and 99%, respectively.[26]

Dentists and dental-based providers play an important role in detecting oral cavity cancers in their early stages. A 2023 survey of 91 dentists at the University of Toronto revealed that their knowledge of the presentation and risk factors associated with oral cavity cancer was good. Eighty-seven point five percent believed that visual examination is an effective screening method for oral cavity cancer. Ninety-one point four percent performed screening in all new patient appointments, 75.3% did in asymptomatic patients, and 60.4% did in follow-up patients. Nine point nine percent discussed risk factors for oral cavity cancer with every patient and 12.4% counseled on risk factor management.[27] Similar results were reflected in data from 2011 to 2018 collected in the National Health and Nutrition Examination Survey. Of patients aged 30 and above with self-reported tobacco use and a dental visit within the past year, 22.1% had oral and OPC screening. Of the 41% who reported having a conversation with a dental professional about smoking cessation, 9.8% reported having screening as well. Males were less likely than females to have neither screening nor discussion regarding smoking cessation.[28]

Targeted Screening Strategies

As outlined previously, a successful cancer screening program should identify a target high-risk population to focus screening efforts and resources. A 2023 systematic review described oral inspection every 2 or 3 y as a strategy for oral cavity cancer screening in 11 articles. Screening significantly increased the detection rate of stage I or II cancers in 4 trials and 6 observational studies. Universal screening of asymptomatic adults improved 3 to 5-y overall survival but not cancer-specific survival in 4 trials, while targeted screening improved overall and cancer-specific survival in 2 trials and 2 observational studies.[29]

The largest cluster-randomized controlled trial on oral cavity cancer screening was conducted in Kerala, India, where oral cavity cancer is the leading cause of cancer and cancer-related death in men.[30] Its impact in the region is attributed to the widespread popularity of betel quid chewing. The trial randomized clusters of healthy people aged

35 y or older with no past history of oral cavity cancer to an intervention group and a control group. In the intervention group, individuals were interviewed on high-risk habits, such as tobacco chewing, smoking, and alcohol use, and were screened every 3 y with visual oral examination by trained health care workers. Those who screened positive were referred for specialist care to confirm the diagnosis and receive appropriate treatment. In the entire study population, the intervention resulted in a non-significant 21% reduction in overall mortality, but in subgroup analysis of high-risk individuals who used tobacco or alcohol, the intervention resulted in a significant 34% reduction in mortality. Screening compliance was 90% in the intervention group, and two-thirds of those who screened positive complied with specialist referral. Overall, the findings support the implementation of oral cavity cancer screening programs by visual inspection in high-risk populations. In Ontario, Canada, first-generation and second-generation immigrants of south and south-east Asian origin had oral cavity cancer rates comparable to those in their countries of origin, where screening programs have demonstrated success.[31]

Elderly smokers represent another high-risk population for oral cavity cancer. National US modeling data suggested that targeted screening for male smokers with over 60 pack-y smoking history or male former smokers over the age of 50 could reduce oral cancer mortality by 4.6%.[32] Although oral screening examinations are primarily performed by dentists, 50% of adults in the United States over the age of 65 have not seen their dentist in over 5 y.[33] According to population-level data in the United States, the frequency of physician visits exceed dental visits in the elderly, increasing from 6.5 visits per year in 55 to 64 y olds, to 8.3 visits per year in those 75 and older.[34]

Telemedicine can aid in disease surveillance and provide specialist consultation in remote or low-resource settings. A pilot mobile phone-based screening program launched in India allowed first-line health workers and dental surgeons to perform thorough oral cavity examinations and upload photos of suspicious lesions for remote review by an oral cancer specialist at a tertiary center. In characterizing a lesion as premalignant or malignant, the specialist's diagnostic agreement was 45% with first-line health workers, and 100% with dental surgeons.[35] Other mobile applications have been devised to educate the general population on oral cavity cancer, risk factors, and home oral self-examination.[36]

SUMMARY OF SCREENING CONSIDERATIONS FOR HUMAN PAPILLOMAVIRUS-NEGATIVE HEAD AND NECK SQUAMOUS CELL CARCINOMAS

While the USPSTF does not recommend oral cavity cancer screening of asymptomatic adults by primary care providers, screening is more effective when focused on individuals identified to be at high risk. Given their higher disease burden and associated mortality and treatment-related morbidity, public health agencies should consider promoting oral health clinics run by Otolaryngologists or dentists for these populations. In Ontario, for example, screening clinics might target cities like Brampton with a disproportionate representation of south/south-east Asians, following the strategy employed in Kerala, India. These screening clinics may also offer valuable opportunities for education and counseling around risk factor management (**Fig. 2**).

CLINICAL CARE POINTS FOR HUMAN PAPILLOMAVIRUS-NEGATIVE HEAD AND NECK SQUAMOUS CELL CARCINOMASS

- A good cancer screening program utilizes accurate, cost-effective methods targeted at a high-risk population to enable effective interventions in treatment and prevention.

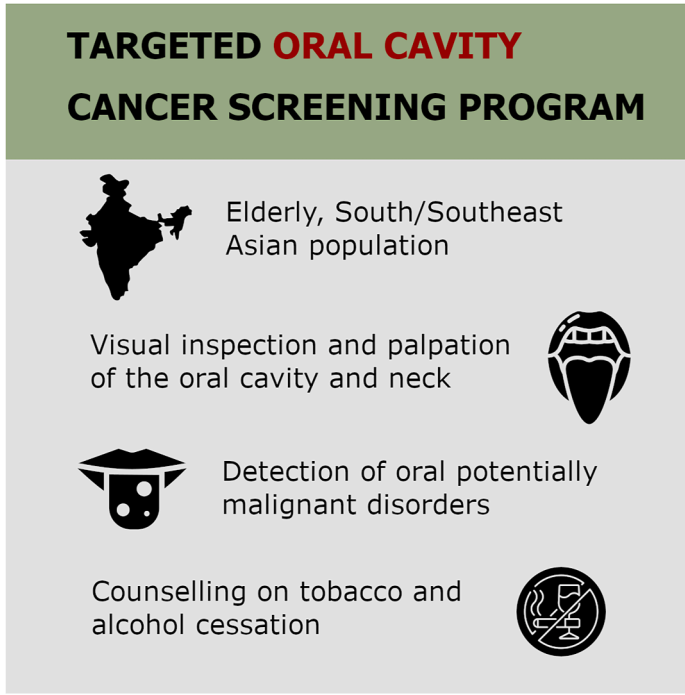

Fig. 2. Targeted oral cavity cancer screening program.

- At present, the USPSTF does not recommend screening of asymptomatic adults for oral cavity cancer by primary care physicians, but this recommendation does not apply to otolaryngologists or dental providers.
- South and south-east Asians may represent a targetable population for oral cavity screening examinations given their proportionally higher prevalence of tobacco chewing.
- Counseling on risk factor reduction, such as smoking cessation, should be an important part of a cancer screening visit.

HUMAN PAPILLOMAVIRUS-MEDIATED OROPHARYNGEAL CANCER

Introduction

Viral-associated cancers of the head and neck exhibit unique screening opportunities and established, or potential, screening paradigms relative to HNCs caused by chemical carcinogens. Herein, we discuss considerations in screening for HPV + OPC.

DISCUSSION OF HUMAN PAPILLOMAVIRUS-MEDIATED OROPHARYNGEAL CANCER

Epidemiology

HPV + OPC has risen in incidence in the United States since the mid-1990s, primarily among non-Hispanic White men of middle age.[37–39] However, the median age is rising and suggests a birth cohort effect, as the highest incidence of these cancers arise among individuals born in the 1950s and 60s. While preventive vaccination in the United States was initiated in, HPV+ OPC incidence rates continue to increase, a finding likely attributable to low vaccination rates, lower efficacy in adults (after sexual exposure), and older age of onset. In fact, a recent modeling study suggests that no

real impact of HPV vaccination will be seen for decades to come, and significant benefits will be substantive only for those born since 2000.[40]

While the HPV + OPC epidemic primarily affected middle-aged and older non-Hispanic white men of higher socioeconomic groups, rising rates are now seen among women, individuals of Black race or Hispanic ethnicity, and lower socioeconomic groups. HPV + OPC patients typically present with silent or limited symptoms of the pharynx, and approximately 90% have regional metastatic disease at presentation requiring multimodality treatment.[41] Cancer-specific survival outcomes are much better than chemical carcinogen-related OPC.,[42,43] For patients with HPV + OPC, 4.5-5-y progression-free survival rates range from 78% to 91% and the most common grade 2 to 4 late toxicities are xerostomia, dysphagia, and hearing loss.[44,45]

Prevention

The public health problem of HPV + OPC can be eliminated with widespread implementation of HPV vaccination of children and adolescents, as recommended by the Center for Disease Control (CDC).[46] With hundreds of millions of doses administered, it is well-established that these vaccines are safe, highly effective, and offer longstanding immunity.[47] In countries with high-HPV vaccine uptake, rates of HPV-related cancers have already begun to decline, particularly for cancers sites with younger median ages of onset (cervical cancer in women and anal and penile cancer in men).[47,48] However, vaccine efficacy is lower if administered after sexual debut, and because of this and low uptake rates, it is estimated that the United States may not see substantive declines in OPC incidence rates until 2060.[40] Furthermore, a pervasive culture of doubt raised by anti-science and anti-vaccine advocates has introduced skepticism toward public health authorities and created more generalized vaccine-hesitancy among parents. To combat this regressive ideology, the highest rigor in vaccine development, testing, and ongoing monitoring must be maintained. Further, it is incumbent on the medical community to champion HPV vaccination as a cornerstone of cancer prevention.

RATIONALE FOR SECONDARY PREVENTION OF HUMAN PAPILLOMAVIRUS-MEDIATED OROPHARYNGEAL CANCER

There is a strong rationale to explore screening for HPV + OPC. An at-risk population can be detected, valid biomarkers have been identified, and evidence-based treatments of detected HPV + OPC are available. Further, early detection of HPV + OPC may confer benefit. Approximately 90% of HPV + OPC patients undergo multimodal treatment, resulting in increased long-term toxicities and treatment-related mortality.[49] Consequently, earlier diagnosis prior to regional metastases may allow for single modality treatment with less long-term sequelae. Indeed, the central premise of HPV + OPC screening is that patients with earlier diagnoses will (1) have accrued less cancer-related morbidity due to their earlier stage of disease, (2) receive lower toxicity cancer treatment with lower long-term morbidity, and (3) enjoy improved survival outcomes and quality-adjusted life years (at a societal level).

TARGET SCREENING POPULATION

Several demographic and behavioral factors have been linked to an increased risk of HPV + OPC, facilitating identification of an at-risk screening population. Male sex, middle-to elderly-age, and elevated number of lifetime oral sex and penetrative sex partners are among the strongest known risk factors for HPV + OPC.[50] Given the

potential challenges associated with collecting sensitive sexual behavior data, a sex-based and age-based HPV + OPC screening approach may be the most feasible.

BIOMARKER SCREENING TESTS

There are 2 primary categories of candidate biomarker tests for HPV + OPC, most of which leverage features or markers of HPV: oral and oropharyngeal-based biomarkers, and blood-based biomarkers. Urine-based biomarkers have also been described.[51] Given the low-incidence rate of HPV + OPCs relative to other, more common cancers, all current biomarkers exhibit insufficient validity to justify screening as part of routine clinical practice. However, the validity of select biomarker tests continues to rapidly improve, suggesting we may overcome this barrier to screening soon.

Continued evaluation of oral and oropharyngeal biomarkers for the purpose of screening is indicated. Relative to its absence, the presence of oral and oropharyngeal oncogenic HPV DNA collected via an oral rinse and gargle technique predicts a 22-fold increased likelihood of HPV + OPC. However, this test is limited by its low validity (72% sensitivity and 92% specificity) and the high-risk of false positive results given the modest prevalence of transient oral oncogenic HPV infections in at-risk target populations. An oropharyngeal "Pap smear" to localize abnormal cells or HPV DNA within the oropharynx is promising but has not yet proven effective, presumably because HPV + OPCs arise deep within the tonsillar crypts where they are inaccessible to brush or swab sample collection techniques.

While blood-based biomarkers of HPV-related cancer exhibit improved validity relative to their oral and oropharyngeal counterparts, they fail to localize the potential site of disease. Patients with HPV16 E-antibodies detected via serology (sensitivity: 83%, specificity: 99%) exhibited a ~450-fold increased likelihood of HPV + OPC. Similarly, circulating tumor tissue-modified viral HPV DNA (targeting genotypes 16, 18, 31, 33, and 35) has been shown to be 92% sensitive and 100% specific in a recent single-institution study.[16] Other blood-based biomarkers leveraging unique methylation and RNA profiles and urine-based biomarkers also exhibit promise.[50–53] As discussed earlier, however, a positive blood-based or urine-based biomarker test could signal an infection or cancer at an oropharyngeal or anogenital primary site, and would require further evaluation by clinical examination and or imaging.

CLINICAL EVALUATION OF BIOMARKER-POSITIVE INDIVIDUALS

Clinical detection of HPV + OPC is more challenging than identification of HPV-mediated cervical and anal cancers in high-risk populations. These pre-malignant lesions and early cancers arise from a smooth, serially evaluable, mucosal surface and are amenable to detection and treatment. Similarly, other non-HPV mediated HNCs involving the oral cavity and larynx might be easily evaluated via serial direct transoral examination or flexible fiberoptic laryngoscopy, respectively, in high-risk populations amenable to screening (which is not the standard of care). However, as noted earlier, HPV + OPCs most often arise within crypts of lymphoid tissue in the palatine and lingual tonsil tissue, impeding their early detection by direct and transnasal fiberoptic nasopharyngoscopy.

EVIDENCE-BASED TREATMENTS FOR DETECTED CANCERS

A prerequisite of screening is the availability of evidence-based treatments for detected cancers. As alluded to mentioned earlier, primary surgery ± radiation ± chemotherapy

and primary radiation ± chemotherapy are established, evidence-based treatments for OPCs, which exhibit similar survival rates and unique toxicity profiles.[54]

POTENTIAL SCREENING APPROACHES

Potential approaches to screen for HPV + OPC may draw from the emerging, evidence-based approach to screening for Ebstein-Barr Virus (EBV)-mediated nasopharyngeal carcinoma (NPC; EBV + NPC) in Asia. Blood-based EBV antibody and EBV DNA are highly sensitive and specific biomarkers for NPC.[55,56] Therefore, blood-based biomarker screening is the initial step in a targeted screening program yielding significantly earlier-stage diagnoses and lower mortality. While this screening program is promising, it is not yet the standard of care pending further cost-effectiveness evaluations.[57,58]

SCREENING BENEFITS AND HARMS

The potential benefits of screening have been discussed earlier.

There are several potential harms of screening, which we review in more details as follows. These include false positive or inconclusive biomarker-based screening findings, morbidity from unnecessary screening procedures after a false positive test result, and uncertain outcomes associated with detecting and treating incidental, non-HPV-related cancers.[59]

False positive biomarker screening results will yield harm. A recent modeling study suggests that screening men aged 45 to 79 y would result in 1 in 67 testing positive for an oral HPV16 infection and/or HPV16 E6 antibodies with NNS of 561 per screen-detected cancer assuming an annual screening schedule.[59] Older modeling studies assuming an HPV16+ OPC incidence rate of 16/100,000, and an overly favorable biomarker test sensitivity and specificity of 100% and 99.5%, respectively, demonstrated that screening 100,000 patients would yield 484 false positive cases.[60] Patients with false positive results will likely experience misplaced anxiety; further studies are needed to characterize the prevalence and severity of this consequence. Following a false positive result, patients may undergo a routine head and neck examination and flexible nasopharyngoscopy, which carry little to no risk for harm apart from physical discomfort. They may also undergo further imaging work-up. As we discuss as follows, these additional clinical and radiographic tests may identify incidental findings requiring further, potentially morbid, work-up, and treatment.

Specific harms associated with work-up and treatment of incidental clinical and radiographic findings identified during the screening have not yet been characterized. Incidental oropharyngeal or neck findings may generate additional imaging, outpatient biopsies, or biopsies in operating room. For example, imaging work-up may detect an incidental, indolent, thyroid cancer with its own associated potential harms of work-up and treatment. Further, it is unknown whether an indolent form of OPC exists and can be safely observed. Although this is unlikely, the morbidity (and even mortality) of unnecessary cancer treatment would be substantial.

False negative biomarker screening results will also yield harm. Although the prevalence of this problem has also not yet been characterized, we suspect patients with these results may experience misplaced confidence and ignore early symptoms of a cancer.

As described earlier, there are different causes of NPC, which require distinct screening approaches. Most NPCs globally, as well as among Asian populations in North America, are attributable to EBV. However, a rising proportion of NPCs in North

America are now caused by HPV.[61] The biomarkers discussed earlier to select those at high risk for HPV + OPC will almost certainly be effective in identifying those at risk of HPV + NPC. Consequently, blood-based HPV biomarker-positive individuals will require a detailed nasopharyngeal examination as part of their comprehensive head and neck evaluation. These HPV biomarker positive subjects will also need access to anogenital screening.

RECENT PROGRESS IN EVALUATING SCREENING FOR HUMAN PAPILLOMAVIRUS-MEDIATED OROPHARYNGEAL CANCERS

Beginning in 2017, we established an HPV + OPC screening trial (HOUSTON) based upon HPV16 early (E) protein serology to select a high-risk population for a head and neck examination, neck ultrasound, and anogenital examination.[62] Subsequently, this double-blind screening trial was expanded to 1567 men aged 50 to 64 y (TRINITY), funded by the Cancer Prevention and Research Institute of Texas, incorporating an additional blood-based biomarker (TTMV-HPV DNA), and accruing subjects in both Houston and Dallas, Texas. Of 25 subjects with positive blood-based biomarkers, 2 HPV-related cancers developed prior to a scheduled in-person examination while others remain in serial in-person follow-up.

In 2024, we established the next phase of this work to further develop these assays for biofluids obtained via at-home self-sampling (oral rinse, unstimulated saliva, and urine), which could be mailed in for analysis. Over 1100 men and women aged 45 to 69 y are being recruited across the state of Texas (TEJAS; funded by NIH/NIDCR U01). Assays on these self-collected biofluids are done in parallel with blood samples, and any subject testing positive is offered a head and neck examination, neck ultrasound, and anogenital examination. In a separate NIH/NCI EDRN U01 funded study the serologic assay is being optimized on unstimulated saliva in over 2500 men and women aged 45 to 69 y in Arizona. Additionally, a lateral flow serologic assay is being developed for point of care testing on finger prick blood sampling.

Others are also utilizing HPV16 E protein serologic assays to prospectively select individuals for OPC screening. The Men Offering Understanding of Throat HPV (MOUTH) study enrolled 1108 high-risk individuals with a 3.7% prevalence of oral HPV16 DNA and/or HPV16 E6 serum antibodies, higher than observed in the general population.[63] A study at the University of Kentucky is screening 4000 men in rural primary care clinics for seropositivity to HPV16 E6 and will document the prevalence of oral HPV and OPC in seropositive men; however, the results are yet to be published. In an ongoing study in Hamburg, Germany, 4424 men and women have been tested with 35 seropositive for HPV16 E6 antibodies, of which 11 were confirmed positive on repeat testing. Two OPCs were found (1 early and 1 late stage) and 1 additional OPC was a prevalent case.[64] A national multi-center trial leveraging these assays and requiring regimented follow-up of biomarker-positive individuals is needed. Such a trial would more firmly establish the prevalence of biomarkers and HPV + OPCs in the general population, to formalize how biomarker-positive individuals should be initially evaluated, determine how serial follow-up should ensue, and evaluate the benefits, harms, and cost-effectiveness of screening.

Further studies are needed to determine how, and if, an early HPV + OPC primary tumor can be consistently identified in a biomarker-positive, screened population. We believe that advanced imaging, existing procedures, and novel technologies being developed to improve transoral surgery margin assessment and identification of unknown primaries show promise in screening these high-risk individuals, but costs

and procedure invasiveness will be an ongoing concern. Other immunoprevention-based options may include topical or therapeutic vaccination for biomarker positive individuals without an identified primary to prevent cancer development.

SUMMARY OF SCREENING CONSIDERATIONS FOR HUMAN PAPILLOMAVIRUS-POSITIVE HEAD AND NECK CANCERS

HPV + OPC is now the most common HPV-mediated cancer in North America. HPV vaccination is safe for all ages and prevents HPV-mediated cancers if given before sexual debut. Blood-based HPV biomarkers, and potentially saliva-based and urine-based biomarkers, can be used to select a group of the general population who are at extreme risk for later development of OPC. New screening procedures and technologies are needed to reliably identify early OPC within this high-risk group to allow for less morbid, single-modality treatments.

CLINICS CARE POINTS FOR HUMAN PAPILLOMAVIRUS-POSITIVE HEAD AND NECK CANCERS

- Otolaryngologists must be vigilant to identify HPV + OPC, given the often-subtle signs and symptoms typically occurring before overt disease, which often first presents as a neck mass).
- HPV vaccination is the cornerstone of HPV-related cancer prevention, and otolaryngologists must support CDC HPV vaccination recommendations.
- At present, the USPSTF does not endorse routine OPC screening.
- A potential HPV + OPC screening paradigm may involve screening high-risk subjects using biofluid-based biomarkers, followed by a comprehensive head and neck and anogenital examination, as well as imaging.
- Advanced imaging and augmented visual examination may be needed to consistently identify small primary HPV + OPCs in this high-risk cohort.

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DISCLOSURE

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