



# Seton Network Notes

A Publication of the Pharmacy and Therapeutics Committee

## Head and Neck Squamous Cell Carcinoma (HNSCC) and Human Papillomavirus (HPV)

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HNSCC is the sixth-most common solid tumor diagnosed in the world. In 2002, the incidence of new HNSCC cases was 500,000 with 300,000 deaths worldwide.<sup>1</sup> In a study assessing the burden of HPV-associated cancers in the United States from 1998-2003, it was determined almost 5,700 men and more than 1,700 women are diagnosed each year with potentially HPV-associated invasive squamous cell carcinomas of the oropharynx and oral cavity.<sup>2</sup> More than 17,300 cases of HPV-associated cancers are diagnosed in women and almost 7,600 cases are diagnosed in men each year.<sup>3</sup> The incidence of squamous cell carcinomas of the oropharynx and oral cavity associated with HPV that occur in men account for almost 23 percent of all HPV-associated cancers.

There is no treatment for HPV, but the lesions (or warts) associated with the virus may be treated. There are more than 100 types of HPV; however, there are only 40 known types of HPV that infect the genital area.<sup>4</sup> The Centers for Disease Control and Prevention estimates 20 million Americans are currently infected with HPV. It is also estimated more than 6.2 million new sexually transmitted HPV infections occur each year in the United States in people ages 14-44.<sup>5</sup> The primary mode of transmission of HPV to the head and neck region is suspected to be oral genital contact.<sup>1</sup>

HPV-16 and HPV-18 are the two most common HPV types found in HPV-associated head and neck cancers. In HPV-positive head and neck cancers, HPV-16 is reported in 90 percent of oropharyngeal cancers, 69 percent of laryngeal cancers and 68 percent of oral cavity cancers, while HPV-18 is found in 8 percent of oral cavity cancers, 4 percent of laryngeal cancers and 1 percent of oropharyngeal cancers.<sup>6</sup> HPV-16 in HPV-positive HNSCC is reported to occur in 85-95 percent of cases worldwide compared to its presence in cervical carcinoma (50-60 percent).<sup>7</sup> HPV-positive HNSCC incidence is higher in people younger than 50, those who smoke marijuana, those who engage in oral sex and those with multiple sexual partners.<sup>1,7</sup> HPV-positive HNSCC patients tend to be of higher economic status, have minimal tobacco exposure, better dentition, healthier nutritional status and improved overall health compared to HPV-negative HNSCC patients who have a higher exposure to alcohol and tobacco and much poorer dentition.<sup>1</sup> Higher levels of HPV DNA are found in the oral cavity of individuals who first experience sexual intercourse at a younger age and individuals with higher numbers of lifetime sexual partners. HNSCC patients with more than six lifetime oral sexual partners have a five-fold increased risk of having HPV in their tumor. While the incidence of HNSCC is decreasing with the increased awareness of tobacco and its associated risks, HPV-positive HNSCC cases are increasing in number.<sup>1,7</sup>

Several studies have shown HPV-positive tumors treated with chemotherapy and radiation, surgery and radiation, and concurrent chemoradiation have a better prognosis than similarly treated HPV-negative tumors. It is postulated HPV-positive HNSCC may be more radiosensitive than HPV-negative tumors due to the differences in p53. p53 is intact in HPV-positive tumors while there is a high percentage of mutated p53 in HPV-negative tumors. Radiation activates the intact p53 in HPV-positive tumors resulting in increased levels of p53 protein and induced programmed cell death.<sup>1</sup>

Gardasil®, manufactured by Merck and Company Inc., is a quadrivalent vaccine that protects against HPV types 6, 11, 16 and 18.<sup>8</sup> It is a killed, inactivated vaccine. In June 2006, the United States Food and Drug Administration approved the use of Gardasil® for the prevention of cervical, vulvar and vaginal cancer as well as genital warts in females ages 9-26. In October 2009, the FDA approved the use of Gardasil® in males ages 9-26 for the prevention of genital warts associated with HPV types 6 and 11. A randomized, double-blind, placebo-controlled trial in men ages 16-26 studied the efficacy of the quadrivalent HPV vaccine against persistent infection with HPV types 6, 11, 16 and 18. It found the overall efficacy of the vaccine against persistent infection to be 85.6 percent (efficacy for individual HPV types 6, 11, 16 and 18 were 88 percent, 93.4 percent, 78.7 percent and 96 percent). The authors of the study concluded the quadrivalent HPV vaccine (Gardasil®) is effective in decreasing the incidence and persistence of infection with HPV 6, 11, 16 and 18 in men ages 16-26.<sup>9</sup>

In October 2009, the FDA approved the use of Cervarix® in females ages 10-25. Cervarix® is a bivalent vaccine that protects against HPV types 16 and 18. It is a killed, inactivated vaccine. It is indicated for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2 or worse and adenocarcinoma in situ, and cervical intraepithelial neoplasia grade 1 caused by oncogenic HPV types

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16 and 18.<sup>10</sup> It is not approved for use in males; however, a recent study of the immunogenicity and safety of Cervarix® in males ages 10-18 years was conducted in Finland. The study found all seronegative subjects in the treatment group seroconverted for HPV-16 and 18 at month two. At month seven, all subjects were seropositive and had very high antibody titers for HPV-16 and 18.<sup>11</sup>

A national survey conducted in the United States prior to the release of Gardasil® studied the seroprevalence of all four HPV types included in the vaccine. It found the seroprevalence for HPV types 6, 11, 16 and 18 were 17 percent, 7.1 percent, 15.6 percent and 6.5 percent in women and 6.9 percent, 2 percent, 5.1 percent and 1.5 percent in men. For any HPV vaccine type, the seroprevalence in women was 32.5 percent and 12.2 percent in men. It postulates the difference in seroprevalence in men versus women is “due to the differences in the immune response induced by HPV infection rather than to lower infection rates.” The authors mention a hypothesis that “HPV infection of the keratinized epithelium in males may be less likely than infection of mucosal surfaces to induce an immune response.” There is another thought that the “duration of infection in men may be shorter and antibodies are less likely to develop after transient HPV infection.” The authors concluded the serologic data for males due to lower seroconversion rates after infection and shorter durations of antibody persistence make translation to cumulative exposure improbable. Not every woman will have antibodies present if they have cleared an HPV infection, so the task of determining the risk of developing cancer due to a previous HPV infection for men or women is an intricate endeavor likely to result in an underestimated risk.<sup>12</sup>

Three clinical trials are currently underway to study the use of vaccines against HPV-16 for the treatment of squamous cell carcinoma of the head and neck<sup>13</sup>, patients with advanced or recurrent head and neck cancer<sup>14</sup> as well as the safety of experimental cancer vaccines containing HPV-16 peptides and the necessary doses to stimulate an immune response<sup>15</sup>, respectively.

HPV is prevalent in the United States and 40 types of HPV are acquired as sexually transmitted infections. HPV has been shown to cause cervical, vulvar, penile, anal and some head and neck cancers. It also causes genital warts and other cutaneous lesions. Studies in both men and women involving the quadrivalent and bivalent vaccines, Gardasil® and Cervarix®, have shown these vaccines to be effective in protecting against infection with HPV types 16 and 18. HPV types 16 and 18 are the most common HPV types found in HPV-positive head and neck cancers. The incidence of squamous cell carcinomas of the oropharynx and oral cavity associated with HPV that occur in men account for almost 23 percent of all HPV-associated cancers reported in the United States. There are ongoing trials involving the use of HPV vaccines to treat patients with advanced or recurrent HPV-associated cancers, but there is currently no published data regarding the effectiveness of these immunotherapy-based treatments. It is difficult to estimate when the impact of global vaccination against HPV-associated cancers will be evident since these types of cancers are diagnosed at varying stages of life in men and women. When data becomes available from the recent clinical trials and seroprevalence studies are performed on the vaccinated generation, HPV vaccines may play a larger role in the treatment and prevention of HPV associated HNSCC.

## **Network Policies Approved for treprostinil (Remodulin®) and epoprostenol (Flolan®)**

As of January 2010, policies on the administration of both epoprostenol (Flolan®) and treprostinil (Remodulin®) are in effect. These two medications are potent vasodilators used in the treatment of pulmonary hypertension. For this indication, both have proven to be efficacious, demonstrating improvements in exercise capacity, dyspnea and cardiopulmonary hemodynamics. They are both administered via a continuous IV infusion; however, treprostinil can also be administered via a continuous subcutaneous infusion. The subcutaneous route eliminates the need for a permanent central venous catheter and achieves equal effectiveness to the IV route. A major area of concern for both medications is that cessation of the continuous infusion, even for a few minutes, can be fatal. Being such high-risk medications, the Seton Family of Hospitals' policies delineate that only physicians with expertise in pulmonology, critical care and/or cardiology may prescribe and manage them, and that patients receiving these medications must either be in an intensive care or intermediate care unit. The policies define procedures for patients either initiated on treprostinil or epoprostenol within the SFH or patients continued on their home infusion. Safe management of both subsets of patients requires ongoing communication among medical, nursing and pharmacy staff.

The policies are available on the SFH Patient Care Policies and Procedures intranet site. A network guideline is attached to each policy. The network guidelines contain detailed information regarding dosing, monitoring, product stability and important patient considerations. In addition, information from the manufacturers is located here including enrollment forms, Web sites and the 24-hour helpline phone number.