CLINICAL UPDATE

Human Papilloma Virus (HPV) – More Than Just Cervical Cancer

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There are more than 100 different types of HPV. Most are associated with genital warts and infections. Many sexually active men and women will contract HPV at some point in their lifetime. In fact, HPV infection is the most commonly diagnosed sexually transmitted disease in the United States. Often, the body can clear HPV infection on its own within two years or less. Some types of HPV, typically HPV 6 and HPV 11, are considered low-risk HPV. Other HPV types are classified as high-risk because they lead to cellular mutagenesis and can cause cervical cancer as well as vulvar and anal cancer. Nearly all cervical cancers are caused by the high-risk HPV viruses. The most common of the high-risk strains of HPV are types 16 and 18, which cause about 70% of all cervical cancers.[1]

But while the rates of cervical cancer have decreased through the effective screening use of Pap smears, it is now known that there has been a dramatic rise in head and neck cancers associated with HPV. Population studies have estimated that approximately 50 percent of oropharyngeal cancers are attributable to HPV,[2] while more recent studies suggest that HPV may account for much as 70-80% of these cancers in the United States.[3] Estimates show that there are approximately 10,000 oropharyngeal cancer cases in the United States each year, a number that could climb to 16,000 by 2030.[4] HPV will be the causative agent in a significant number of these cases. Worldwide, cancer centers report that the virus is responsible for 45% to 90% of oropharyngeal cancers.[4]

The mechanism of how HPV causes head and neck cancer is very similar to how it causes cancer in the cervix. The DNA of the virus integrates into DNA of normal healthy cells, it and produces two harmful proteins, E6 and E7. These proteins bind and shutdown two important tumor-suppressor proteins, p53 and pRb. Active pRb prevents excessive cell growth; therefore without that protein, proliferative growth can occur. Active p53 arrests the cell-division cycle when DNA is damaged and then either activates DNA repair or initiates cell death. Without p53, proliferative growth can happen even if mutational DNA damage has occurred.[5]

Evidence, however, has shown that people with HPV-positive oropharyngeal cancer have a better response to treatment. There is a suggestion that chemotherapy and/or radiation may somehow reactivate p53 in HPV-positive cancers, turning the protein back on to fight the cancer.[6] Other theories are that HPV positive head and neck cancer patients are typically younger, healthier, and at less risk for developing secondary smoking-related malignancies like lung cancer. There is no denying that tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer.[7] However, the toxicities to therapy can be challenging. Concurrent chemotherapy and radiation is often utilized, potentially causing long-term side effects such as xerostomia and dysphagia. Common chemotherapy drugs include cisplatin, which can also cause ototoxicity and nephrotoxicity. Because of the favorable results seen in HPV positive head and neck cancer, currently there are trials looking at de-escalating therapy based on HPV positivity in order to limit potential long-term side effects to treatment.[8]

But rather than focusing on treatment for HPV positive head and neck cancer, vaccination has come to the forefront of primary care now for prevention of HPV related cancers. The Advisory Committee on Immunization Practices (ACIP) recommends that routine HPV vaccination be initiated at age 11 or 12 years. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Vaccination is also recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection), if not vaccinated previously. Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV. Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV. The 2vHPV, 4vHPV, and 9vHPV all protect against HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-associated cancers in the United States. The 9vHPV targets five additional cancer causing subtypes, which account for about 15% of cervical cancers. The 4vHPV and 9vHPV also protect against HPV 6 and 11, subtypes that cause anogenital warts.[9] Table 1 shows the characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States.[9]

According to recent statistics, a number of girls who received at least one dose of HPV vaccine increased between 2012 and 2013 (53.8% in 2012 vs. 57.3% in 2013). Completing recommended three doses increased but still remained low from 2012 to 2013 (33.4% in 2012 compared to 37.6% in 2013). For boys, there was a 13.8 percentage point increase for at least one dose of HPV vaccine (from 20.8% in 2012 to 34.6% in 2013). Meanwhile, 13.9% of boys aged 13-17 years received all three recommended doses of HPV vaccine in 2013 (compared to 6.8% in 2012).[10] These statistics pale in comparison to other viral vaccination schedules and reflects the slow adoption rate of new medical practices.

While HPV is well-known and associated with cervical cancer, there is a new epidemic now rising in the oncology world with HPV induced oropharyngeal cancer. Survival rates have proven to be high in these malignancies but so are toxicities related to treatment. With treatment advances along with further implementation of HPV vaccination, progress in prevention and treatment of head and neck cancers may prove to be one of the most successful cancer fronts.

Figures

Table 1. Characteristics of the three human papillomavirus (HPV) vaccines licensed for use.

Characteristics	Bivalent (2vHPV)*	Quadrivalent (4vHPV)	9-valent (9vHPV)
Brand Name	Cervarix	Gardasil	Gardasil 9
Virus Particles	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., and Inc.
Administration	Intramuscular	Intramuscular	Intramuscular

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