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COMMENTARY

Morbidity, mortality and cost from HPV-related oropharyngeal cancer: Impact of 2-, 4- and 9-valent vaccines

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ABSTRACT

Objective: The incidence of oropharyngeal squamous cell carcinoma (OPSCC) related to human papillomavirus (HPV) is increasing at a dramatic rate, with men affected more commonly than women. Individuals who develop this disease suffer significant morbidity and potential mortality from their cancer and its associated treatment. We aim to evaluate the possible impact that the currently available HPV vaccines will have on this group of cancers. Data sources: Available peer-reviewed literature, practice guidelines, and statistics published by the Center for Disease Control and Prevention. Review methods: Contemporary peer-reviewed medical literature was selected based on its scientific validity and relevance to the impact HPV vaccination may have on the morbidity, mortality and cost resulting from HPV-related OPSCC in the United States. Conclusions: The incidence of HPV-related OPSCC is increasing at a near epidemic rate in the United States. The cost of treatment of HPV-related OPSCC is high, and the disease and its therapy result in significant morbidity and potential mortality to individuals. Using a cut-off of $50,000/Quality-Adjusted Life Year, expansion of current HPV vaccine indications to include prevention of OPSCC in both men and women should be recommended.

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Introduction

The oropharynx is the area of the upper aerodigestive tract located behind the oral cavity and above the larynx. The oropharyngeal subsites include the soft palate, posterior pharyngeal wall, tongue base, and paired tonsillar fossae. The latter 2 subsites contain lymphoid tissue in the form of lingual and palatine tonsils, respectively, and these are the areas primarily affected by human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC).

The oropharynx plays a critical role in many functions including swallowing, speech, and the maintenance of a patent airway. When affected by cancer or the sequelae of cancer therapy, these functions can be impaired, resulting in significant detriment to quality of life.[1]

Squamous cell carcinoma is the most common malignancy that arises in the oropharynx, with other tumors such as lymphomas, sarcomas and cancers from minor salivary glands occurring much less frequently. Traditionally, the primary risk factors for development of OPSCC included tobacco smoking and alcohol abuse. The incidence of these tumors, however, has been declining in recent years, mirroring the lower rates of tobacco consumption in the United States population.[2] Over this same time frame, oropharyngeal cancers due to infection with high-risk HPV (in particular, HPV-16) have been increasingly recognized. In fact, the incidence of HPV-related OPSCC has grown by 225% over the past 3 decades while the rate of tobacco-related OPSCC has declined,[3] with current trends suggesting that it has now overtaken cervical cancer as the most common HPV-related malignancy.[4] Currently, HPV DNA can be found in over 70% of newly diagnosed oropharyngeal cancers.[3]

Now, with the rollout of 2-, 4- and 9-valent HPV vaccines, there is the potential to slow the development of new HPV infections, decrease the societal burden of infection, and eventually decrease the development of HPV-associated benign, premalignant, and malignant conditions. This review aims to look at the potential benefit that would be obtained by preventing HPV-related OPSCC, with particular focus on the reduction in morbidity, mortality, and health care costs associated with this disease.

Methods

Relevant peer-reviewed medical literature was obtained using the Pubmed Search Engine. Key words included HPV vaccination, HPV oropharyngeal cancer morbidity, HPV oropharyngeal cancer survival, Cost of HPV vaccination, and HPV oropharyngeal cancer cost. Additional practice guidelines and publically available statistics provided by the Center for Disease Control and Prevention were also reviewed. At the discretion of the authors, information was selected based on its scientific validity and relevance to the impact HPV vaccination may have on the morbidity, mortality and cost resulting from HPV-related OPSCC in the United States.

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Discussion

Recent population-based estimates found that nearly 13,000 Americans are diagnosed with HPV-related OPSCC each year, with the male to female ratio being approximately 4:1.[4] Over time, HPV-related OPSCC has been recognized as a distinctly different clinical entity from its HPV-negative counterpart. For example, the typical presentation of HPV-positive OPSCC is a painless lateral neck mass. In contrast, individuals with HPV-negative OPSCC most frequently present with a sore throat.[5] Even on a fundamental level, HPV-positive and HPV-negative OPSCC are unique disease processes. Whole-gene sequencing studies conducted on over 100 OPSCC specimens by 2 independent research groups have demonstrated that the mutation rate of HPV-positive tumors was approximately half of that found in HPV-negative OPSCC.[6,7]

The average age at diagnosis is younger for HPV-positive OPSCC than for HPV-negative OPSCC (53 versus 57 years).[8] HPV-positive patients are also more likely to be male, Caucasian, college educated, have an annual income of $50,000 or higher, and to be non-alcohol and/or tobacco abusers.[9] Risk factors for HPV-positive OPSCC include early age of onset of sexual activity, a higher numbers of sexual partners and oral sex with partners that have genital warts.[9,10] In addition, epidemiologic studies have suggested a trend of increasing oral sex partners in younger cohorts, which may increase OPSCC incidence in the future.[11] However, even saviolum—commonly known as 'French kissing'—can serve as a vector of HPV transmission.[12]

Morbidity of treatment of HPV-related OPSCC

Treatment of OPSCC is with surgery or radiation therapy, either alone or in combination with each other. Chemotherapy may be combined with radiation therapy in patients with advanced treatable disease, or it may be used alone for palliation in the context of distant metastases or unresectable local or regional recurrence. Due to the constraints of the anatomy of the oropharynx, traditional surgical resections required open surgical approaches, which can include splitting the mandible for access. No matter the combination of treatment modalities, morbidity rates from OPSCC are significant. Post-surgical changes, post-radiation effects, and chemotherapy can result in significant disruption of normal breathing and swallowing physiology.

In patients treated with upfront open surgical resection followed by radiation therapy, good locoregional control can be achieved, but 29% of patients are left with long-term tracheostomy or gastrostomy tube dependence.[13] This, combined with distant metastasis rates that approached 30% in these patients, spurred the implementation of upfront chemoradiation therapy regimens, reserving surgery only for residual or recurrent disease.[14-16] These methods resulted in similar survival rates and a decrease in the rate of distant metastases, all while allowing for "organ-preservation." This is analogous to the evolution observed for therapy of laryngeal cancer.[17]

While these non-surgical approaches avoided the need for invasive open surgery, patients treated with radiation or chemoradiation still suffer considerable morbidity from their therapy. In fact, up to 88% experience transient dysgeusia.[18] and 36% suffer radiation-induced nausea and vomiting of grade 2 or worse.[19] In addition, high-grade mucositis with concomitant weight loss is worse in HPV-related OPSCC compared with HPV-negative OPSCC.[20] Approximately 5% of these patients treated with chemoradiation therapy develop cervical esophageal strictures, and many require repeat dilations for stenosis.[21] Despite development of more focused radiation strategies, up to 29-38% of patients have long-term xerostomia.[22] and more than 27% experience loss of one or more taste modalities after radiation therapy.[18]

Recent advances in transoral surgical techniques have allowed upfront surgical resection to again play a role in the management of patients with oropharyngeal cancer. In these situations, with the primary tumor and the involved and at risk lymph node basins removed, a lower dose of adjuvant radiation or chemoradiation can be provided in an effort to decrease treatment-related side effects. In a multi-institutional trial of patients receiving transoral laser microsurgery as part of their management, 97% of patients achieved local control of their disease and 87% of patients reported normal swallowing or only episodic dysphagia.[23] For early stage disease, patients treated with transoral robotic surgical resection and neck dissection had transient dysphagia, pain, and decreased quality of life, but this resolved within one year of surgery.[24,25] In such patients, where upfront surgery can allow for decreased use of adjuvant therapy, transoral robotic surgery has also been found to be cost-effective, decreasing expensed by $1,366 per patient and increasing quality adjusted life years by 0.25 when compared to radiation or chemoradiation therapy regimens.[26] However, such techniques are more commonly performed at academic centers and results are dependent on the volume of these resections performed at the institution.[27] As a result, such resources may not be available to many who are affected by the disease.

Disease control and mortality in HPV-related oropharyngeal cancer

HPV-related OPSCC has been found to be more responsive to therapy than HPV-negative OPSCC.[8,28] Ang et al, compared patients with stage III and IV HPV-positive and HPV-negative OPSCC, treated with chemoradiation therapy and found a 3-year overall survival of 82% in the HPV-positive cohort compared to 57% in the HPV-negative group.[8] Moreover, as previously mentioned, transoral techniques have been developed utilizing robotic instruments.[29,30] and/or laser microsurgery,[23,31] to allow for up front tumor excision in a less invasive manner, thus allowing for elimination or reduction of the radiation or chemoradiation therapy that is required.

Recently, due to the evidence of excellent locoregional control rates and survival for patients with HPV-related OPSCC, attention is now also being focused on trying to minimize treatment-related side effects through de-escalation of therapy. This is the subject of an on-going multi-institutional clinical trial looking at upfront transoral resection of the primary tumor and neck dissection(s). Patients are then assigned to undergo standard post-operative adjuvant therapy or a de-intensified adjuvant therapy regimen (Ferris RL, ECOG 3311). In addition, a phase II international trial is currently recruiting

early stage OPSCC patients and randomizing them to either upfront radiation or trans-oral surgery to compare both morbidity and mortality outcomes (ORATOR trial). This may reduce morbidity in a disease that has seen an escalation of chemotherapy administration and shift toward nonsurgical therapy in recent decades.[16]

Despite advances to reduce morbidity for HPV-related OPSCC, with increasing annual incidence comes greater annualized mortality. Thousands die each year from the disease and thousands more deal with sequelae from their treatment. Now with vaccines targeting the carcinogenic strains of HPV available, prevention would become the ultimate form of disease control.

Cost of HPV-related OPSCC

The nearly 13,000 annual new cases of HPV-related OPSCC that occur annually in the United States now exceed the new cases of cervical cancer.[4] Moreover, this number is likely to increase as some of those harboring the virus may go on to develop cancer in the absence of an established screening program. The impact on the patient, their loved ones, and the health care system of HPV-related OPSCC is significant. It was estimated that the mean lifetime cost per new case of HPV-related head and neck cancer was $43,200 with a total annual cost in the United States of $306 million, based on 2004–2007 numbers.[32] Since that time, the annual incidence of HPV-related OPSCC has doubled and the cost of care has continued to increase.

Due to the extended latent period between HPV infection and the development of oropharyngeal cancer, an immediate impact of HPV vaccination on OPSCC incidence will not be observed. However, it has been estimated that, by vaccinating boys and men, 5,416 and 51,168 additional cases of HPV-related OPSCC would be prevented at 50 and 100 years, respectively.[33] Moreover, the societal cost of HPV vaccination has been predicted to be well below the $50,000/Quality-Adjusted Life Year threshold used to determine cost-effectiveness of many public health initiatives.[34]

HPV vaccination

The approval of 2-, 4-, and 9-valent HPV vaccines has resulted in renewed optimism for disease prevention with regards to HPV-related cancer. However, the impact on HPV-related OPSCC will likely be much more delayed for many reasons. First, the recommendation for male vaccination has occurred much later and has been less widely adopted than for women. In 2006, the quadrivalent vaccine was approved by the Food and Drug Administration for use in girls and women, ages 9 to 26 years. In 2009, the FDA officially approved the use of the quadrivalent HPV vaccine for the first time for use in boys and men ages 9 to 26 years but did not recommend routine use at that time.[35] Its stated indication in males is the prevention of genital warts and premalignant and malignant disease in the anogenital region. As a result, early uptake in males ages 18 to 26 was a mere 1.1%.[36]

To date, prevention of oropharyngeal cancer is still not a recognized indication for HPV vaccination. However, since high-risk subtypes HPV-16 and -18 are implicated in over 95% of HPV-related OPSCC, all 3 vaccines would, in theory, provide immune protection, and thus prevent carcinogenesis.[37] Herrero, et al, evaluated a cohort of 7,466 women given either a HPV-16 and -18 bivalent vaccine or a Hepatitis A control vaccine and showed the HPV vaccine to be 93.3% effective at preventing oral HPV infection.[38] However, due to the extended latent period between infection and carcinogenesis, as well as the rarity of the disease and the lack of precursor premalignant lesions, executing a study to prove efficacy in preventing OPSCC is unlikely.

The current 3-dose vaccination rates for girls is 39.7% and boys is 21.6%.[39] These numbers are higher than initial reports but still represent a tremendous opportunity for improvement. The low implementation in males is particularly alarming because, as mentioned previously, these individuals are the predominant group that is at risk for developing HPV-related OPSCC. In addition to the slow adoption of HPV vaccination by the health care community, there is a tremendous lack of public awareness of the link between HPV and oropharyngeal cancer. In one study, only 0.8% of individuals recognizing HPV as a risk factor for head and neck cancer, and this knowledge was even lower in individuals without a college degree.[40] As a result, patients and their parents with poor understanding of the potential benefits may be less receptive to HPV vaccination.[41] A 2009 US panel of 18 to 59-year-old men reported factors associated with HPV vaccine acceptability and showed that that more respondents were willing to be vaccinated when the vaccine was presented as a cancer-preventing vaccine than when framed as preventing genital warts alone.[42]

In addition to the lack of public awareness of HPV-related OPSCC, there is a significant lack of recognition of the link between HPV and head and neck cancer in primary care specialties such as pediatrics and family medicine. As a result, the use of HPV vaccines to prevent OPSCC may not be strongly endorsed by these practitioners. Moreover, even if HPV vaccination is recommended, practitioners still need a comprehensive approach to ensure all 3 doses are administered.[43]

Conclusions

The incidence of HPV-related OPSCC is increasing at an alarming rate and has now surpassed cervical cancer as the most common HPV-related cancer in the United States. Epidemiologic data suggest this trend will continue. The disease, and the therapy used to treat OPSCC, result in significant morbidity and potential mortality, with substantial cost to our health care system. Increased utilization of commercially available 2-, 4- and 9-valent HPV vaccines would result in decreased prevalence of high-risk HPV infection, and would likely decrease the incidence of HPV-related cancers in the future. Using a cut-off of $50,000/Quality-Adjusted Life Year, expansion of current HPV vaccine indications to include prevention of OPSCC in both men and women should be recommended.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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