COMMENTARY

Otolaryngologists and their role in vaccination for prevention of HPV associated head & neck cancer

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ABSTRACT

As Otolaryngologists we have witnessed a rise in a new disease with human papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (OPSCC). As of 2018, HPV associated OPSCC has surpassed the incidence of HPV associated cervical cancer within the United States. Non-HPV related head and neck cancer is largely a preventable disease through avoidance of various environmental factors, and we have seen a significant decline in cancer rates through anti-tobacco campaigns and other public health efforts. Given the success of HPV vaccination campaigns and reduction in HPV associated cervical and other anogenital cancers, some would argue HPV OPSCC is largely a preventable disease through vaccination as well. The question remains is how do we as otolaryngologist, non-primary care providers yet surgeons for this disease, help to promote public health efforts to reduce HPV related OPSCC. Within this article, we discuss preliminary data that supports HPV vaccination with HPV related OPSCC and the ongoing needs by our profession to help support public efforts in reducing the burden of this HPV related cancer.

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Introduction

The face of head and neck (H&N) cancer has been transformed by our growing understanding of the human papillomavirus (HPV) and its role in the carcinogenesis of oropharyngeal squamous cell carcinoma (OPSCC). Remarkably, we as treating physicians and Otolaryngologists, have witnessed a new disease arise over the last three to four decades. We are now seeing a new type of HPV-related cancer that presents in young, healthy, and often male patients. HPV associated head and neck cancers now encompass about 40–80% of head and neck cancer practice today.^{1,2} Over the last three decades, the incidence of HPV positive OPSCC has increased by 225%, with an associated 50% decline in the traditional tobacco-related HPV negative OPSCC.^{2,3} In 2011, one study projected that the incidence of HPV associated OPSCC cancers would surpass that of cervical cancer by 2020.² Remarkably, in 2018 we have already hit that benchmark; the CDC has recently reported the number of HPV positive oropharyngeal cancers far exceeds the number of HPV associated cervical cancers.⁴

OPSCC has been increasingly recognized as two distinct diseases; HPV associated OPSCC and the traditional tobacco and alcohol associated HPV negative OPSCC.^{5,6} This distinction is paramount, as these two cancers differ in prognosis.⁷ This distinction has recently been recognized on a national level as of January 2018, when the American Joint Committee on Cancer (AJCC) and National Comprehensive Cancer Network (NCCN) published new guidelines and revised staging for HPV associated OPSCC.^{8,9}

HPV positive OPSCC has a 5-year overall survival rate consistently exceeding 80–85%.¹⁰ Given the recent recognition of OPSCC's two distinct disease types, research efforts are focused on investigating treatment de-escalation for HPV positive OPSCC without compromising the 80–85% 5-year survival prognosis.^{11,12} As Otolaryngologists, we treat HPV related cancers many years after the causative infection and so our focus has been on treatment rather than on prevention. This narrowed focus has translated to our research endeavors and we often ignore the public health arm. Interestingly, head and neck cancer is a largely preventable disease through avoidance of various environmental risk factors. Through patient education and public health awareness campaigns we have seen a 50% decline in tobacco associated H&N cancer.^{1–3} Finally, given the success of HPV vaccination against HPV 16 and 18 in preventing over 90% of cervical and other anogenital cancers;^{13,14} many would argue HPV OPSCC is largely a preventable disease given over 95% HPV associated OPSCC are HPV 16 or 18.^{2,15,16} This begs the question, what can we as Otolaryngologists do from a public health perspective to improve HPV vaccination and slow the rampant progression of this disease?

We need to close the educational chasm for the general population, patients and providers

Routine screening for H&N cancer is not currently recommended by the US preventative services task force and uncommonly performed on asymptomatic patients.¹⁷ Like

many cancers, earlier detection is associated with improved outcomes. Five year survival for early stage HPV-related OPSCC is typically around 80–90% compared to 30–60% for late stage OPSCC.^{18,19} Early diagnosis is dependent on prompt recognition of different signs and symptoms by referring providers and patients, and subsequently with adequate and timely referral. Taken together, this makes not only patient but also referring primary care provider education paramount.

It is important that collectively as health care professionals we learn from lessons and the past success of public awareness campaigns on antismoking. We have seen a decline over the last three decades in tobacco related OPSCC which is largely attributed to decreasing smoking rates.^{20,21} The success of these campaigns are tied to educating the public about the risks of tobacco use.²² Multiple studies have confirmed the lack of knowledge among populations with regards to H&N cancers.^{23–27} In a survey of over 2,100 adults, 54.5% of respondents and 32.7% of respondents identified smoking tobacco and chewing tobacco as risk factors for cancer. Remarkably only 0.8% of respondents identified HPV infection as a risk factor for H&N cancer.²⁸ Although up to 70% were aware of vaccines that help prevent HPV²⁸, most adults are oblivious to the fact that HPV infection can cause cancers of the head and neck. Just like seeing the laryngectomy patient and his electrolarynx on television can make “it real” for patients about not smoking, we need to make “it real” for the HPV vaccine. One study found that by simply doing community-based screening, they were able to make a significant impact on smoking cessation.²⁰ Given the lack of screening tools for H&N cancers, screening programs may serve to educate. Currently the U.S. preventative services task force (USPSTF) recommends against routine screening for H&N cancer; however, the American Head and Neck Society (AHNS) does support the use of community based screening as an avenue for H&N cancer education as it relates to HPV.²⁹

Public awareness of H&N cancer can be achieved through awareness campaigns, media, and encouraging oral cancer screenings. Could similar public awareness campaigns and oral cancer screening with an HPV focus improve vaccination rates in certain populations? However, the challenge is screening adults between the age of forty and sixty, while promoting vaccination in a pre-adolescent and adolescent population. The AHNS has only recently within the last couple of years publicly endorsed the HPV vaccination.³⁰ In a survey of AHNS H&N surgeons, an overwhelming 96% supported further efforts to educate other clinicians of all specialties and increase media coverage.³⁰ It is important we show the disease and cancer burden of HPV OPSCC to improve awareness and discussion amongst patients.

On the other side of the educational pendulum, we as Otolaryngologists need to do a better job in educating providers and physicians across all specialties on HPV and OPSCC. In a study of about 350 pediatricians, about 50% reported ever discussing HPV vaccination and OPSCC, and over 92% reported needing further education and or training on HPV and its role in OPSCC. In a separate survey of over 400 practicing physicians, 50% of general practitioners (GPs) had never seen HPV associated OPSCC and only 20% of GPs and

10% of trainees had heard about HPV related OPSCC.³¹ Furthermore only 30% of all survey members had ever heard of HPV vaccination and possible prevention of OPSCC. We as Otolaryngologists are most familiar and arguably best poised to educate providers on HPV related OPSCC and must take it upon ourselves to help spread awareness and provide education to physicians and primary health care providers across all specialties to enhance their vaccinations strategies and earlier recognition this new disease entity.

Finally, there is a call for further education amongst our own. We as H&N surgeons have never received formal training in counseling patients with sexually transmitted infections (STIs), such as HPV. Yet, lifetime number of oral sex partners is the most strongly associated risk factor for HPV related OPSCC.^{32,33} One study found that over 89% of ENT physicians always or sometimes spoke with their OPSCC patients about HPV; however only about one-fourth felt comfortable they had adequate knowledge on HPV to properly counsel.^{20,34} Another study found following diagnosis patients were most encouraged by HPV association with improved prognosis; however the majority were concerned around the communicability of HPV, sense of embarrassment and or stigma with the HPV diagnosis, and the effect on their sex life and partners.³⁵ This study highlights the need for clinicians to facilitate both the patient’s asked and unasked questions. As a profession we must educate ourselves about HPV and its epidemiology and then learn how to become more comfortable talking about sexual behaviors. These areas can be addressed through educational workshops within resident programs, continuing education, and by role modeling of leaders within the profession. As with many multidisciplinary cancer teams, using a specialist to assist with time intensive conversations and providing written materials or reliable web-based resources all serve to educate patients. By enhancing our counseling roles as Otolaryngologists, we can help to destigmatize, educate and enhance patient knowledge that may in turn result in better compliance and education of families and their communities.

What is the role of HPV vaccination in preventing OPSCC?

The goal of HPV vaccination is to generate a durable immune response to HPV viral strains prior to exposure, ultimately protecting the patient host. The data on HPV vaccination efficacy and direct prevention of OPSCC is limited at this time. Interestingly, one study demonstrated prevalence of oral HPV infection was lower in those that had received the vaccine compared to controls.⁶ However, definitive conclusions are limited since baseline HPV rates were unknown and eventual progression to HPV positive OPSCC is theoretical. In a separate study looking at 2,627 adults as a representative sample of the US population, they found the prevalence of oral HPV 16/18/6/11 were significantly reduced in vaccinated (0.11%) compared to unvaccinated individuals (1.61%).¹⁶ In addition, cervical and other anogenital HPV vaccination studies are based on detection of premalignant disease and prevention of cancer as a primary endpoint.³⁶ Several studies have shown that HPV vaccination is effective in over 90%

for prevention of both viral infection and premalignant cervical lesions.^{13,14,37} Furthermore, follow up studies showed similar efficacy in the prevention of HPV related anogenital warts and premalignant growths.³⁸ The lack of premalignant disease for OPSCC makes a similar study difficult to evaluate efficacy of HPV vaccination. Despite conclusive evidence that oral HPV infection is a precursor to HPV positive OPSCC, further studies demonstrating an appreciable decline in oral HPV rates (and declines hopefully eventual declines in OPSCC incidence) post HPV vaccination will help support its role in prevention of HPV OPSCC.

Gynecologists and adult providers are in a unique position to address HPV vaccination with patients because PAP smears and HPV testing is included within their consensus guidelines for Cervical Cancer Screening.³⁹ A positive side effect of these guidelines is that every young adolescent female is required to have the conversation with their Gynecologist over HPV and the role of vaccination. However, despite evidence that demonstrates HPV related OPSCC is more common than cervical cancer in the US, we have no screening equivalent in Otolaryngology.^{2,4} Recognizing that most women undergoing Pap testing are beyond the age recommended for HPV vaccine, their personal experiences and knowledge clearly are influential in the vaccination of their offspring. This begs the question, would a similar screening tool for OPSCC ultimately increase vaccination rates and decrease HPV associated OPSCC? Further studies could look at the role of oral cancer screenings and simultaneous HPV education, and subsequent vaccination rates in small population groups.

To date, not only is there no screening tool for oral HPV infection, but the significance and clinical implications for patients with oral HPV infection is unknown. There exists both an oral rinse and oral swab test that have shown good accuracy in detection of oral HPV infection. However, they are most commonly used today to study HPV prevalence and efficacy of vaccination.⁴⁰ Vaccination efforts are often confronted with the criticism that no data has successfully linked oral HPV detection and OPSCC. Not only do most HPV infections clear spontaneously, but there exists no treatment for oral HPV infection. It becomes difficult to know what to do with those patients that are HPV positive on an oral swab. Do these patients require increased surveillance? Furthermore, what drives HPV infection to clearance versus a latency state that progresses to cancer? Ultimately this question may be nearly impossible to answer, as the latent period alongside other confounding variables such as tobacco use, alcohol, and other environmental exposures are difficult to disentangle. Interestingly, preliminary studies have shown that oral HPV testing may serve as an effective way to supplement surveillance in HPV related OPSCC and help predict risk for recurrence.^{41,42} Despite these unknowns, any type of meaningful HPV screening or detection of premalignant lesions could drastically change the landscape for HPV related OPSCC for patient education and vaccination by our profession.

What is our role as otolaryngologists – head and neck surgeons in promoting HPV vaccination?

The CDC currently recommends routine HPV vaccination for both boys and girls starting as early as 9 years of age and catch up

immunization up to 26 women and age 21 for men (with permissive recommendations up to 26 years).⁴³ With the ever-increasing rise in HPV OPSCC alongside the wide clinical age range Otolaryngologist treat, the question arises on our role in promoting vaccination. Despite the effectiveness of HPV vaccination in HPV related diseases/cancer, HPV vaccination rates are low (only 43% of teens have received all recommended doses), and even lower for adolescent males (31.5% having received all recommended doses).⁴⁴ HPV vaccination has lagged in contrast to other vaccines for adolescents, and vaccination is dismal in countries with the highest rates of HPV related cancers.^{45,46} As head and neck surgeons, we play a critical role in early detection, diagnosis, and treatment of H&N cancer and arguably in the best position to educate patients, families, and the public on prevention of HPV associated OPSCC. We have done a tremendous job in successfully campaigning against alcohol and tobacco as risk factors, why can't we do the same with HPV?

In order to successfully move forward with HPV vaccination promotion amongst H&N surgeons, it's important to understand their attitudes, current practices, and beliefs on HPV and vaccination. A recent survey conducted by the American Head and Neck Society (AHNS) that included just under 300 H&N surgeons discovered that over 90% of providers discuss HPV as a risk factor for OPSCC, but less than 50% actually discuss HPV vaccination with patients and families.^{40,47} The two factors most often cited were appropriateness for their adult population and the safety and effectiveness of the HPV vaccine as it relates to OPSCC; both barriers that can be easily overcome with future research endeavors.⁴⁷ Studies are now starting to show some preliminary data that vaccination may prevent oral HPV infection, however as stated before the direct benefit of vaccination for OPSCC will likely remain unresolved for some time. While over fifty percent of H&N Surgeons do not consider part of their role to discuss HPV vaccination in their clinics, close to 70% believe HPV vaccination efforts should go beyond pediatricians alone.⁴⁷ Over 90% of H&N surgeons strongly support public awareness campaigns, various educational efforts, and supporting CDC statement recommending HPV vaccination. However, only 68.5% reported their daughter and 55.8% of their sons has or will receive the HPV vaccine.⁴⁷ These findings suggest that despite most H&N surgeons support for educational efforts, personal beliefs and barriers exist within families that need to be addressed as well to assure non-ambivalent recommendations.

As H&N surgeons we primarily treat patients with OPSCC, adults well beyond the indicated age of vaccination. Ultimately despite our best intentions to discuss vaccination, the conversation can only go as far as promoting vaccination for age appropriate family members. However, Pediatricians, other primary care providers, and Pediatric Otolaryngologists are in a unique position to help spread awareness on HPV related ENT manifestation, education, and vaccination. In a survey of 348 pediatricians, 63.3% and 52.9% reported never discussing recurrent respiratory papillomatosis (RRP) and OPSCC respectively.⁴⁸ Interestingly, over 92% of respondents strongly felt the need for further education regarding HPV role in RPR and OPSCC. This study indicates that providers of pediatric care should be a targeted group for further education to enhance their efforts in

promoting HPV vaccination. While HPV vaccination in OPSCC may be controversial, the role of HPV vaccination in RRP is well accepted. Recent evidence has shown HPV vaccination in RRP reduces incidence rates⁴⁹ as well as role in preventing recurrent RRP.^{33,50} Taken together, this only reinforces the role otolaryngologists play in the propagation of HPV vaccine uptake. Thus, pediatric ENTs are in a great position as well to help promote HPV education and vaccination. However, studies will need to assess pediatric ENTs comfort in discussing HPV vaccination, their attitudes and beliefs, and setting that is most appropriate to disseminate this information.

As specialists, we must turn evidence-based research into successful education and vaccine safety communication strategies. Concerns over vaccine safety and provider lack of recommendation continue to hinder HPV vaccine rates despite the epidemiological evidence for HPV related cancers. We should continue to promote vaccination as an effective cancer strategy for cervical and anal cancer, recognizing that added benefits may be a reduction in H & N cancers without harm given its safety profile.

Conclusion

HPV associated OPSCC is on the rise and its incidence now exceeds that of HPV associated cervical cancer in the United States. We as Otolaryngologists must continue to not only focus on the treatment aspect but also on the preventative public health arm. Although conclusive evidence on the efficacy of HPV vaccination in preventing OPSCC remains elusive, there is significant momentum and an abundance of data that all points in the same direction; HPV associated OPSCC is likely a preventable disease through vaccination. We cannot ignore lessons learned on HPV vaccination and prevention of cervical and other anogenital cancers. We cannot and should not reinvent the wheel. Studies have shown education is key in moving forward, both to patients and medical care providers. Despite the fact there are still barriers that need to be addressed before the majority of Otolaryngologists promote HPV vaccination, the overwhelming majority of us are in favor of promoting education on HPV and OPSCC. Since we diagnose and treat HPV positive OPSCC, we as Otolaryngologists are best poised to disseminate information to patients and other medical providers through educational efforts, public awareness campaigns, and oral screenings. However, we must be unified in our efforts. While we are not poised to be the front line of vaccinators, we must continue to advocate for vaccination through awareness, public policies, and respond to misinformation and address barriers to vaccination. We need to continue to encourage partnership, research, and collaborative efforts with other leaders within the field, within our own communities, and on a national level.

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