Prevention of recurrent respiratory papillomatosis: Role of HPV vaccination

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Received 7 April 2006; received in revised form 6 June 2006; accepted 7 June 2006

KEYWORDS
Recurrent respiratory papillomatosis; Human papilloma virus; Vaccine; Cervical cancer; Cervical intraepithelial neoplasia; Genital warts; Gardasil\textsuperscript{1}; Cervarix\textsuperscript{1}

Summary Recurrent respiratory papillomatosis is a rare, but devastating, cause of airway lesions in children and adults. This disease is caused by human papilloma virus subtypes 6 and 11. At this time there are two vaccines in late stages of development seeking Food and Drug Administration (FDA) approval to prevent cervical cancer, which is also caused by human papilloma virus. One of these vaccines has been developed to stimulate immunity to the most common subtypes that cause cervical cancer but also includes those responsible for recurrent respiratory papillomatosis. With the possibility this could drastically reduce the incidence of RRP, the otolaryngology community should advocate for implementation of a vaccine program that provides effective prevention of HPV infection with subtypes 6 and 11.

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1. Discussion

Recurrent respiratory papillomatosis (RRP) is a frustrating disease to manage due to its unpredictable nature and potential for producing airway compromise. RRP is usually caused by infection with human papilloma virus (HPV) subtypes 6 and 11 and is generally considered to be a vertically sexually transmitted disease from mother to child in the birth canal. We present information for the clinician regarding the potential for new vaccines that could impact the incidence of this disease.

Infections caused by human papilloma virus are common throughout the world. HPV is not a single virus but a family of closely related viruses, each designated as a type, numbered in order of discovery. Typing is based on nucleic acid sequencing. There are currently greater than 100 subtypes of HPV that have been identified and at least 30 can be detected in the anogenital tract [1]. These subtypes cause infection in different anatomic areas and in different epithelial types. HPV types associated with malignancies are classified as "high-risk"
types, and those associated with warts (condylomas) are rarely found in cancers and are referred to "low-risk" types.

Typically, HPV infections are classified by their location and are broken down into three classes: anogenital, nongenital cutaneous and nongenital mucosal. Although these subtypes are separated, various HPV subtypes can cause infection in multiple areas of the body. For example, HPV 6 and 11 can cause both genital warts and laryngeal papillomatosis. No simple in vitro culture methods are available for identifying HPV infection. Unfortunately, serologic testing is insensitive, too. Techniques for identifying the virus are based on nucleic acid detection, either via direct hybridization or after PCR amplification.

The Centers for Disease Control (CDC) estimates that there are currently 20 million Americans with an anogenital HPV infection and that 6 million new infections occur annually [1]. Among the anogenital HPV infections, up to 90% are clinically undetectable at 2 years follow-up. The CDC also estimates that up to 80% of sexually active women will have had an HPV infection by the age of 50 years [1]. Sexual transmission is the dominant mechanism for acquiring genital HPV. Infection is usually transient and may not be associated with symptoms. Studies have detected HPV in >90% of cervical cancers worldwide, and plausible biologic mechanisms have been offered to explain oncogenesis. The magnitude of the risk association between HPV and cervical cancer is greater than that between smoking and lung cancer [2]! However, infection alone is clearly insufficient to cause cancer, and additional factors are required for the development of neoplasia. A wealth of epidemiologic data regarding HPV has been pursued to establish its role in causing cervical cancer. This includes population studies as well as establishing evidence on a cellular pathway level.

The subtypes that are most commonly associated with cervical cancer are HPV 16 and 18. These subtypes account for approximately 70% of cervical cancer in the United States [3]. It takes many years for the cellular changes from normal mucosa to cervical intraepithelial neoplasia to cervical cancer to occur. Once infected, the cell can be influenced by viral products that cause disruption in the cell cycle. HPV gene products E6 and E7 impact tumor suppressor genes retinoblastoma and p53 [3]. Initially, this causes cellular atypia that can be detected with a Papanicolaou test (Pap smear). The progression continues, if not addressed, from superficial to deep in the epithelial layer. This is termed "cervical intraepithelial neoplasia" (CIN) and is graded on its depth (1–3). Once the basement membrane is invaded a histologic diagnosis of cervical cancer is made. Though cervical cancer is highly curable when detected early, it remains one of the leading causes of cancer death in women worldwide. Early detection is effective because the precursor lesions evolve slowly into invasive cancer, typically over a period of >10 years. These precursor lesions (dysplasias or cervical intraepithelial neoplasias [CIN]) are detectable with cervical cytology screening, the Pap smear. In every country where a Pap smear screening program has been introduced, rates of cervical cancer have been substantially reduced. The discovery that human papillomaviruses (HPV) are etiologically linked with cervical cancer has led to efforts to apply this knowledge to improve cervical cancer screening and to potentially prevent cervical cancer through vaccination.

Considering the medical and economic toll of anogenital cancer, intense research efforts have been directed at the development of prophylactic vaccines. With the evidence that a substantial percentage of the cancers were caused by a finite numbers of HPV subtypes the vaccine development has focused on these. Initial vaccine development was directed at HPV 16 alone as it may be responsible for up to 60% of cervical cancers. More recently, the experimental vaccines have included HPV 18, 6 and 11 as well.

Condylomatous lesions (warts) of the anogenital tract are most commonly associated with HPV 6 and 11. These viral subtypes also are responsible for causing recurrent respiratory papillomatosis (RHP). In contrast to HPV 16 and 18, HPV 6 and 11 are considered to be "low-risk" for causing malignancy. There are generally considered to be two relatively distinct clinical presentations for RRP: adult onset (AORRP) and juvenile-onset (JORRP). The adult form typically occurs when patients are in the third decade of life and infection is thought to represent either a reactivation of a latent infection or as a newly acquired sexually transmitted disease. Adult patients develop oral, hypopharyngeal, laryngeal, tracheal and pulmonary lesions that often initially cause hoarseness but can lead to airway obstruction. These papillomas virtually always require management operatively. The etiology of JORRP is generally agreed to be due to transmission of virus during gestation or through exposure to the virus during transit through the birth canal at the time of delivery. The risk is thought to be highest in women with frank condylomas or actively shedding disease from a recent HPV infection at the time of delivery though a third or more of these women have no visible lesions. The risk of transmitting the disease is estimated as 200–400-fold increase compared to a child delivered to a woman without condyloma [4]. This is a rare disease with nation-
wide estimates of prevalence ranging from 80 to 2300 cases [5,6]. There is similar estimates of prevalence 0.8/100,000 cases reported in European studies as well [7]. The juvenile-onset version is clinically more aggressive, though this may be more related to the relatively small size of the infant and child's larynx [8—10]. Some children can require greater than 100 lifetime surgical interventions to manage their airway. Death related to RRP may be as high as 1—2% while spread outside of the larynx into the trachea occurs in up to 25% and into the lung parenchyma in 2—5% [11]. Once spread of these lesions occurs below the larynx, they become very difficult to manage and may lead to complete airway obstruction.

Currently there are two human papilloma virus vaccines in development. These are Gardasil® from Merck, and Cervarix® from GlaxoSmithKline (GSK). GSK is likely to submit for FDA approval in late 2006 while Merck has recently received FDA approval for their vaccine. Both of these vaccines were developed with virus-like particles (VLPs) that simulate the surface of HPV. This is combined with an aluminum adjuvant to boost immunogenicity. The resulting antibody response is more potent than the response when infection occurs. The GSK vaccine contains VLPs to stimulate response to HPV 16 and 18. The Merck product is a quadrivalent vaccine with VLPs for not only HPV 16 and 18 but for HPV 6 and 11 as well. The HPV 6, HPV 11, HPV 16, and HPV 18 L1 VLP vaccine is manufactured in Saccharomyces cerevisiae (yeast). Yeast-derived vaccines have been safely administered to millions of children and adults world-wide. The vaccine includes amorphous aluminum hydroxyporphosphate sulfate adjuvant and is given in a three-dose (0-, 2-, 6-month) scheme. Phase I trials (300 participants) established immunogenicity and tolerability of a range of doses of monovalent HPV L1 vaccines.

The data from the phase II trials for both of these vaccines have been published [12—14]. Phase II trials (3500 participants) were performed to establish the immunogenicity and tolerability of a range of HPV L1 VLP vaccine dose formulations and provide preliminary proof of concept. The trials thus far have shown excellent safety data with no serious vaccine-related side effects. The response to the vaccine has been very good with 99.7% of those vaccinated developing an antibody response [11—13]. The primary endpoint of the phase II Gardasil® trial in 2392 young women was persistent HPV 16 infection (detection in consecutive visits) and HPV 16-related CIN. In 16—23-year-old women who were HPV 16-naïve at baseline, the vaccine was 100% effective; HPV 16 and CIN were detected in 41 unvaccinated (placebo) women and in no vaccinated women. The vaccine was generally well tolerated, and no serious vaccine-related adverse events were seen.

Combined, there are approximately 25,000 women in 33 countries and 100 sites enrolled in the phase III trials. The goal of these trials is to determine safety and efficacy in 16—25-year-old women and 15—25-year-old men using prevention of type-related CIN I, genital warts, and CIN II/III as the endpoints. The evaluation includes Pap testing and HPV polymerase chain reaction at defined intervals. An adolescent program (for girls 9—15 years of age) is ongoing to demonstrate vaccine immunogenicity and tolerability in boys and girls. In addition, a study utilizing the Nordic Cancer Registries is planned for long-term (>10 years) follow-up post-licensure to determine duration of efficacy, long-term safety, and replacement of vaccine types with other HPVs. The results of these phase III studies show that there was one case of CIN II or III in the treatment group and 53 in the placebo group [15]. Additionally, the vaccine group had no cases of genital warts while the placebo group had 40 cases [16]. In evaluating the data there was testing of women using both PCR techniques and serology. The vaccine was shown to be effective prophylactically, in preventing infection recurrence and also was found to reduce progression to CIN II/III when used as post-exposure prophylaxis. However, the vaccine was not shown to be effective for treating chronic HPV infection [17].

At the time of this article, both GSK and Merck are working towards FDA approval for their products within the next year or two. Under the best of circumstances, an HPV vaccine could be commercially available within the next several years.

There are a number of questions that confront the pending availability of an HPV vaccine. Important issues to resolve are: who will be vaccinated (women or women and men); when (at adolescence, in early adulthood, along with other vaccines such as for hepatitis B, Mumps or meningococcal disease) and how often (will boosters be needed). In considering the question as to when to vaccinate, a comparison was made in the level of immune response between 9—15 and 18—26 year olds. The immune response was significantly higher in the younger patients across all four HPV subtypes [18]. From this data, it would appear that the most benefit will come from vaccinating young women prior to their sexual debut, though older women may still benefit if they have yet to be exposed to the HPV subtypes in the vaccine. Although heterosexual boys may receive less direct benefit from vaccination, reduction of pathogenic HPV strains from males may be essential to the overall societal...
benefit of these vaccines. The duration of efficacy thus far indicates that boosters will not be needed. Durability of the vaccine has been shown out to 3.5 years suggesting that boosters will not be needed when vaccinated according to protocol [19]. There are other significant public health and social concerns, not the least of which is, what will be the acceptance of this vaccine by the public and will women who are of lower socioeconomic status have access?

The Red Book online recently published a table of new vaccines and recommended populations for vaccine [20]. This starts to address the issues of when to give the vaccine, and how it could be coordinated with other vaccines in an administration schedule.

One issue that will be important to the practicing otolaryngologist is which vaccine (Gardasil®, Cervarix® or both) is going to be approved for use. It is our opinion that the quadravalent product (Gardasil®) could have a significant impact on RRP. The pre-clinical, rodent data showed high levels of protective antibodies against HPV 6 and 11 in the offspring of vaccinated animals at 13 weeks post-partum. If this holds true in humans, then there is a strong likelihood that the future incidence of RRP will decline. Children with RRP have a diminished quality of life in addition to the significant financial burden imposed from repeated operative interventions, estimated at $ > 100 million per year in US health care costs [7,21]. Although this is a rare disease, we believe that otolaryngologists should advocate for the use of a vaccine that could reduce the impact of RRP on children. As an additional benefit, although the impact is likely decades away, we may also see a decline in the incidence of squamous cell carcinoma of the head and neck, since HPV 16 and 18 are implicated in this disease process as well.

2. Conclusions

Discussions leading to the approval and recommended administration of HPV vaccines are likely to be charged as there are both public health and political implications involved in the approval process for these products. The cost of the vaccines, third-party coverage and whether either or both will receive approval are yet to be determined and will have bearing on their universal use. Given the upcoming approval process, it would seem prudent for the otolaryngology community to express their views and advocate on behalf of their patients since there is a possibility of preventing a disease such as RRP in the course of also preventing cervical intraepithelial neoplasia and cervical cancer.

References

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