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Prevention of recurrent respiratory papillomatosis: Role of HPV vaccination

Gary L. Freed [a,b], Craig S. Derkay [a,b,*]

[a] *Department of Otolaryngology, Eastern Virginia Medical School, 825 Fairfax Avenue, Suite 510, Norfolk, VA 23507, United States*
[b] *Department of Pediatrics, Eastern Virginia Medical School, 825 Fairfax Avenue, Suite 510, Norfolk, VA 23507, United States*

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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.

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''

* Corresponding author. Tel.: +1 757 668 9853; fax: +1 757 668 9329.
E-mail addresses: craig.derkay@chkd.org, derkaycs@chkd.com (C.S. Derkay).

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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 subsites 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 (RRP). 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-