

Identical but Different: Mechanism of Cancer Development and Response to Treatment for Human Papillomavirus-Related and Non-Related Squamous Cell Cancer of the Head and Neck

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Abstract:

Head and neck squamous cell carcinoma (HNSCC) continues to be a significant cause of cancer worldwide. Tobacco and alcohol use are the most common risk factors for HNSCC. Over the past five years, research has identified the human papillomavirus (HPV) as a factor in the development of approximately 25 percent of HNSCC. Current research at the Sanford Cancer Research Center shows that the immune system can recognize HPV induced cellular changes, making HPV+ cancer more curable than HPV- cancer. Clinical trials are being developed that will improve cancer therapy by selectively treating sub-types of HNSCC through immunotherapy. The role of the primary care physician in the care of head and neck cancer is in the identification, referral and follow-up of these affected patients. The risk factors and signs and symptoms of head and neck cancer are discussed as well as indications for referral to a head and neck oncologist

Due to the initial diagnosis and long-term follow-up, primary care physicians play a key role in the diagnosis and oral management of squamous cell carcinoma of the head and neck (HNSCC), which remains the ninth-leading cause of cancer in the world.¹

Despite advances in surgical resection and reconstructive techniques, survival has improved little over the last 30 years. One of the major reasons for the lack of advances is a relatively poor understanding of cellular changes in the development of cancer. During the past five years, molecular medicine has allowed us to discover that human papillomavirus (HPV) plays a key role in cancer development for about 25 percent of all HNSCCs. While HPV+ cancers remain histologically identical to their HPV- counterparts, their response to treatment and biology is very different.² The following article will briefly review this dichotomy of cancer development from epidemiological, biological and treatment perspectives.

From an epidemiologic perspective, alcohol and tobacco use remain prominent risk factors for the development of HNSCC. However, persistent HPV infection is nearly as important. Patients who develop HPV+ cancers tend to be

younger and have lower propensity to use alcohol or tobacco. Several studies have shown that risks for HPV+ cancers are related to one's number of sexual partners and certain sexual practices.^{2,3} Unlike tobacco-related head and neck cancers, HPV+ cancer cases have increased in the last 15 years. This surprising trend may be altered in the next several years with the development of the HPV vaccine, but education regarding these risks will need to be considered to further decrease this trend.

Much has been understood regarding the biology of HPV-related cancer. The virus produces a protein which degrades a cellular protein (p53), which is important for normal cell death.⁴ It also produces a second protein that degrades another cellular protein (pRb) that is important in stopping a cell from dividing.⁵ Due to viral-induced cellular changes, the HPV+ infected cell does not need as many mutations to undergo malignant transformation as a normal HPV- cell. These same viral proteins that predispose to the development of cancer also may supply the key to treatment. Work from our lab at the Sanford Cancer Research Center has shown that the immune system can recognize the cancer cells during patient treatment, and it helps explain why HPV+ cancers are more curable (compared to their

HPV- counterparts), despite presenting with advanced disease. We currently are implementing clinical trials to help improve therapy through immunotherapy.

Changes in treatment based on HPV status will be evolving rapidly over the next five years. Currently, both tumor types are treated with the same multi-modal treatment combinations of surgery, chemotherapy and radiation. Due to the complexity of treatment, HNSCC's are best completed at cancer centers with multidisciplinary oncology groups that include the following specialists: a surgical oncologist, a reconstructive surgeon, medical oncology, radiation oncology, PET imaging, a head and neck radiologist, dentistry/OMFS, a speech pathologist and a nutritionist. This multidisciplinary team helps in assessment, treatment and post-operative support needed for these patients. Due to its prognostic value – HPV+ cancers have a 30 to 40 percent improvement in survival – it is currently indicated to HPV-type all HNSCC.

Current clinical trials, including trials that are being undertaken by the Sanford ENT-Head and Neck surgery multiple disciplinary team, will be developed to selectively treat this HNSCC cancer sub-type. This approach will be one of the first examples of how understanding molecular biology of a tumor is changing treatment approaches for these patients and hopefully will offer us novel ways to decrease morbidity and increase survival for HNSCC patients.

For the Primary Care Physician

The role of the primary care physician is in the identification, referral and follow-up of patients with head and neck cancer. Currently, there is no screening method for head and neck cancer that is shown to improve overall survival. A thorough examination of the head and neck is recommended at yearly screening physicals. The annual examination also allows one to identify risks factors as well as signs and symptoms of head and neck cancer. Major risk factors for head and neck cancer include age, tobacco and alcohol use, extensive exposure to sunlight, and prior exposure to radiation in the head and neck region. Additional risk factors include HPV infection, poor oral hygiene, occupational inhalant exposure such as asbestos and wood dust, GERD, immunodeficiency, and a family history of head and neck cancers.⁶

Head and neck cancer patients often present with vague symptoms that can mimic infectious processes and are unimpressive on physical exams. If an infectious process is suspected after a thorough history and physical exam, it is reasonable to treat the patient with antibiotics with a follow-up evaluation in one to two weeks. If an infectious

process is not suspected, the patient should return for a follow-up physical examination in two to four weeks.⁷ Signs and symptoms that would warrant immediate referral to a specialist include dysphagia, odynophagia and otalgia lasting greater than six weeks, hoarseness for greater than two weeks, unilateral nasal obstruction, epistaxis and cranial nerve palsies, an enlarging, nontender neck mass greater than 1.5 cm, or any enlarged lymph node in the supraclavicular fossa. Additional signs and symptoms may include persistent rhinorrhea and sinusitis, trismus, non-healing oral ulcers, leukoplakia and erythroplakia, halitosis, hemoptysis and numbness of lower teeth, as well as weight loss, fatigue and anorexia.^{6,7}

While the multidisciplinary head and neck cancer team will continue follow-up care of the head and neck cancer patient, the role of the primary care physician is not eliminated. Regular check-ups with the primary care physician are recommended for management of existing medical problems as well as identification and diagnosis of new illnesses. Proper screening for depression and suicide is especially important in newly diagnosed head and neck cancer patients. Additionally, the primary care physician remains an important source of support and can act as an advocate for the head and neck cancer patient.

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