

Preventing RRP and Other HPV-Associated Head and Neck Disease with Prophylactic HPV Vaccines

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Human papilloma virus (HPV) affects 75 percent of sexually active men and women at some point in their lives. There are more than 100 types of HPV, which can be divided into high-risk, oncogenic types, the most common of which are HPV 16 and 18, and low-risk types, the most common of which are HPV 6 and 11. High-risk HPV is a necessary cause of cervical cancer, and is also implicated in other ano-genital cancers and some oropharyngeal cancers, while low-risk HPV causes anogenital warts and recurrent respiratory papillomatosis (RRP). HPV 6 and 11 are vertically transmitted from mothers to their newborns, rarely causing hoarseness and breathing difficulties several months or years later. Not only do children develop RRP, but so, too, do adults, where the transmission is thought to be horizontal.

The new quadrivalent HPV vaccine is licensed and indicated for the prevention of cervical cancer, adenocarcinoma in situ, and intraepithelial neoplasia 1-3; vulvar and vaginal intraepithelial neoplasias grades 2-3; and genital warts associated with HPV 6, 11, 16, and 18. The CDC's Advisory Committee on Immunization Practices (ACIP) has recommended vaccination for all girls ages 11 to 12, girls and women ages 13 to 26 who have not yet been vaccinated, and girls as young as age 9 where the physician feels it would be appropriate. The vaccine is predicted to reduce the incidence, morbidity, and mortality of cervicovaginal HPV disease. An added, and often overlooked, benefit may be a concomitant decrease in the incidence of RRP and HPV-associated head and neck cancers.

RRP

RRP is a rare but potentially fatal result of HPV 6 and 11 (and rarely HPV

16) infection, resulting in significant morbidity. Warty growths typically develop on the vocal folds. Distal spread of the warts may occur and as many as 1 to 3 percent of children with RRP may die as a result of pulmonary disease. Multiple operations are required to remove the growths, but they often recur, with persistence of HPV infection in nearby, visibly unaffected sections of the mucosa. Management of RRP is quite costly; the average case incurs expenses approaching \$60,000 annually.

Head and neck cancer

Cancers of the oral cavity and pharynx affect more than 30,000 Americans

each year, and kill more than 7,400. HPV is implicated in a substantial portion of these oral, oropharyngeal, sinonasal, and laryngeal squamous cell carcinomas (SCCs). HPV has been found in close to a third of precancerous lesions of the oral mucosa. The HPV type detected is almost three times as likely to be a high-risk type as a low-risk type. Of all oral cancers, tonsillar SCC is most strongly linked with HPV. In a pooled analysis of 432 cases of tonsillar SCC, HPV DNA was present in more than half the specimens, with 84 percent of those being type 16. By comparison, HPV DNA is present in 9 percent of normal tonsillar mucosa or benign lesions.



Preventing HPV infection with prophylactic vaccination

The ability of the quadrivalent vaccine to prevent HPV 6/11/16/18-associated cervical and genital disease was established in the phase 3 FUTURE I and II trials. In FUTURE I, the quadrivalent vaccine was 100 percent effective in preventing cervical intraepithelial neoplasia (CIN) or worse, genital warts, and vulvovaginal neoplasia. In FUTURE II, the vaccine was 100 percent effective in preventing HPV 16/18-associated CIN. Both Future I and II were conducted in women in the age range at highest risk for HPV acquisition. However, it appears that the vaccine will be most effective if administered to individuals who have not yet become sexually active. Immunogenicity-bridging studies demonstrated that the vaccine does indeed yield serologic responses among younger girls that are equal to if not superior to the responses among 16- to 23-year-old women. A separate study in 9- to 15-year-olds established that immunogenicity lasts at least 18 months.

There is also a bivalent HPV vaccine currently in phase 3 trials. This vaccine provides protection against HPV 16 and 18, but not 6 and 11. Early phase 2 data for this vaccine suggests that it is 100 percent effective in preventing incident and persistent cervical HPV 16 and 18 infections in the according-to-protocol (ATP) sample, and 93 percent effective in preventing HPV 16- or 18-related disease in the intention-to-treat analysis; efficacy against disease was not presented for the ATP cohort. Like the quadrivalent vaccine, the bivalent vaccine may reduce the incidence of HPV-associated head and neck cancers. However, because the bivalent vaccine does not protect against HPV 6 and 11, it will not likely affect the transmission necessary for RRP.

Conclusion

Widespread use of the quadrivalent HPV vaccine promises to dramatically reduce the morbidity and mortality of cervical cancer and drastically reduce the incidence of genital warts. If the vaccine

is as effective in preventing HPV infection of the oral cavity as of the cervix and genital tract, then vaccination could be expected to reduce the incidence of HPV-associated oropharyngeal cancers by as much as 30 percent. In addition, a near-universal vaccination program providing the quadrivalent vaccine could eradicate RRP in future generations. Thus, vaccination against HPV offers additional benefits above and beyond prevention of cervical cancers, some of which are unique to the quadrivalent vaccine. Whether or not these hopes will be realized remains to be seen, and only through post-introduction epidemiological surveillance will we be able to ascertain the empiric data. Modern medicine has witnessed the abolition of disease following vaccine introduction (epiglottitis, smallpox, and in some countries, polio) while in other instances the problem has remained, such as that of Hepatitis B despite the introduction of the vaccine more than 20 years ago. **B**



Can Curcumin Prevent Cancer?

A Complementary Integrative Medicine (CIM) committee spotlight



Complementary and Alternative Medicine Use

According to a 2004 report by the National Center for Complementary and Alternative Medicine (NCCAM) and the National Center for Health Statistics (NCHS, part of the Centers for Disease Control and Prevention), 36 percent of adults use some form of complementary and alternative medicine (CAM). The U.S. public spent an estimated \$36 billion to \$47 billion on CAM therapies in 1997. Of this amount, between \$12 billion and \$20 billion was paid out of pocket for the services of professional CAM healthcare providers. These fees represent more than the public paid out of pocket for all hospitalizations in 1997 and about half of what it paid for all out-of-pocket physician services. Of this out-of-pocket spending, \$5 billion was on herbal products.

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The eye-opening statistics in the sidebar should be no surprise to otolaryngologists, who no doubt have patients using complementary medicines and therapies. One of the goals of the Academy's Complementary and Integrative Medicine (CIM) committee is to highlight and evaluate these medicines for their suitability in disorders of the head and neck. A 2005 study on the use of curcumin as an anticancer treatment is one such instance that has sparked the committee's interest.

Alternative treatment for head and neck cancer

Current treatment for advanced head and neck cancer includes surgery,

radiation, and chemotherapy. Surgery can be risky and disfiguring and a high risk of morbidity is associated with each method. Therefore, it is evident that alternative treatment methods are needed; curcumin might be the answer. The major substance in the spice turmeric, which is used in curry, has recently been found to have significant anticancer properties. An article published in October 2005 by *Clinical Cancer Research* (by Marilene B. Wang, MD, of UCLA, among others), detailed a study that demonstrated that curcumin treatment resulted in suppression of head and neck squamous cell cancer growth, both in vitro and in vivo.

Is curcumin a possible method?

Curcumin may have a number of possible anticancer mechanisms.

An antioxidant, it is a free radical scavenger and prevents cell damage by inhibiting lipid peroxidation and limiting DNA damage. It also induces apoptosis, or programmed cell death, in cancer cells.

Chemoprevention trials are now under way to see if curcumin can be used in this manner. Skin, prostate, and colon cancer are being looked at, among others. The 2005 study suggests such a role in human head and neck cancer. In that study, three different head and neck cancer cell lines were treated with curcumin and tested for growth inhibition. All showed suppression of growth in a dose-dependent fashion. Furthermore, in a mouse head and neck tumor model, application of curcumin paste resulted in inhibition of tumor growth.

A word of caution

Despite promising research giving cause for optimism, there are some

issues of concern regarding curcumin. Research has shown that curcumin may have carcinogenic properties, through interference with the well-known p53 tumor suppressor protein. While this was not a factor with the mice in this particular study, more studies are needed to test this effect. Another concern surrounding the use of curcumin is that it is a potent inhibitor of the cytochrome P450 enzyme, which is a key liver enzyme for the metabolism of many different drugs, and thus concurrent use with certain drugs must be carefully studied. Additionally, while topical application has been shown to be an effective delivery method, curcumin is poorly absorbed orally. Doses of up to 2 grams resulted in low systemic levels in serum. However, the addition of piperine, an extract of black pepper, may increase absorption by 2,000 percent. Furthermore, in human trials, up to 10 grams administration has been found to be safe.

Future plans

According to Dr. Wang, "Curcumin's potential as a suppressive agent for head and neck cancer definitely merits further investigation." The team of researchers in Wang's study recently received funding from the National Cancer Institute to continue their study of curcumin's mechanism of action and the optimal delivery method for tumor treatment. The team is currently investigating a liposomal formulation of curcumin, which allows the drug to be absorbed better and improves delivery to the tumor site. This method appears to show promise in their mouse models.

Reference

1. LoTempio MM, Veena MS, Steele HL, et al. Curcumin suppresses growth of head and neck squamous cell carcinoma. *Clin Cancer Res.* 2005; 11(19, 1): 6994-7002. **B**

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