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Expert Review of Anticancer Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iery20

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To cite this article: Ari Schuman, Karen S. Anderson, Andrew T. Day, Jay Ferrell, Erich M. Sturgis & Kristina R. Dahlstrom (2022) Is 2045 the best we can do? Mitigating the HPV-related oropharyngeal cancer epidemic, Expert Review of Anticancer Therapy, 22:7, 751-761, DOI: 10.1080/14737140.2022.2088514

To link to this article: https://doi.org/10.1080/14737140.2022.2088514

Published online: 17 Jun 2022.

EXPERT REVIEW OF ANTICANCER THERAPY
2022, VOL. 22, NO. 7, 751–761
https://doi.org/10.1080/14737140.2022.2088514

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REVIEW

Is 2045 the best we can do? Mitigating the HPV-related oropharyngeal cancer epidemic

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ABSTRACT

Introduction: Oropharyngeal cancer (OPC) will be among the most common cancers in men by 2045 due to a rapid rise in human papillomavirus (HPV)–related OPC. Those who survive their cancer often suffer life-long treatment effects and early death. HPV vaccination could prevent virtually all HPV-related cancers but is not an effective preventive strategy for those already exposed. Without a dramatic increase in vaccine uptake in the U.S., HPV vaccination will have a negligible effect on OPC incidence through 2045 and no substantial impact until 2060. Additionally, targeted screening for earlier diagnosis may soon be feasible for those inadequately protected by vaccination.

Areas covered: PubMed search for English-language articles related to incidence, screening, and prevention of HPV-related malignancies, focused on OPC in the U.S.

Expert opinion: HPV-related OPC incidence will continue to increase for the foreseeable future with prophylactic vaccination offering no substantial public health impact for decades. Consequently, we must rapidly increase vaccination rates and develop screening methods to identify high-risk individuals. Such individuals would be eligible for potential preventive treatments and screening to diagnose early-stage HPV-related OPC allowing less morbid treatments. These methods will bridge the population into an era of decreasing incidence after vaccination takes effect.

ARTICLE HISTORY
Received 5 January 2022
Accepted 7 June 2022

KEYWORDS
Cancer screening; cancer early detection; cell-free nucleic acids; early diagnosis of cancer; HPV vaccine; human papillomavirus (HPV); oropharyngeal neoplasms

1. Introduction

Oropharyngeal cancer (OPC) is a malignancy with growing incidence, currently estimated at 11.9 per 100,000 population (21 per 100,000 among men) and rising in the U.S [1]. The overwhelming majority of oropharyngeal lesions are squamous cell carcinoma associated with human papillomavirus (HPV), most prominently type 16 (HPV16), commonly transmitted by sexual contact [2]. Typically, these cancers require extensive multimodality treatment, usually radiation with concurrent cisplatin, though in selected cases transoral surgery or radiation alone can offer a less morbid option. While most patients with HPV-related OPC are cured, approximately 20% will die within 5 years while those who survive suffer debilitating life-long treatment effects with high non-cancer mortality [3,4].

A prophylactic HPV vaccine was approved by the Food and Drug Administration (FDA) in 2007 for the prevention of HPV-related cancers and shortly thereafter was recommended by the Centers for Disease Control and Prevention (CDC) for both girls and boys (and adolescents through age 26) [5]. In 2018, the HPV vaccine was approved by the FDA up to age 45 [6], though in those with prior HPV exposure (typically occurring shortly after sexual debut) the vaccine may not fully protect from an HPV-related cancer. In 2020, oropharyngeal cancer was officially added by the FDA to the list of HPV-related cancers preventable with vaccination.

Recent estimates suggest that OPC may become one of the top three cancers among middle-aged men in the U.S. by 2045 [7], but HPV-related OPC will become the most common among elderly men in the coming decade [1]. Zhang et al. published important modeling work in 2021 that projected HPV vaccination rates and the impact on OPC incidence rates over the next several decades [1]. OPC incidence was projected to decrease by almost half among 36–45-year-olds (48% for men and 42.5%) by 2045, but with no meaningful decrease among those 56 years and older. HPV vaccination will prevent 6,334 cases of OPC and as expected, the vast majority (89%) will be among those aged 55 years or younger [1]. These findings are a major public health concern and disappointment: HPV vaccination will have very limited impact on OPC incidence by 2045 and no substantial impact until 2060. Additionally, these projections may be optimistic given that sluggish HPV vaccination rates have further dropped because of the COVID-19 pandemic and growing anti-science beliefs/vaccine hesitancy [8,9]. While there are several strategies to mitigate the impact that this cancer will have on society, we must

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Article highlights

- OPC incidence has been rising since the mid-1990s due to an epidemic of HPV-related cancers.
- This rising incidence will transition from a predominantly middle-aged male demographic to an elderly male demographic over the next decade.
- Current projections of HPV vaccination rates and the impact on HPV-related OPC incidence reveal that only limited effects will be observed through 2045 with substantial public health gains not likely until 2060.
- HPV vaccination rates must be dramatically increased in the next 5 years to impact these 2045–2060 timelines. Because HPV-related OPC is primarily a disease of the middle-aged and elderly, HPV vaccination is most effective as a preventive strategy if given before sexual debut.
- OPC treatment has a high degree of morbidity and treating early in the course of disease is ideal to mitigate unnecessary sequelae; consequently, screening techniques including oral rinse detection of persistent oncogenic HPV, circulating HPV DNA, and antibodies to HPV early (E) proteins are under investigation. (https://clinicaltrials.gov/ct2/show/NCT02897427).

prioritize rapid increase in HPV vaccination rates among children and adolescents.

In this review, we discuss the HPV-related OPC epidemic, HPV vaccination, and the need for/potential of increased vaccination, HPV-related OPC screening, and novel treatment strategies for those at high risk for OPC, focusing largely on the U.S. experience. To substantially reduce the impact of HPV-related OPC on society and to do so more quickly than projected by Zhang et al. [1], an aggressive increase in HPV vaccination of all eligible individuals is essential. However, rigorous testing of OPC screening strategies and novel means to identify individuals at high OPC risk for close monitoring and possibly preventive therapies will also be needed.

2. The ongoing HPV-related OPC epidemic

Over the past decade, the rise in the number of OPC cases has been well documented [7,10–16]. While HPV is the primary cause of cervical cancer, OPC has historically been a disease of tobacco smokers and heavy alcohol users. An increase of OPC among nonsmokers was observed and later attributed to a rise in HPV-related OPC [17–19]. In 2000, Gillison et al. provided evidence for an etiologic link between HPV and OPC in an analysis of 253 head and neck cancer patients [19]. HPV positivity was strongly associated with the tumors of the oropharynx compared with other head and neck sites (odds ratio [OR] = 7.7; 95% confidence interval [CI] = 4.0–15). Of 60 patients with OPC, 34 (57%) were positive for HPV, the majority arising from the tonsils/base of tongue (n = 32). Ernster et al. showed that HPV positivity rate among OPC specimens increased from 33% in 1980s to 82% in the early 2000s [20], and this was subsequently confirmed by others [2,21]. Since then, HPV positivity of OPC specimens has continued to rise, from 65% to 75% among men and from 54% to 60% among women during the period 2010 to 2015 [10]. Overall, the incidence of OPC increased 225% in the U.S., from 0.8 per 100,000 population to 2.6 per 100,000 population from 1988 to 2004 [2]. Incidence rates have continued to rise and currently are estimated to be 11.9 per 100,000 population, representing the most common HPV-related cancer in the U.S. of any site [1].

Other HPV-related cancers, such as anal, penile, and vulvar cancer have also experienced significant increases in recent decades [15,22]. Anal cancer is currently the most common HPV-related cancer among white women aged 65 years and older, and if trends continue, anal cancer will be the most common HPV-related cancer among women overall by 2030 [23]. For several decades, cervical cancer incidence has been in decline in the U.S. due to broad adoption of screening [24–27]. However, the full public health benefit of screening and HPV vaccination on cervical cancer incidence may be unrealized for decades in the U.S [28]., while in Australia, a country with extremely high HPV vaccine uptake, cervical cancer is expected to be eliminated as a public health problem (i.e. incidence <4 per 100,000 women) by 2028 [26]. A similar reduction in OPC incidence is not expected in Australia for at least another decade as herd immunity among males is reached [29]; furthermore, it is noted that the elimination of cervical cancer public health problem in Australia is in part credited to broad adoption of cervical cancer screening (transitioned from cytology-based to primary HPV testing in late 2017).

The demographic characteristics of patients with HPV-related OPC appears to be unique compared to those with smoking-related OPC: younger, limited or no smoking history, non-Hispanic white, male, and higher socioeconomic status [12,30,31], though these demographics are not exclusive and have evolved over time. HPV-related OPC is approximately four times more common among men than women (five times higher among middle-aged men) [16]. Xu et al. showed that from 2000 to 2015, OPC increased four times faster among men than women, and projected that, among non-Hispanic white men 55–69 years old, OPC will be the third most common cancer by 2045 [7]. However, the age of diagnosis of OPC is rising – Windon et al. showed that, in 2013, the median age of diagnosis for HPV-related OPC had increased from 53 to 58 years [32]. Tota et al. described the change in birth-cohorts, with an expected increase in incidence among men aged 65–74 and 75–84 years, while remaining stable among men aged 45–54 years [30]. The authors predict that cases will increase in the U.S. from 7,976 per year for men over 65 in 2016 to 18,072 in 2029. Xu et al. similarly projected that the incidence of OPC will increase 130% by 2045, with the greatest increase (268%) among men older than 70 [7]. Although the majority of those diagnosed with HPV-related OPC are non-Hispanic white men, those of other races and women are also now experiencing increasing incidence. OPC incidence among Hispanic men increased 1.2% per year during 1992–2015, while incidence among non-Hispanic white women increased 0.7% per year during this same period [30]. In light of this, the demographic characteristics of OPC patients are expected to change as the demographics of the U.S. population shift over time.

HPV is a sexually transmitted infection primarily passed through mucosal contact, and a key mode of transmission to the oropharynx is oral sex. The strongest behavioral risks associated with HPV-related OPC are lifetime number of sexual partners and oral sexual behaviors, and many of the trends

described above may be due to sexual behaviors and exposure differences between demographic groups [33–37]. HPV viral load appears to be particularly high at the cervix compared to other mucosal sites for those with an HPV infection [38], and it might be presumed that exposure to such secretions increases risk of infection. Additionally, women are thought to have a stronger immune response to HPV infection by being more likely to seroconvert and having higher antibody titers [39,40]. This may explain why HPV-related OPC is 4 to 5 times more common in men than women [16], and why among women OPC is significantly more common among lesbian and bisexual women than among heterosexual women [41].

The epidemic rise in HPV-related OPC beginning in the mid-1990s and the shift from a middle-aged demographic to an elderly group may be attributable to differences in sexual behaviors between birth cohorts. High-risk HPV infection has been associated with more sexual partners and a higher lifetime number of oral sex behaviors, which has been noted among the birth cohorts that are now part of the population of white men over 65 [40,42]. Therefore, the HPV-related OPC epidemic, chiefly among those born in the decade after World War II, may be attributed to this birth cohort coming of age during the liberalization of societal sexual norms occurring in the 1960s and 1970s, while for subsequent birth cohorts increasing OPC incidence has slowed [30].

2.1. The morbidity of oropharyngeal cancer

While HPV-related OPC has a better prognosis than smoking related (HPV-negative) OPC, approximately one-quarter of all OPC (about 20% of HPV-related OPC) will die within 5 years of their cancer diagnosis [4]. Additionally, Hispanics and African Americans have a higher mortality rate, with recent studies reporting 16% lower survival in Hispanic Americans as compared to non-Hispanic whites, and lower survival in African-Americans [4,43–45]. HPV-related OPC treatment subjects patients to significant lifelong and debilitating morbidity and early non-cancer mortality. Dahlstrom et al. recently described the long-term outcomes of a large cohort of patients who had radiation for OPC and had already survived five years [3]. Mortality in this group was four times higher than the general population, even though only 18% had a cancer event after having survived 5 years [3]. Of note, patients who had a lower dose of radiation had improved survival – 72% at 10 years for ≤66 Gy compared to 58% for >70 Gy. At 10 years (15 years after diagnosis), patients with less tobacco exposure (75% for ≤10 vs. 50% for >10 pack-years) and those who underwent intensity-modulated radiation therapy (IMRT) also had improved survival (69% vs. 58%) [3].

Given the growing incidence of HPV-related OPC among older individuals, late morbidity of treatment and increased non-cancer mortality is especially concerning. Patients with OPC have a higher incidence of hypertension, cerebrovascular disease, and chronic obstructive pulmonary disease than those without a history of cancer [46]. Pooled analysis of multiple Radiation Therapy Oncology Group trials for head and neck cancer more broadly have shown that the most significant factor associated with severe late toxicity was age, with a 4% increase in the odds of severe late toxicity for every year increase in age (with toxicities including feeding tube dependence, pharyngeal or laryngeal dysfunction, and death) [47]. Other authors have found increased rates of trismus with increasing radiation, and significantly restricted oral diets in those with severe trismus [48,49]. Cardoso et al. showed that up to 31% of patients with OPC report at least some trismus after radiation, with worse quality of life and increasing self-reported dysphagia with increasing trismus [48]. Some rare complications, such as cranial neuropathies, have been reported as side effects years after the end of treatment [50]. Patients treated with IMRT have an estimated 10% cumulative lifetime risk of lower cranial neuropathy (LCNP) [51]. Late LCNP (occurring >3 months after therapy) is associated with poor swallowing-related quality of life, feeding tube placement, aspiration pneumonia, tracheotomy, and patient-reported poor functional status [52]. In a cohort of 93 patients with p16-positive OPC, 7.5% developed late progressive dysphagia beyond one year following treatment [53]. Baudelet et al., observed that severity of dysphagia decreased during the first 5 years after treatment but increased thereafter among 747 patients with squamous cell carcinoma of the head and neck, 60 of whom had follow-up tome of ≥8 years. Additionally, patients experienced decreasing severity of xerostomia but increasing severity of neck fibrosis over time [54]. Additionally, given the age profile of patients with HPV-related OPC, most will return to work – but those that do report fatigue and difficulty at work due to dysphagia and dysphonia [55]. In the U.S., it is estimated that the projected lifetime earnings lost in 2017 due to OPC was approximately $321 million [56]. Healthcare system costs have likely been underestimated and recent analysis that estimated payments from private payors in Texas found a cost of $140,000 for the first 2 years after diagnosis [57]. In recent years, treatment de-escalation trials have been conducted to find the ideal balance between favorable clinical outcomes and minimum treatment-related morbidity but so far, the evidence from these trials do not support changes in current treatment protocols [58–60]. Since clinical outcomes are heterogeneous even among patients with the same tumor HPV status, work is ongoing to identify prognostic biomarkers and develop better risk stratification models to allow individualized treatment protocols.

3. HPV vaccination: a missed opportunity

There are currently four HPV vaccines available worldwide, all providing protection against types 16 and 18, the most common oncogenic types [61]. The quadrivalent vaccine additionally protects against types 6 and 11 and the nonavalent vaccine protects against types 6, 11, 31, 33, 45, 52, and 58. Countries with high HPV vaccination coverage are already experiencing dramatically reduced HPV-related benign and premalignant genital HPV-related diseases and early evidence of reduced cervical cancer incidence in younger populations [62,63]. Australia is projected to eliminate cervical cancer as a public health problem this decade [26]. Therefore, HPV vaccination should be the cornerstone of HPV-related cancer prevention. Unfortunately, global coverage in 2020 was 13%,

down from 15% in 2019 [64]. In the U.S., Healthy People 2020 goals (80% of adolescent women vaccinated) were not met and consequently, cervical cancer control in the U.S. will likely be delayed until at least 2038 [28]. Only 75% of adolescents have received one or more doses of the HPV vaccine and only 59% are fully up to date [8]. Although the number of HPV vaccine doses administered to adolescents have recently increased substantially compared to the period March–May 2020, the true effect of the COVID-19 pandemic on HPV vaccination is currently unknown [8]. The number of individuals presenting to primary care for in-person appointments, where these vaccines can be given, has also remained low [65].

Modeling studies on HPV-related OPC trends agree that incidence will keep increasing, at least for the next several decades [1,7,30]. Furthermore, the highest incidence rates will be among white men with an increasing burden on older individuals. According to modeling by Xu et al., by 2045, 93% of all cases will be among 55–69-year-old non-Hispanic white men, but the largest percent increase will be among those 70 years and older [7]. Similarly, Tota et al. projected that the highest rate of increase will be among older non-Hispanic white men, with rates remaining stable among men aged 45–54 years through 2029 [30]. These studies did not account for vaccination; however, the report by Zhang et al., suggest that HPV vaccination will have only a negligible effect on overall OPC incidence through 2045 and will have no substantial impact until 2060 [1]. By 2045, HPV vaccination will only reduce total OPC cases by 6,334 out of 736,518 cases projected without vaccination, with virtually all being among those born since 1990. These estimates are based on projections that 72% of those born between 2000 and 2010 (36–45 years old in 2045), 37% of those born between 1990 and 2000 (46–55 years old in 2045), only 9% of those born between 1975 and 1990 (56–69 years old in 2045), and none of those born before 1975 will be vaccinated [1]. These projections for vaccination rates in part assume greater uptake among adults (i.e. those who missed the CDC recommended HPV vaccination as a child, before their 15th birthday). While HPV vaccination is approved up to age 45 years, the vaccine's efficacy in preventing HPV-related disease drops with increasing age of administration, and most born prior to 2000 have already been exposed to HPV. Additionally, the future HPV vaccination rates projected by Zhang et al. have not considered or estimated the impact of the COVID-19 pandemic nor the future impact of growing distrust of science and vaccine hesitancy [9]. A recent modeling study predicted that the COVID-19 pandemic would result in up to 6,200 (95% uncertainty interval = 5900–6460) additional cases of OPC among males by 2100 [66]. Consequently, the predicted timeframe before substantial impact on OPC incidence may be further delayed.

4. Mitigation strategies

4.1. Vaccination

The study described above from Zhang et al., describes the relatively insignificant impact vaccination will have on the incidence of OPC in the next 25 years without significant increase in HPV vaccination rate [1]. Models of drastically increased HPV vaccination rates confirm the potential to eliminate cervical cancer, but in order for this the happen quickly vaccination rates will need to quickly reach 80% to 100% [67]. It has been 15 years since the initial FDA approval and CDC recommendation of HPV vaccination (of children and young adults) to prevent HPV-related cancers; however, in 2020 only 59% of adolescents are fully vaccinated [8]. In order to change the very disappointing timeline of substantial impact on HPV-related OPC incidence to sooner than 2060, we will need to rapidly increase vaccination rates above the 80% threshold required to reach herd immunity. This is particularly true among the young in whom HPV vaccination has the best chance to prevent HPV-related cancers, as immunity can be achieved before individuals have their first exposures with sexual debut. Zhang et al. do not predict that those born between 2000 and 2010 will reach the 80% HPV vaccination goal until after 2045 [1], it is precisely this group in whom we have an opportunity in the next five years to dramatically shift the timeline of substantial declines in HPV-related OPC incidence.

The FDA recently approved the HPV vaccine for individuals up to age 45 years and added OPC prevention to the approved indication of the vaccine. Unfortunately, it is estimated that only 20% of women and 3% of men born between 1980 and 1990, and therefore now eligible, will have been vaccinated by 2025 [1]. These rates are similar to the reported 18% of 18- to 44-year-olds that initiated the vaccine series in a recent study [68]. Overall, experts expect that vaccinating up to age 45 regardless of gender will prevent approximately 56,000 cancers [69]. However, barriers exist to vaccination on both the provider and patient sides. A meta-analysis of 29 studies showed a mean acceptability of 50.4 on a 100-point scale for the HPV vaccine among men. The factors that influenced male respondents most in the analyzed studies were increased education and knowledge of risks, the opinion of their partner, and the opinion of their health-care provider [70]. However, a survey of primary care providers showed that only 17% would recommend the HPV vaccine for men between the ages of 26 and 45 [71]. In addition to strong, consistent, and universal recommendation of HPV vaccination for children and adolescents, support of health-care providers for HPV vaccination among adults up to age 45 will also be needed in order to fully mitigate the ongoing HPV-related OPC epidemic and to more quickly realize the full cancer prevention impact of vaccination.

A variety of strategies have been explored to effectively increase vaccination rates. In the pediatric population, the combination of targeted interventions from providers and direct environmental interventions, such as vaccination in schools, has been extremely effective [72]. Of note, the environmental interventions have been broadly implemented in Australia, where vaccinations are done in school. A cost-effectiveness analysis of these strategies showed that the cost-effective approach is to give providers a checklist for appointments that includes HPV vaccination, but the most cost-effective environmental approach is to vaccinate in schools [73]. Of note, all approaches – clinic-based quality

improvement, school-based vaccination, and a statewide vaccination registration system with reminders – were cost-effective at the standard cutoff of $50,000 per quality-adjusted life year.

HPV vaccination is cost-effective in that it prevents virtually all HPV-associated lesions – including common diagnoses such as genital warts and precursor lesions for cancers at anogenital sites as well as more rare diagnoses such as OPC, but also cervical, vulvar, penile, and anal cancers. The Human Papilloma VIrus Vaccine Immunogenicity ANd Efficacy (VIVIANE) trial showed that no new cases of cervical intraepithelial neoplasia (CIN) grade 1 or higher were observed in patients over 25 in a 7 year follow-up period [74]. As mentioned previously, projections suggest that Australia will have a cervical cancer incidence under 4 per 100,000 by 2028 with standard vaccination and screening protocols [26]. Beachler et al. showed that the HPV vaccine was efficacious at preventing cervical, anal, and oral HPV infection among women without a history of CIN who received the HPV vaccine with a 0% oral HPV prevalence [75]. Chaturvedi et al. demonstrated similar findings, showing an 88% reduction in the prevalence of oral HPV 6/11/16/18 infection among vaccinated individuals [76].

4.2. Early diagnosis

A recent meta-analysis showed that time to cancer treatment initiation is one of the most important risk factors for patient survival as it prevents stage migration between presentation and treatment [77]. However, to shorten the time to diagnosis, symptoms must be recognized early in the absence of accepted screening paradigms. HPV-related OPC most commonly present with a neck mass (69%), though vague oropharyngeal symptoms may often precede metastatic adenopathy [78]. Primary care providers recognize the association between HPV and OPC and the need for subspecialty evaluation, understanding the gravity of a neck mass in an adult is critical [79–81]. In a survey of primary care providers working at a Federally Qualified Health Center, only 30% felt they were adequately trained to evaluate an oral cavity lesion, though 80% did recognize the importance of a neck mass when an oral lesion was noted [81]. However, this percentage varies widely between studies. In a meta-analysis, physicians were less likely to recognize the need for a neck exam in a patient with an oral lesion [79]. Notably, the American Academy of Family Practice guidelines do recognize the importance of prompt referral in any patient with neck mass with concerning symptoms or a cystic neck mass, and the adequate workup of any persistent neck mass for greater than 4–6 weeks [81–83].

For the specialist, there are emerging tools to assist in the evaluation of early lesions of the oropharynx. As noted above, there is no equivalent precancerous lesion in the oropharynx compared to anogenital mucosal sites. OPC are often subtle lesions and difficult to see within the crypts of the base of tongue and tonsils. Technologies that are emerging as useful for the evaluation of the oropharynx are narrow band imaging (NBI) and ultrasound (US) [84–87]. Tirelli et al. found that 8.5% of patients in their study of oral cavity and oropharyngeal cancers had an additional finding on NBI, all of which changed management. In three of these four patients, they found a synchronous primary; in the other, they were able to identify an unknown primary in the tonsil [88]. Muto et al., in a prospective trial of NBI compared to conventional white light imaging, found that NBI had a sensitivity of 100% of for the identification of superficial lesions in the head and neck and esophagus, compared to only 8% for white light alone [89]. The majority of these lesions, 75%, were then removed entirely by biopsy or endoscopic excision with minimal morbidity. In a comparison of magnetic resonance imaging (MRI) and US, Faraji et al. showed that 98% of OPC tumors were detected with US, although this is likely an overestimate as the sonographers were unblinded [87]. The high sensitivity and relatively low cost make US an attractive modality for diagnosis of OPC.

4.3. Screening

Efforts to screen for HPV-related OPC are unlikely to affect the true incidence of OPC because, unlike other HPV-associated cancers, there is no known precursor lesion that can be identified and treated prior to development of a true cancer. However, the goal of many of these screening strategies will be to identify the patients at highest risk of developing OPC and identify cancers early in their course, at the time-point when the treatment has its best chance of success with the lowest rate of treatment-related morbidity.

Unlike cervical cancer screening or anal cancer screening in selected high-risk populations, there are no established screening paradigms for OPC. As noted above, there is no comparable precancerous lesion in the oropharynx to cervical, vulvar, anal, or penile intraepithelial neoplasia. Consequently, prevention of OPC by diagnosis and subsequent treatment of a premalignant lesion is currently not possible. There are a few published experiences with head and neck cancer screening with some successes in diagnosing cases earlier, but these have shown some benefits for oral cavity cancers where premalignant lesions and early cancers can be identified by routine examination of the mouth in high-risk populations (smokers) [90–94].

Tota et al. recently performed a synthetic case-control study using cases of OPC from their institution and the National Health and Nutrition Examination Survey to identify individuals who were at highest risk of OPC [95]. Risk increased with older age, male sex, increased smoking and alcohol use, and oral HPV status. The authors used a series of patients with OPC with previous oral rinses tested for the presence of HPV DNA and found that HPV positivity in the oral rinse was also significantly higher in their case population. In their model, 70% of all OPC cases and 99% of HPV-positive OPC cases occur in the 10% of patients they identify as being at highest risk [95]. Similar risk factors for HPV-related OPC were identified in a machine learning model from Tewari et al [96].

4.4. Screening techniques: HPV DNA in oral rinses

HPV DNA has been identified in oral rinses by PCR testing in both patients with a known OPC and as a screening technique. Multiple studies have shown that approximately 1% of the general population will have an oncogenic HPV strain identified in an oral rinse [97,98]. The HPV in Men (HIM) study found that most high-risk oral HPV infections will clear in 6–7 months of follow-up, but that approximately 20% will persist beyond 24 months [99]. Others have documented HPV DNA from oral rinses in patients with a known HPV-related OPC. Rettig et al. found that HPV16 DNA can be identified in 54% of patients with HPV-related OPC at diagnosis, and the detection of persistent HPV in rinses after treatment was associated with a 36-fold higher rate of recurrence and 16-fold higher risk of death [100]. To evaluate rinses as a possible screening tool, multiple studies have estimated their sensitivity and specificity in patients with a known OPC. In a meta-analysis of five studies, sensitivity of oral rinse or swab was 55% (95% CI 25%–82%) and specificity was 94% (95% CI 85%–98%) for detection of an HPV-positive OPC tumor among patients with OPC [101]. A nested case-control study within two prospective cohort studies (the Prostate, Lung, Colorectal, and Ovarian Cancer screening study and the American Cancer Society Cancer Prevention Study II Nutrition Cohort) examined oral rinses from 96,650 patients, cancer free at baseline, and found that patients with oral HPV16 had 22 times higher odds (95% CI 1.8–276.7) of developing OPC [102]. The limited sensitivity of oral rinse may reflect the nature of the oropharyngeal mucosa, which is cryptic in nature, and shed HPV DNA from infected cells (or early lesions) is only transiently present at the surface and captured by current rinse sampling techniques. However, as has been shown for other HPV-related cancers, it is likely that identification of persistent oncogenic HPV over time will be an even stronger risk factor and screening tool; however, there is limited data on OPC incidence within those with and without persistent oral HPV [103,104].

4.5. Screening techniques: cytology

Several authors have attempted brush cytology of the oropharynx similar to Papanicolaou smear as used for decades in cervical cancer screening and more recently in anal cancer screening in men who have sex with men. In a study of 51 patients with HPV-related OPC, dysplastic cells were identified in 88% of oropharyngeal brush cytology samples [105]. The authors were able to test 95% of dysplastic samples for HPV, of which 54% were positive for an oncogenic HPV type (HPV16 in 19 and HPV33 in 3), and 63% were p16 positive by immunohistochemistry staining (an accepted surrogate marker for tumor HPV status). Of cancers that were HPV positive, 91% were also p16 positive [105]. Another group found that 53% of brushes of obvious lesions were HPV positive, and of lesions with known HPV positive status, 80% were positive on cytology [106]. The same group tested HIV-positive individuals in a nested case-control study, collecting both oral rinses and cytology. In that cohort, they found no association between HPV16 positivity on brushing and cytologic abnormalities on pathologic review of the brushings [106]. It is likely that oropharyngeal brushings are less representative compared to cervical brushings due to cryptic nature of the tonsils and base of tongue, and that abnormal cells from lesions deeper in oropharyngeal crypts are only transiently present and accessible to surface brushings [107].

4.6. Screening techniques: HPV serology

While natural human serologic response to an HPV infection may include development of antibodies to the L proteins (viral capsid proteins), development of antibodies to the oncogenic HPV early (E) proteins appears to be restricted to those with an HPV-related cancer or in the process of developing an HPV-related cancer. This association appears particularly strong for HPV-related OPC [108,109]. In a nested case-control study within a large prospective cohort, Kreimer et al. found HPV16 E6 antibodies in 35% of subjects who later developed HPV-related OPC as compared to only 0.6% of those remaining free of an HPV-related cancer (adjusted OR = 274 [95% CI 110–681]) [108]. Similar associations were found in a separate nested case-control study within another large cohort (adjusted OR = 140 [95% CI 40–491]) [110]. Dahlstrom et al. have reported similar associations (adjusted OR = 453 [95% CI = 199–1030]) for a composite test of seropositivity to all the HPV16 E proteins in two separate large case-control studies and have estimated sensitivity at 83% and specificity at 99% [111]. Meta-analysis suggested that the sensitivity for HPV16 E6 positivity is 83%, and specificity is 95% [112].

Two small prospective studies have already demonstrated initial utility of serologic assays to the HPV16 E proteins as markers for HPV-related OPC. In a study of men at high-risk for anal cancer (men over 35 years of age who have sex with men), Waterboer et al. identified 13 out of 603 who were serologically positive for HPV16 E6. Of these 13 men, one had a prior HPV-related OPC (previously treated but which recurred in the lungs shortly after serologic testing). Of the remaining 12, nine agreed to undergo head and neck examination and positron emission tomography-computed tomography (PET-CT) scanning as a screen for an HPV-related malignancy and one of these 9 was found to have an HPV-related T1N1 OPC cancer [113]. In a prospective clinical trial of screening for HPV-related cancers (principally OPC) among 553 men aged 50 to 64, Dahlstrom et al. identified 6 men who were serologically positive as a composite score to HPV16 E proteins. One of these 6 went on to develop and HPV-related pharyngeal cancer and another was found to have a high-risk HPV-related anal premalignant lesion, while none of the controls were identified with an HPV-related cancer or lesion [114].

4.7. Screening techniques: circulating HPV DNA

Because HPV is an epithelial infection, it should not be detected in peripheral blood. However, the detection of circulating HPV DNA is rapidly being established as a means to monitor patients with HPV-related malignancies after treatment, and this assay has already demonstrated the ability to detect small volume recurrences before they become clinically apparent by examination or complicated imaging modalities.

Consequently, circulating HPV DNA represents a potential marker for HPV-related cancers before they become clinically apparent, and its use is a promising option for blood-based screening. In one study, 84 of 103 patients with known OPC had detectable circulating HPV DNA in samples that had been obtained prior to diagnosis, giving 84% sensitivity and 97% specificity [115]. The same group has also investigated the role of circulating HPV DNA during treatment, and has found that patients who clear their circulating HPV DNA during or after treatment have a favorable prognosis [115,116].

4.8. Future directions

Further trials are needed to better understand what these options mean for patients who are not yet diagnosed with OPC. Published reports have largely been limited to case-control studies. However, two prospective cohort studies (Throat and Other HPV-Related Cancers in Men: Identifying Them Early [TRINITY], ClinicalTrials.gov Identifier: NCT02897427 and Men and Women Offering Understanding of Throat HPV [MOUTH], ClinicalTrials.gov Identifier: NCT03644563) are currently recruiting with the aim of evaluating the utility of HPV biomarkers in screening for HPV-related OPC [117,118]. The TRINITY study is evaluating circulating HPV DNA, antibodies to E antigens, and oral rinse HPV16 DNA in screening for the development of oropharyngeal and anogenital cancer in men aged 50 to 64 years and the MOUTH study is evaluating antibodies to E antigens and oral rinse oncogenic HPV DNA among adult men and women. While it is unlikely any of these solutions will be perfect, they will be a vital measure in bridging management of OPC until we meet adequate levels of HPV vaccination to dramatically reduce OPC incidence. If this study is successful, it will answer the vital question of who needs to be screened more closely, and what factors can identify the truly high-risk patient for screening and treatment. However, this study is of limited size, and a large multi-center population-based prospective screening trial is needed. Additionally, improvements to early oropharyngeal lesion identification are also a critical need.

4.9. Immunoprevention

For oropharyngeal cancer, where there is no premalignant lesion, the primary goal of screening is to identify patients who have already developed a malignancy in early stages, where treatment has minimal morbidity. However, screening for other cancers, like cervical or vulvar, involves the detection of precancerous lesions. These can then be treated, either with excision or medical options. The key medical option, which may hold promise for OPC, is immunoprevention through therapeutic vaccination. One such method was developed by Kenter et al., who used a vaccine against HPV16 E6 and E7 proteins as a treatment for high grade vulvar intraepithelial neoplasia (VIN). They found that 79% (95% CI 54%–94%) responded, with complete response in 47% (95% CI 24%–71%) [119]. In another immune-modulating approach, imiquimod, which activates toll-like receptor 7, has been used to treat VIN [120]. Additionally, multiple authors have attempted adjuvant HPV vaccination after excision of cervical intraepithelial neoplasia (CIN) in unvaccinated women, reducing the risk of recurrent CIN 1 or greater by one-third (RR 0.67, 95% CI 0.52–0.85) and CIN 2 or greater by 59% (RR 0.41, 95% CI 0.20–0.85) in a meta-analysis. It is possible that therapies similar to these – either targeted vaccination to other aspects of HPV, or another type of immunoprevention – will be valuable for the patients with persistent oral HPV infection or otherwise identified as high risk by screening who do not yet have an oropharyngeal lesion amenable to surgical removal [121].

5. Conclusion

OPC is a challenging cancer from a public health perspective – increasing in incidence due to a modifiable risk factor, but it must be modified many years if not decades in advance with vaccination. In the next 20 to 25 years, it is likely that the incidence of OPC will continue to rise, regardless of screening. Though success with screening techniques, such as described above will allow us to mitigate the effects of OPC by diagnosing OPC as early as possible allowing for less morbid treatments. Additionally, exciting opportunities are arising for novel treatments and immunoprevention for those identified at high-risk to subsequently develop an HPV-related malignancy. However, currently the only way to truly prevent this potentially devastating disease is to enhance widespread HPV vaccination, and a renewed and urgent effort to increase HPV vaccination is needed to avoid a public health failure: thousands of lives lost and affected by preventable HPV-related cancers.

6. Expert opinion

This review highlights the HPV-related OPC epidemic and how we might eliminate this public health problem with HPV vaccination. An important recent projection of future vaccination rates in the U.S. and their impact on future OPC incidence rates suggests that HPV vaccination will result in only limited reductions in HPV-related OPC through 2045 and that a substantial effect on OPC incidence will not occur until 2060 [1,16]. HPV vaccination rates in the U.S. remain sluggish and may very well worsen due to the pandemic effect on routine medical care along with a surge in anti-science beliefs and vaccine hesitancy [9,122]. These timelines, 2045 and 2060, are extremely disappointing, especially given that the HPV vaccine was originally approved by the FDA in 2006. While the last 15 years have been a missed cancer prevention opportunity for the un-vaccinated, a rapid uptake in HPV vaccination among all qualified groups could meaningfully shorten these timelines.

Without mandatory HPV vaccination and/or school-based vaccine programs, many parents and patients continue to need clear fact-based counseling that HPV vaccination is safe and critical to preventing HPV-related cancers, as well as that HPV exposures are extremely common. Broader recognition of the HPV-related OPC epidemic and of the extreme long-term morbidity of HPV-related OPC treatment is needed among providers on the frontline meeting with parents and patients and providing vaccines. These conversations in primary care

offices today can impact the future of the HPV-related OPC epidemic and whether thousands more unvaccinated will suffer and die from HPV-related OPC and its treatment. The most important thing any of us can do for the OPC problem is to advocate for HPV vaccination at every opportunity and to explain once again that the vaccine is safe, effective, and long-lasting.

Secondly, we have reviewed other potential strategies to mitigate the public health impact of the HPV-related OPC epidemic. Classified as secondary prevention, methods to diagnose HPV-related OPCs earlier in their course and/or to identify the group of individuals who are at the highest risk to have an early HPV-related OPC or to develop one will provide an opportunity to screen for OPC and treat more OPC at an earlier stage with less morbid therapies. Additionally, opportunities to prevent future development of HPV-related OPC among those at highest risk to have/develop OPC through treatment/elimination of persistent high-risk HPV and/or the treatment of a yet undefined HPV-related OPC premalignant process.

Prompt referral to an otolaryngologist for a neck mass or for unexplained throat symptoms in an adult will help avoid delays in HPV-related OPC diagnosis and the added morbidities associated with treating more advanced disease. However, developing means to identify groups of individuals at high-risk to later develop HPV-related OPC and to screen for and identify early HPV-related OPC will be critical to our goals of secondary prevention and to mitigating the HPV-related OPC epidemic as we await the substantial reductions predicted from broad HPV vaccine uptake. An important future direction is to prospectively test what methods of identifying those individuals at high-risk. HPV E protein serology, circulating HPV DNA, and persistent HPV DNA in oral rinses are the most promising current biomarkers to identify those individuals at the highest risk of having an early HPV-related OPC or of developing one. Importantly, none of these assays require significant technical skill nor cost, and they likely can be implemented efficiently broadly in the community. As paradigms of identifying high-risk groups are agreed upon, guidelines could developed, perhaps like those of other HPV-related cancers, to determine who would benefit from undergoing head and neck exams and other approaches to identify an HPV-related OPC early in the disease course. However, finding an early HPV-related OPC with routine head and neck exam is easier said than done, and other imaging techniques will likely be needed to supplement routine head and neck examination. Well-designed studies to evaluate for screening techniques take large cohorts and many years. Screening trials, such as the TRINITY study (ClinicalTrials.gov Identifier: NCT02897427), which is currently accruing middle-aged men, hold promise in identifying individuals at high-risk of HPV-related OPC. However, for several years, the field will be testing these biomarkers of risk and the means to identify early primaries as well as the implementation costs of such methods before a paradigm of HPV-related OPC screening can be implemented broadly and efficiently.

Acknowledgments

The authors thank Sherri Patterson for manuscript editing.

Funding

This paper received no funding.

Declaration of interest

KR Dahlstrom has received research reagents from Roche Diagnostics.

KS Anderson has served on the advisory board and has received sponsored research from Merck and Company, has served on the advisory board for Immunomedics, has served as a CME Lecturer for Eli Lilly and Company, and has received sponsored research from Founder FlexBio Tech and SafeGen Therapeutics.

EM Sturgis has received research reagents from Roche Diagnostics, in 2021 served as the Board Chair for The Immunization Partnership (a non-profit organization) and served on the Medical Advisory Board Member of The Prevent Cancer Foundation (a non-profit organization).

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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