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Rethinking the Head and Neck Cancer Population: The Human Papillomavirus Association

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Head and neck squamous cell carcinoma (HNSCC) is the tenth most commonly diagnosed form of cancer in males worldwide. Although the incidence of HNSCC is relatively low in the United States, the affected population is changing from older males to young Caucasian males. High-risk strains of the human papillomavirus (HPV) already are associated with cervical, oral, and anal cancers; however, HPV DNA has been detected in about a third of head and neck malignancies. Nurses play major roles in educating the public and treating patients with HPV and HNSCC. Many possibilities for outreach and research exist that could decrease HPV and HNSCC rates.

During the early 1980s, the incidence of head and neck squamous cell carcinoma (HNSCC) in the United States was decreasing. Because the decrease corresponded with decreases in smoking, many experts considered HNSCC to be related to tobacco use and, therefore, preventable (Westra, 2009). Historically, older males with multiple comorbidities who drank excessive amounts of alcohol and smoked cigarettes were more prone to developing HNSCC (Lowry, 2009).

As of 2008, HNSCC was the tenth most commonly diagnosed form of cancer in males worldwide (Jemal et al., 2011). An estimated 650,000 new cases of HNSCC are diagnosed worldwide each year (Westra, 2009). In the United States, however, HNSCC accounts for less than 3% of newly diagnosed malignancies and approximately 1% of cancer-related deaths (Bernstein & Klausner, 2008). According to the most current statistics from the Centers for Disease Control and Prevention (CDC, 2009), an estimated 9,000 males and 2,300 females develop head and neck cancer each year. Although the incidence of HNSCC is relatively low in the United States, the incidence of human papillomavirus (HPV)-associated HNSCC has increased (Marur, D’Souza, Westra, & Forastiere, 2010) and HPV DNA has been detected in about 35% of head and neck malignancies (Lohavanichbutr et al., 2009).

At a Glance

- The strongest association between human papillomavirus (HPV) and head and neck squamous cell carcinoma (HNSCC) occurs in the tonsils within the oropharynx.
- HPV-associated HNSCC has been detected in patients with five or fewer lifetime oral-genital sex partners.
- The incidence of HPV-associated HNSCC is expected to increase.

According to Lowry (2009), young Caucasian males who are well-educated and otherwise healthy are now developing HNSCC. As a result, many HNSCC experts predict that the incidence of HPV-associated HNSCC will continue to increase in the United States (Gillison, 2008).

Human Papillomavirus and Cancer

Often acquired in the early years of sexual activity, HPV is a common sexually transmitted infection (see Figure 1). According to the CDC (2009), 20 million Americans are believed to be

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infected with HPV. Although the annual incidence of HPV in the United States is about 6.2 million people, HPV-related cancers claimed the lives of 3,710 Americans in 2005 (CDC, 2009). Ultimately, sexually active individuals have a 50%–75% lifetime risk of HPV exposure (CDC, 2009; Giuliano, Palefsky, et al., 2011; Mayeaux, 2008). The American Cancer Society (2010) estimated that 36,540 Americans were diagnosed with oral pharynx cancer in 2010.

Many have considered HPV to be a condition mostly affecting females. However, a study by Giuliano, Lee, et al. (2011) found that genital HPV was prevalent in 50% of males ages 18–70. A total of 4,074 males from three countries (Brazil, Mexico, and the United States) agreed to attend 10 appointments over a four-year period of time. During the biannual visits, researchers obtained tissue specimens to assess HPV genotype status. In the first subcohort of 1,159 males recruited from June 2005 to December 2006, 584 (50%) of the males were found to have oncogenic and nononcogenic genital HPVs. Although the average clearance time was 7.5 months (95% confidence interval [CI] = 6.8–8.7), males ages 18–30 required significantly longer time to clear any strain of HPV (9.53 months; 95% CI = 7.13–11.50 months) (Giuliano, Lee, et al., 2011).

Overall, females and males develop different immune responses to HPV (Giuliano, Palefsky, et al., 2011). More females become HPV-seropositive (175% versus 79% of males). In addition, females have higher levels of HPV antibodies than males. Experts believe that the higher incidence and prevalence of HPV infections in males may be attributed to the decreased immune responses of males.

Giuliano, Lee, et al. (2011) suggested that males may have a consistent risk for developing HPV infections throughout their lifetimes. Unlike females, who have demonstrated decreased risks of developing HPV as they age, research has shown that males have lower HPV antibody titers despite having increased genital HPV DNA prevalence. As they aged, older males were able to clear their oncogenic HPV infections more rapidly than younger males (Giuliano, Lee, et al., 2011). Giuliano, Lee, et al. concluded that an increased prevalence of HPV antibodies in older males may be associated with the more rapid clearance.

A total of 118 HPV strains have been identified and described, with 50 found to infect anogenital surfaces (Tran, Rose, & O’Brien, 2007). Many of these strains also have been detected in head and neck mucosal lesions. HPV may be classified as low or high risk. Low-risk strains, including HPV types 6 and 11, are associated with genital warts (Tran et al., 2007), low-grade cervical dysplasias, and recurrent respiratory papillomatosis (Mayeaux, 2008). High-risk strains, including HPV types 16 and 18, are associated with cervical (Tran et al., 2007), oral, and anal cancers (Haddad et al., 2008).

At least 90% of cervical cancer cases have been linked to HPV types 16 and 18 (Haddad et al., 2008), making the association between HPV and carcinogenesis well known for cervical cancer. Common risk factors for genital HPV infections include (a) early age of initial intercourse, (b) increased numbers of sexual partners, (c) infrequent use of condoms, and (d) coinfection with Chlamydia trachomatis or herpes simplex (Haddad et al., 2008). Additional HPV risk factors include compromised immunologic status and having intact penile foreskin (Mayeaux, 2008).

Extending from the soft palate to the epiglottis and incorporating the tonsils and base of tongue (Marieb & Malatt, 1992), the oropharynx is the most common site for HPV infection within the head and neck region (Haddad et al., 2008; Hobbs et al., 2006). According to Hobbs et al.’s (2006) meta-analysis of 17 studies, the association between HNSCC and HPV type 16 was strongest for tonsils (odds ratio [OR] = 15.1; 95% CI = 6.8–33.7), intermediate for other tissues within the oropharynx (OR = 4.3; 95% CI = 2.1–8.9), and weakest for oral (OR = 2; 95% CI = 1.2–3.4) and larynx (OR = 2; 95% CI = 1–4.2).

Similar results were reported by Tran et al. (2007), who acknowledged the findings of a multicenter case-control study of 3,400 patients conducted by the International Agency for Research on Cancer. In this large trial, the researchers demonstrated that HPV caused many cancers within the oropharynx. Specifically, within the oropharynx, the association between HPV and the tonsil was the greatest (Tran et al., 2007). Although the mechanisms are unclear, the tonsils contain deep mucosal invaginations that may trap viral particles (Haddad et al., 2008).

Additional studies confirm HPV type 16 as a causative agent in oropharyngeal cancers. HPV DNA type 16 has been detected in 36%–72% of malignant oropharyngeal samples (D’Souza et al., 2007; Haddad et al., 2008; Westra, 2009). Notably, Syrjänen (2005) reported that HPV type 16 may have been detected in 84% of HPV-positive tumors. HPV-associated HNSCC have separate and specific risk factors, appearances, and structures from other HNSCC cases (see Figure 2). Citing a 50% detection rate of high-risk HPV in tonsillar carcinomas, Singh and Westra (2010) concluded that HPV should be recognized as a distinct oncogenic factor in HNSCC.
Additional risk factors for HNSCC include alcohol consumption, tobacco use, poor oral hygiene, and genetics (Marur et al., 2010). Regardless of alcohol and tobacco consumption, HPV type 16 seropositive individuals have a 30-fold increased risk of developing pharyngeal cancer (Applebaum et al., 2007), distinguishing HPV type 16 carcinogenesis from alcohol and tobacco-associated carcinogenesis in HNSCC (Haddad et al., 2008; Psyrri, Gouveris, & Vermorken, 2009).

Giuliano, Lee, et al. (2011) also observed that the median time required to clear HPV type 16 was approximately twice as long as the median time required to clear non-HPV type 16 oncogenic strains. That increased time suggests that type 16 (which also has been reported in females) is the most virulent form of HPV.

Overall, the incident rate for HPV-associated HNSCC is higher in males than females (3:1) (Westra, 2009). Males may increase their chances of acquiring HPV when they perform oral-genital sex on females, as HPV has an increased prevalence in cervical tissue compared to penile tissue (Marur et al., 2010). According to Tran et al. (2007), HPV-associated HNSCC also is now being detected in younger patients. Marijuana use and immunosuppression may contribute to HPV-associated HNSCC (Westra, 2009), as well as the presence of bacterial infections resulting from poor oral health (D’Souza et al., 2007). Furthermore, herpesvirus 8 in the presence of HPV may potentiate malignant transformation of normal epithelial cells (Underbrink, Hoskins, Pou, & Albrecht, 2008).

Sexual Behavior

Regardless of alcohol or tobacco intake, HPV-associated HNSCC usually is acquired through oral-genital sex (D’Souza, Agrawal, Halpern, Bodison, & Gillison, 2009; Gillison, 2008). In a case-control study by D’Souza et al. (2009), oral-genital sex and open-mouth kissing were associated with the development of oral HPV infections. Furthermore, the chances of developing oral HPV infections in college-aged males increased with the number of oral-genital sex and open-mouth kissing partners (but not vaginal sex partners). Interestingly, two cases of couples with HPV-associated tonsillar cancer have been reported (Andrews et al., 2009; Haddad et al., 2008), suggesting an infectious nature among nondrinking and nonsmoking adults.

**Human Papillomavirus (HPV)-Positive HNSCC**
- Being detected more often in young Caucasian males
- Usually acquired through oral-genital sex and open-mouth kissing
- Likely to develop in the tonsils within the oropharynx
- Improved chances for survival, particularly for those with p16-positive/p53-negative/HPV-positive characteristics

**HPV-Negative HNSCC**
- More likely in African Americans than Caucasians
- Risk factors include alcohol and tobacco use.
- Decreased chances for survival

**Figure 2. Characteristics of Head and Neck Squamous Cell Carcinoma (HNSCC)**

Note: Based on information from D’Souza et al., 2009; Haddad et al., 2008; Hobbs et al., 2006; Lowry, 2009; Smith et al., 2010; Tran et al., 2007; Westra, 2009.

**Pathophysiology**

Many complex molecular characteristics of HPV and HNSCC have been discovered in the past few years (Fakhry et al., 2008; Licitra et al., 2006; Lohavanichbutr et al., 2009; Nichols et al., 2009; Smith et al., 2008, 2010). Notably, Tran et al. (2007) found that HPV travels along the same two molecular pathways as alcohol and tobacco—ubiquitin protein ligase E3A and E7. The E6 oncoprotein binds to ubiquitin protein ligase E3A and degrades TP53, which causes the abrogation of TP53 and transcription elongation factor A (SII)-like 1 pathways, and leads to uncontrolled cell growth. At the same time, the E7 oncoprotein binds with the retinoblastoma protein and transcription elongation fact A (SII)-like 1, causing uncontrolled cell division (see Figure 3).

Currently, polymerase chain reaction testing on frozen specimens is the standard means of detecting HPV UBE3A oncogene expression (Marur et al., 2010). In addition, cyclin-dependent kinase inhibitor 2A immunohistochemistry and HPV in situ hybridization may provide additional information useful for determining overall prognosis and treatment (Singhi & Westra, 2010). As distinct subtypes, tonsillar and base-of-tongue carcinomas have nonkeratinizing features and unique immunophenotypes (El-Mofty & Patil, 2006).

**Treatment and Patients’ Responses**

Most patients with HPV-associated HNSCC are diagnosed with stage III or IV disease (Marur et al., 2010). These patients should receive multimodality treatment to include surgery, chemotherapy, and radiation (Haddad et al., 2008) in accordance with National Comprehensive Cancer Network ([NCCN], 2011) guidelines. Presently, surgery followed by concurrent chemoradiation with cisplatin and fluorouracil for speech and swallowing preservation is the standard of care for locally advanced disease (Marur et al., 2010). NCCN (2011) suggests that all patients with cancer are best managed in clinical trials. Biologics, such as cetuximab, have been shown to extend the median overall survival (10.1 months versus 7.4 months, p = 0.04) in patients with HNSCC (Smart, 2009).

HPV-positive HNSCC responds favorably to treatment. According to Smith et al. (2010), individuals with p16-positive/p53-negative/HPV-positive tumors had the best overall survival (84%). Multivariable adjustments evaluating HPV-positive HNSCC have been associated with increased overall survival.
Gardasil® (Merck) has been approved by the U.S. Food and Drug Administration (FDA) for girls and women ages 9–26 for the prevention of HPV types 6, 11, 16, and 18, which are associated with (a) cervical, vaginal, and vulvar cancer; (b) precancerous lesions; and (c) genital warts. Gardasil also has been approved by the FDA for boys and men ages 9–26 for the prevention of HPV types 6 and 11 genital warts (Merck & Co., Inc., 2010). Cervarix® (GlaxoSmithKline) has been approved by the FDA for girls and women ages 10–25 for the prevention of HPV types 16 and 18 associated with cervical cancer (GlaxoSmithKline Biologicals, 2011).

Giuliano, Palefsky, et al. (2011) conducted a randomized, placebo-controlled, double-blind trial to demonstrate that Gardasil reduced the incidence of external genital lesions in males. A total of 4,065 healthy boys and men from 18 countries participated in the study. Ultimately, Gardasil was found to reduce HPV types 6, 11, 16, and 18 external genital lesions by 90.4% (95% CI = 69.2–98.1). Notably, 97.4% of the vaccinated participants seroconverted to protect against HPV types 6, 11, 16, and 18 within one month of receiving all three vaccines as directed by the manufacturer.

Gardasil demonstrated 92.4% efficacy against external genital lesions in heterosexual males and 79.0% efficacy in males with male sexual partners (not statistically significant). The vaccine also demonstrated an 89.4% efficacy (95% CI = 65.5–979) against Condylomata acuminata, the most commonly detected external genital lesion, and an 85.6% efficacy against persistent HPV types 6, 11, 16, or 18 in the per-protocol participants (Giuliano, Palefsky, et al., 2011).

However, several years may pass before Gardasil and Cervarix receive FDA approval for primary prevention of HPV-associated malignancies to include oropharyngeal squamous cell carcinoma (Bernstein & Klausner, 2008), anal cancer, and penile cancer (Smeets et al., 2007). These important studies may need to be conducted with longitudinal methods and, given the age range of those eligible to receive Gardasil and Cervarix, participant accrual may be challenging.

Although data for HNSCC prevention obtained through HPV vaccines have not been published to date, healthcare advocates posit that these FDA-approved HPV vaccines may reduce the risk of developing HPV-related malignancies (Haddad et al., 2008). However, Giuliano, Palefsky, et al. (2011) emphasized that such desired results must be clinically proven.

**Nursing Implications**

Nurses in diverse practice settings are involved in patient education. Although parents may know that Gardasil received FDA approval in June 2006 to prevent cervical cancer and genital warts in girls and women (FDA, 2006), many may not know that Gardasil received FDA approval in October 2009 for the prevention of 90% of genital warts in boys and men. Furthermore, parents may not know that Cervarix was approved in October 2009 to prevent cervical cancer associated with HPV types 16 and 18 in girls and women (FDA, 2009). Because of the relatively new indications for Gardasil and the emergence of Cervarix, nurses should ensure that parents and adolescents make informed decisions about HPV vaccines based on the most current information.

Although HPV vaccines offer promise for the prevention of HPV-associated malignancies, the vaccines only have been
approved for the prevention of cervical cancer and genital warts. However, nurses should continue their efforts to decrease the incidence of HPV-associated malignancies by initiating community-wide education efforts to explain HPV and its transmission through various sexual behaviors, as well as developing culturally sensitive educational materials to target high-risk populations. Nurses also should encourage the active participation of adolescents and adults in HPV vaccination discussions and decisions. In addition, nurses should discuss risk factors for head and neck cancer with adolescents and adults. Within their communities, nurses should become knowledgeable about local resources and government agencies that support the control and management of HPV-associated malignancies. Finally, nurses should assume more active roles in research initiatives involving HPV-associated malignancies.

Nurses play a critical role in the treatment of patients with HNSCC. They positively impact patients and families by providing education and emotional support before, during, and after cancer diagnoses and treatment. Nurses also act as patient advocates with members of the interdisciplinary team. Many nursing outreach and research opportunities for patients with HPV and HNSCC exist.

Conclusion

HPV-associated HNSCC is not yet fully understood, but studies show well-educated and otherwise healthy young Caucasian males are now developing the disease regardless of their alcohol or tobacco use. Experts believe that the incidence of HPV-associated HNSCC will continue to increase. Within the head and neck region, the oropharynx is the most common site for HPV infection (Haddad et al., 2008; Hobbs et al., 2006; Tran et al., 2007). Although HPV-associated HNSCC is most commonly acquired through oral-genital sex and open-mouth kissing, sexually active adolescents do not seem to know these facts and, therefore, may not consider oral-genital sex to be risky (Gillison, 2008). Recent research concludes that HPV (particularly type 16) should be recognized as an oncogenic factor in HNSCC. HPV vaccines, although not FDA-approved for the prevention of HPV-associated HNSCC, are essential for preventing genital warts and cervical cancer in young males and females. Ultimately, nurses have multiple opportunities to intervene and potentially reduce the incidence of HPV-associated malignancies, including HNSCC.

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