

TITLE: The Human Papillomavirus Vaccine and its Implications in Otolaryngology

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INTRODUCTION

In the United States, squamous cell carcinoma of the head and neck comprises about 4% of all malignancies. This corresponds to an estimated 17 per 100,000 persons with newly diagnosed squamous cell carcinoma of the head and neck per year. During 1998–2003, the incidence rate of Human Papillomavirus (HPV)-associated cancers in the United States was 10.6 per 100,000 people. While cancers of the oropharynx, oral cavity, and larynx are attributable to tobacco and alcohol use twice as often as HPV association, there is still an average of 7360 cases of potentially HPV-associated cancers in the head and neck region occurring annually in the US, causing significant morbidity and mortality. These cancers, which predominate in men, are second only to cervical cancer in the number of HPV-associated cancers in the United States, and the majority of cases are attributable to HPV16 and 18 infections. Additionally, though rare, recurrent respiratory papillomatosis (RRP) is a condition caused by HPV6 and 11 and a source of major morbidity, especially in children. This condition, as well as cancers of the head and neck, requires monitoring and future studies of the successful prevention of such conditions with the advent of the HPV vaccine.

Combined with avoidance of tobacco and alcohol use, reducing the risk of HPV infection through vaccination and sexual risk reduction could potentially prevent thousands of cases of head and neck cancer, as well as recurrent respiratory papillomatosis, and the associated morbidity and mortality of these diseases. However, for such vaccination recommendations to take place, studies must be conducted examining the pathology and activity of HPV infection in these anatomical regions and the relationship to oncogenesis, as co-infection without oncogenesis can also occur. Further, incidence of these cancers after HPV vaccine administration

in the US should be studied, and if possible, trials should be undertaken as in the studies for approval for cervical cancer prevention. Lastly, vaccine recommendation may require cost-effectiveness studies for approval for state funding, and this funding may need to be extended to boys as well as girls, and possibly to adults.

The goal of this paper is to give background information on the main HPV-associated head and neck pathologies, drawing from findings of the Assessment of the Burden of HPV-Associated Cancers in the United States (ABHACUS) study, as well as other research articles and reviews. Additionally, it will discuss the need to project research requirements and public health and policy considerations such as socioeconomic distribution, age to vaccinate, and state funding for approval of and use of the HPV vaccine for conditions relevant to the field of Otolaryngology.

INCIDENCE AND EPIDEMIOLOGY

Oral Cavity and Oropharyngeal Cancer

According to Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review of the National Cancer Institute, it is estimated that around 35,000 cases of oropharyngeal cancer will be diagnosed in 2010, with an age-adjusted incidence of 10.4 cases per 100,000 persons. Squamous cell carcinoma of this region is about 3-4 times more common in men than women and most often develops in or after the fifth decade of life. According to a study by Ryerson, et al on patient data from 1998–2003, out of this total number, 44,160 cases of potentially HPV-associated cancers of the oropharynx and oral cavity were identified, including 19,239 (43.6%) tonsillar, 16,964 (38.4%) base of tongue, and 7957 (18.0%) other.* oropharyngeal tumors. Over the time period, 35.6% cases of oropharyngeal cancers are HPV+ (87% of these with HPV16) and 23.5% cases of oral cancers are HPV+ (68% of these with HPV16).

The incidence rates for these sites were highest among blacks, and higher among non-Hispanics and men than among Hispanics and women. The annual incidence rates of potentially HPV-associated cancers of the tonsil and base of tongue both increased significantly from 1998 through 2003 while the incidence of head and neck squamous cell carcinoma at other sites declined. Also, it has been suggested in several studies that increases in rates of cancer in certain sites of the oropharynx, despite the reduction in tobacco exposure among Americans over recent decades, could be attributable to HPV infections, with some studies pointing to causes such as particular sexual behavior characteristics.

For example, an analysis of eight multinational observational studies that compared 5642 cases of head and neck cancer with 6069 controls found that the risk of developing oropharyngeal carcinoma was associated with a history of six or more lifetime sexual partners, four or more lifetime oral sex partners, and an earlier age at first sexual intercourse in men. The

* Defined as overlapping lesion of tongue; lateral wall of oropharynx; overlapping lesion of oropharynx; oropharynx, NOS; pharynx, NOS; overlapping lesion of lip, oral cavity and pharynx.

implications of this are discussed further later in this paper. However, cancers of the oropharynx found to be associated with HPV have been shown to have a more favorable prognosis than non-HPV related oropharyngeal carcinoma, particularly in non-smokers.

Laryngeal Carcinoma

According to SEER, an estimated 12,720 men and women will be diagnosed with cancer of the larynx in 2010, with an age-adjusted incidence of 3.4 per 100,000 persons. Laryngeal carcinoma is more common in African American than in whites, with a ratio of 3.5:1, and more common in males than females, with a ratio of 5:1. In the 1950s, this ratio was 15:1, but has since decreased, likely due to the greater number of females using tobacco. Laryngeal carcinoma most often affects middle-aged or older men, with a peak incidence between 50 and 60 years.

As mentioned above, the greatest risk factor for the development of laryngeal cancer is tobacco use, the risk of which can decrease after smoking cessation. Alcohol use creates a synergistic effect, but it is unknown whether alcohol is an independent risk factor. HPV is among other causes investigated in laryngeal cancer development and researchers in separate studies have identified HPV DNA in a range of 3.3-50% of biopsies of laryngeal carcinoma. In a meta-analysis of studies completed on the presence of HPV in non-cervical cancer biopsy samples, Mammas, et al found two studies with <20%, four studies with 20-40% and 3 studies with >40% detection rates of HPV through polymerase chain reaction (PCR).

Recurrent Respiratory Papillomatosis

In the United States, between 1500 and 2500 new cases of childhood-onset recurrent respiratory papillomatosis (RRP) are estimated to occur every year, making the incidence among children around 4.3 cases per 100,000 persons. Adult incidence is lower, at 1.8 cases per 100,000 persons. RRP has a bimodal distribution, with a peak in childhood years around two to three years old, and a second peak at age 20 to 40 years old. The male-to-female ratio in children is equal, but in adults the male-to-female ratio may be as high as 4:1. Most children with RRP appear to be the first-born of young mothers and come from families with low economic status.

RRP is more common in children, and is also more aggressive, requiring multiple surgical procedures, averaging 15 in the child's lifetime. Childhood-onset RRP presents with hoarseness and stridor, is often mistaken for asthma or chronic bronchitis, and can lead to complete airway obstruction. While RRP is considered a rare disease with variable clinical caliber, the number of surgeries performed each year can add up to around 15,000, costing an estimated \$100 million.

While many studies have shown a connection between exposure of the upper aerodigestive tract of a child to a mother with an HPV infection during vaginal delivery, there have been numerous children born to mothers with active HPV infection that have not acquired RRP. On the other hand, studies have suggested that HPV can be detected in up to 20% of disease-free mucosa in the anogenital area of pregnant women. However, there has also been a report of a child born by cesarean section who later developed RRP. Regardless of the mode of transmission, because RRP is known to be caused by HPV6 and 11, it will become important to

control the burden of this disease by controlling HPV infections, whether through vaccination of mothers, and/or through childhood vaccinations at an early enough age to prevent occurrence.

CERVICAL CANCER BACKGROUND

Therefore, a pertinent question is, how would the HPV vaccine acquire approval for use to prevent cancers that are believed to be associated with HPV? What kind of evidence is needed? To understand this, a brief history of the research and vaccine approval for use to prevent cervical cancer is needed.

Cervical cancer research has been ongoing since the mid 1990s and it was not until the early 2000s that vaccine trials began. After the beginning phase trials, a benchmark study was completed by the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II Study Group in 2006. They published their findings and suggestions in the *New England Journal of Medicine* in 2007, where it was explained that their phase 3 trial of the quadrivalent HPV vaccine (covering HPV6, 11, 16, 18) had an efficacy of 98% of preventing high-grade cervical intraepithelial neoplasia. This study was conducted using 12,167 females (5,305 in the vaccine group and 5,260 in the placebo group) between the ages of 15 and 26 years over a three-year period.

Both the quadrivalent and bivalent vaccine (covering HPV16 and 18) have been developed and approved by the Food and Drug Administration (FDA) for females aged nine through 26 years to prevent cervical cancer (HPV16 and 18) and genital warts (HPV6 and 11). While each vaccine uses a different adjuvant[†], the concept is the same-- virus-like particles (VLPs) are formed from the L1 protein of the outer surface of the virus, acting as antigens to which the body can form antibodies to fight off and prevent future infections of these particular strains of HPV.

Because of the findings from the vaccine studies, the Advisory Committee on Immunization Practices (ACIP) of the CDC recommends routine three-dose intramuscular vaccination of females aged 11 or 12 years using either the bivalent or quadrivalent vaccine. It can be started at age nine years and is currently recommended for all females between ages 13 and 26 years who have not been previously immunized or who have not completed the three-dose series. These ages are targeted because the ideal time to give the vaccine is before possible contact with HPV, which is most commonly acquired through sexual contact.

As of May 2010, the FDA approved the use of the quadrivalent vaccine in males aged nine through 26 years to reduce their likelihood of acquiring genital warts. However, mathematical models suggested that adding male vaccination was not the most cost-effective strategy when >80% of females were being vaccinated, and that improving coverage in females would be a better use of public health resources. Nonetheless, it is approved for use in males, and as with females, is most effective when given before exposure to HPV through sexual contact.

[†] Quadrivalent vaccine contains aluminum hydroxyphosphate sulfate adjuvant, and is produced in yeast, while the bivalent vaccine contains aluminum hydroxide and monophospholipid A and is produced in a baculovirus expression system.

ASSESSING THE BURDEN OF HPV-ASSOCIATED CANCERS IN THE UNITED STATES (ABHACUS)

In 2008, the Centers for Disease Control (CDC) published a supplement in the November edition of *Cancer* entitled “Assessing the Burden of HPV-Associated Cancers in the United States” (ABHACUS). This supplement was comprised of 18 articles and data from two cancer registries (the CDC National Program of Cancer Registries [NPRC] and the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results [SEER]) to establish a baseline of HPV disease burden at the advent of the use of the HPV vaccine. The goals as outlined by ABHACUS are to monitor:

- Age-specific rates of HPV-associated cancers
- Age-specific rates of HPV-associated cancer precursors
- Distribution of associated HPV types in cancers and cancer precursors
- Incidence of carcinoma precursors and invasive carcinoma along with prevalence of vaccination, and
- Methods of linking screening and risk factor data that are already being collected by other surveillance data.

ABHACUS not only initiated the monitoring of the impact of the vaccine on cervical pre-cancers and cancer, but also the impact of the vaccine on non-cervical HPV-associated cancers, as well as some of their associated precancerous lesions. A continued effort will require funding and an organized national effort led by experts. Baseline incidence of HPV-associated cancers were the following:

- 10,800 HPV-associated cervical cancers occurred per year.
- Nearly 7,400 potentially HPV-associated cancers of the oral cavity and oropharynx occurred per year with a male-to-female ratio of 3.3:1.
- More than 3,000 HPV-associated anal cancers occurred per year.
- About 2,300 new cases of vulvar cancer occurred each year.
- Penile cancer was relatively rare, striking about 800 men each year.
- About 600 women per year developed vaginal cancers.

As shown above, oral cavity and oropharyngeal cancers represent the second-most HPV-affected site, drawing attention to the potential that widespread HPV vaccine use could have on decreasing the number of cases in the United States. However, as ABHACUS and other studies have suggested, HPV presence, activity, and oncogenic potential are different entities, and the mere amplification by PCR of tissue samples does not necessarily equate with HPV as the cause of cancer. Further, the use of the term “HPV-associated” signifies that the researchers of ABHACUS chose these different locations of cancers because of their documented propensity to be sites of cancer directly caused by HPV, but all the cases noted in the SEER and NPRC registries are not caused by HPV. It is still important to continue these studies, as research to validate the role of HPV in cervical cancer were ongoing for almost two decades before the vaccine was developed and approved. On a similar note, in the case of RRP (not investigated in ABHACUS), one study concluded that HPV DNA is present in 2% of tonsillectomy patients,

whereas the incidence of RRP is only 0.004%, suggesting more than infection is needed to cause RRP, namely, host factors such as increased susceptibility to HPV infection.

Relation to Socioeconomic Status

In order to better understand target populations and reduce disparities in the distribution of information and resources, ABHACUS also investigated demographic characteristics of the HPV-associated cancers. With regard to oral cavity and oropharyngeal cancer there was an increased incidence with higher education, low-level to mid-level income, and residence in metropolitan or suburban areas. Ten to twenty percent poverty status was associated with decreased oral cavity and oropharyngeal cancer rates.

In females, Hispanic ethnicity, Asian/Pacific Islander race, and rural residence were associated with lower rates of oral cavity and oropharyngeal cancer. In counties with high school education rates of 75% to <85%, there was a lower incidence rate than those with 85% high school education. As mentioned above, current smoking was associated with increased incidence rates of oral cavity and oropharyngeal cancer.

In males, Hispanics and those residing in a county with <85% high school education had decreased rates of oral cavity and oropharyngeal cancer. Higher smoking prevalence and residence in a county with lower median household income were also associated with increased incidence rates.

Concerning ethnicity and rural-urban status, Asian/Pacific Islanders had significantly higher incidence rates in rural areas while for whites, the adjusted incidence rate was lower in rural counties compared with metropolitan areas. Overall, blacks had significantly higher incidence rates compared with whites in metropolitan as well as rural areas. Asian/Pacific Islanders had a decreased incidence rate compared with whites in metropolitan areas.

While the ABHACUS study covers >76% of the United States population, consistent data collection through the cancer registries must be continued to monitor changes in HPV-associated cancers. Once again, demographics are important in determining allocation of resources and will be discussed further in the policy section.

Years of Potential Life Lost (YPLL) and Productivity Costs

ABHACUS conducted studies to estimate the burden of HPV-associated cancers in terms of years of potential life lost and productivity costs. These values encompass all cervical, anal, vaginal, vulvar, and penile cancers and a subset of oral cavity and oropharyngeal cancers. Of note is the fact that values are derived from the total numbers of cancers in each of these areas, without taking the percentages of each of these cancers that could be attributed to HPV.

In summary, cancer-specific estimates ranged from 3654 YPLL each year for penile cancer to 45,815 YPLL for oral cavity and oropharyngeal cancer in men and from 5199 YPLL for vaginal cancer to 89,936 YPLL for cervical cancer in women. In women, oral cavity and oropharyngeal HPV-associated cancers caused 17,773 YPLL each year. Oral cavity and

oropharyngeal cancer mortality costs were calculated using 2003 data on US mortality, life tables, annual earnings, household services, and labor force participation rate. Among men, oral cavity and oropharyngeal cancer had the highest estimated cost at \$1.1 billion (\$463,623 per death). Among women, cervical cancer had the highest estimated cost at \$1.8 billion (\$541,576 per death). In women, oral cavity and oropharyngeal HPV-associated cancers cost \$270 million.

Concerning ethnic distribution, in white non-Hispanics, the highest mortality costs were cervical cancer accounting for 44.2% of the total, oral cavity and oropharyngeal accounting for 40.9%, and anal cancer accounting for 5.8%. The ABHACUS report quantified burdens by race/ethnicity, which, as mentioned above, can be used to assess relative versus overall burdens of cancer, which then can help inform decisions about the location of and audience for cancer prevention programs and services. The drawbacks of this study, however, were that information on race-specific earnings was not incorporated, possibly causing an under- or over-estimation of productivity losses; pain, suffering, and psychosocial costs were not accounted for; society's value on an individual cannot be calculated; estimates apply to HPV-associated cancers and not necessarily the percentage specifically caused by HPV; and direct and indirect medical costs, as well as caregiver costs, were excluded from the analysis.

Studies on economic burden of a disease and cost-effectiveness of prevention and treatment are generally important in deciding the approach(es) taken against certain diseases and are used in the formulation of healthcare policy. As noted in the ABHACUS study, HPV is present in oral cavity and oropharyngeal cancers, second only to its presence in cervical cancer. Socioeconomic parameters have been researched and the economic burden is apparent. As incidence studies continue following the use of the HPV vaccine, and as more studies on the pathophysiology of HPV-associated cancer continues, the evidence most likely will grow, underscoring the need for HPV vaccination, cancer screening, and other effective early detection programs for HPV-associated cancers.

PUBLIC POLICY AND PUBLIC HEALTH

Given the studies and evidence above, it would seem that the United States is on its way to noticing the potential benefits of the HPV vaccine beyond preventing cervical cancer. However, several questions need to be addressed before the vaccine is not only recommended by the CDC, but also before states will fund distribution and coverage of the vaccine as well as mandate education about its scope of beneficial effects. The vaccine would have to be proven as cost-effective in boys as well as girls, and the decision would have to be made whether or not to mandate coverage for entrance into schools. The question remains unanswered as to how many years surveillance of HPV-related cancers will have to continue before a significant effect on incidence rates is seen, if any.

With recurrent respiratory papillomatosis, several different questions are asked. Because it is a less common disease, in what manner and how long should incidence be tracked? Should studies be constructed to look at mothers who received the vaccine and the incidence of RRP in their children compared to unvaccinated mothers? It would also be difficult to do any prospective analysis for vaccination for this disease, as it would involve either infants at birth or two months, as RRP has been shown to begin in the first weeks of life, though often not symptomatic until six

months at the earliest. If long-term studies of HPV-vaccinated mothers show no change in the incidence of RRP in children, a study such as this may need to be undertaken, in a fashion similar to other vaccines that have been approved for administration at birth or two months (Hepatitis B, DTap, Hib, PCV, IPV, Rotavirus.) Further, another facet that would need to be investigated is the cost-effectiveness of the vaccine, and the disease burden that would be relieved through its determined efficacy.

An additional important factor will be determining the socioeconomic characteristics for population targeting to increase early detection and educate public and providers about the burden of disease. Understanding those audiences most in need, while not neglecting others at the same time, will affect healthy behaviors, health screening, and participation in preventive health care. As information is accrued concerning these populations, legislative bodies will have evidence as to the impact that new laws and funding can have on their individual states.

Further, a major priority at this point is further research, specifically on the activity and oncogenesis of HPV in the HPV-associated cancers. True numbers need to be generated as to the percentage of these cancers actually caused by HPV as opposed to simply being coexistent with HPV infection. As stated by Gillison et al:

“...Laboratory-based assays should include demonstration of the specificity of the viral DNA in tumor cell nuclei, detection of viral oncogene expression, demonstration of a clonal association between virus and tumor (e.g., integration, viral load, variant analysis), and dependence of the malignant phenotype upon viral gene expression.”

A worldwide systematic review did show that HPV16 and HPV18 accounted for almost all oncogenic HPV types detected in head and neck squamous cell cancer biopsies, suggesting that HPV vaccines should also be relevant for this group of cancers. Another related explanation of the shortcomings of recent studies is that they use epidemiological surrogates such as anatomic site, age, and histology which may misclassify HPV-associated or unassociated cancers that can alter vaccine effectiveness estimates derived from pre-vaccine era and vaccine era comparisons. Therefore, the HPV-etiological fraction of the population must be known and followed instead of the HPV-associated fractions for more accurate results. Studies of this focus should be continued, as this was the route that cervical cancers studies took to reach vaccine trials and implementation.

Even if the above concerns are addressed and completely understood, the original HPV vaccine debate of cost, safety, right to refuse, and moral issues remain. One ethical concern of oral cavity and oropharyngeal cancer is its link to sexual practices. As mentioned earlier, a history of more than four oral sex partners has been linked to an increased risk of developing these cancers. Also, it has been noted that there is an increased HPV prevalence in cervical tissue compared to male carrier rates, while there is a higher rate of HPV-associated oropharyngeal cancer in men. Further, one study claimed that men had an increased risk of tonsillar cancer when their wives had documented cervical dysplasia or cancer. However, it also has been shown that this cannot be labeled as the only cause, as some patients with oral cavity/oropharyngeal cancer report few sexual partners and no oral sex partners. Regardless, because at least some

claim increased risk with increased number of partners and oral sex partners, there is a negative stigma placed on the disease that raises similar moral questions as the debate to vaccinate young girls to prevent cervical cancer, which is also linked to number of sexual partners, among other factors. Further, it has to be asked if certain populations with these more “risky” sexual behaviors should be targeted for education or eligibility for vaccines.

Concerning funding, the Advisory Committee on Immunization Practices (ACIP) recommends the HPV vaccine in girls only because administration to females has been established to be cost-effective. However, risks, benefits, and costs would have to be weighed again should vaccine administration be suggested in boys and/or adults for oral cavity and oropharyngeal cancer. The same is true in infants if the vaccine were to be approved for prevention of RRP. Currently, the HPV vaccine is available through the federal Vaccines for Children (VFC) program in all 50 states, which provides vaccines for children ages nine to 18 who are covered by Medicaid, Alaskan-Native or Native American children, and some underinsured or uninsured children. Reconfiguration of allocation of funds would have to occur should the recommended coverage change, and this would be addressed by the legislature of each state. The issue of funding, whether through Medicaid and/or SCHIP, and for uninsured youth, has to be addressed, as well as deciding whether or not to require insurance companies to cover the vaccine.

Despite recommendations by ACIP, school vaccination requirements are decided by state legislatures, with some state legislatures granting regulatory bodies such as the Health Department the power to require vaccines. In 2007, several states attempted to pass legislation to make the HPV vaccine a school-entry requirement. While only the bill for Washington, DC was enacted, from 2007 to the present, 41 other states have introduced legislature to fund or educate the public about the HPV vaccine and at least 19 states[‡] have enacted these bills. Some states, such as New Hampshire, South Dakota, and Washington, are providing the vaccine at no charge to all girls in the state who request vaccination. This could have interesting outcomes as the incidence of oral cavity, oropharyngeal, and laryngeal cancers, as well as recurrent respiratory papillomatosis, are monitored in individual states.

CONCLUSION

In summary, it has been noted that the burdens of HPV-associated oral cavity, oropharyngeal, and laryngeal cancer, as well as recurrent respiratory papillomatosis, are real issues in the United States. With the advent of the HPV vaccine for preventing cervical cancer, it will be important to monitor changes in the incidence of these diseases, to investigate their pathophysiology and causal relationship to HPV infection, and to understand the distribution of disease in the United States. A dialogue on necessary mathematical modeling and cost-effectiveness studies to determine funding, as well as anticipation of potentially difficult questions regarding distribution of the vaccine will be important to address as research develops. The HPV vaccine could affect

[‡] Colorado, Indiana, Iowa, Louisiana, Maine, Maryland, Michigan, Minnesota, Nevada, New Mexico, New York, North Carolina, North Dakota, Rhode Island, South Dakota, Texas, Utah, Virginia and Washington.

disease burden beyond cervical cancer, and the implications of this possibility should not be overlooked.

DISCUSSIONS:

**Susan McCammon, MD;
HPV in Otolaryngology; September. 30, 2010**

Kathryn has a very fascinating background in Public Health and Public Policy Research from her undergraduate days and we settled on this topic as a way to investigate the occurrence of this topic in Otolaryngological literature as well as one that has public health repercussions not necessarily in one which we will wind up doing but the debate and the rhetoric that surrounds the establishment of vaccination as a potential anti-cancer targeted intervention. This was not just a coy way of how to get her to say “oral sex” in all of her ENT interviews

In Texas, the introduction of Gardasil was surrounded by a huge amount of overblown rhetoric and controversy based on the fact that it was explicitly casting cervical cancer as a sexually transmitted disease and behavior- or vice-related disease burden and I remember when that first came out I thought “Hey, I know how to rehabilitate that – we’ll just make sure that everybody knows that tonsil cancer and oropharyngeal cancer are also related to HPV. Interestingly, the research has gone the other way and tarnished head and neck cancer with the same STD condemnation.

We as physicians can be open minded, tolerant, all we want but when you look at the discussions and the controversies of the public policy makers, these are certainly real issues. I think that was a really good summary, Kathryn.

**Vicente Resto, MD, PhD, FACS
HPV in Otolaryngology, September 30, 2010**

Nice job, Kathryn. You raised some interesting issues regarding this topic. As physicians and scientists we try to come up with mechanisms that make sense and use them as rational platforms for all this policy debate. But those theories are numerous and I think we really don’t understand what’s going on. They range all over from the idea that women being exposed to cervical cancer, rather, HPV infection of the cervix which in most cases is overwhelmingly cleared effectively multiple times. There are classic studies done in college that essentially paint a picture of college women being under continuous attack of HPV infection with successful clearance in most cases. And then you wonder whether that is an inherent mechanism that then drives systemic immunity that then can explain why women have less oropharyngeal cancer in comparison to men who are married to women with a history of dysplasia. It would be reasonable to think that it would be going the other way.

It is evidently complex. There are racial overtones in this as well because we did some work here looking at the sero-database specifically looking at survival outcomes by race thinking that no one had looked at Hispanics. There have been studies that looked at outcomes in African-

Americans and showed that they were worse in general. What he ended up finding was that the overall results were intermediate for Hispanics, worse than for Caucasians but better than for African-americans. However, when you case-matched and controlled for primary tumor size, therapy, and a number of other variables those differences completely disappear in a way that Hispanics now came to look just like Caucasians did, suggesting that what drove the disparity was lack of access to care, presentations with more advanced disease, and things of that nature. Yet the disparity between Hispanics and African-americans and Caucasians persisted. Interestingly that difference was driven far and away by disparity in the oropharynx.

Given what we know now, HPV is an immediate topic to consider and he then went a step further and using known rates of HPV positivity began to do some modeling to actuarially understand whether those rates would explain the drive the disparity and the result was, yes, they did. His actuarial data set which was quite massive, basically you can make a statement that the disparity difference between African-americans and the others that persisted only in the oropharyngeal site is likely accounted for by HPV infection. There is a second study, independently confirming that, which is out of the University of Maryland with a population of no Hispanics, and mostly African-americans where they found that Caucasians in their cohort were mostly positive as opposed to African-americans that were negative and again, that drove the difference. So, clearly there are racial components that are going to come to be important in all this with profound effects on how public policy ultimately gets generated and implemented. So obviously race and socioeconomic status can be strong drivers in and of themselves within politics and government. It's an interesting topic with much to be done.

**Harold Pine, MD, FAAP, Pediatric Otolaryngologist
HPV in Otolaryngology, September 30, 2010**

The global public health burden attributable to human papilloma viruses is considerable. Not only is this virus and its many subtypes a major player in cervical cancer, it now clearly plays a role in certain cancers of the head and neck. It makes me wonder for those in the pediatric population who suffer from recurrent respiratory papillomatosis should have their virus sub typed looking for the more virulent and oncogenic strains, ie 16 and 18. For those children who require frequent trips to the operating room for debulking of their disease, I do think it is a good idea to send off a biopsy every once in a while to look for dysplasia or frank malignant transformation.

I really applaud your interest in public health. It's encouraging to see our next generation of otolaryngologists so interested in the global community. From a pediatric perspective, I certainly favor the quadrivalent vaccine which covers not only sub types 16 and 18, but also covers 6 and 11, the players in laryngeal papillomatosis. If this vaccine garners rapid universal support, I wonder if future pediatric otolaryngologists will see less papillomas. Perhaps it will be another topic for the history of medicine much like laryngeal diphtheria. As for my colleagues in head and neck surgery, the continued popularity of smoking and drinking leaves no doubt in my mind there will be continued oral cavity and oropharynx cancers to contend with for a number of generations.

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