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HPV-associated Head and Neck Cancer: An Epidemiologic Challenge with Preventive Possibilities

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Editorial Note

Cancers of the Head and Neck (HNC) comprise approximately four percent of all solid tumors. American Cancer Society (ACS) statistics for 2014 has estimated 42,440 new cases of oral and oropharyngeal cancer, which are the most likely to harbor the Human Papillomavirus (HPV), [1]. Eighty to ninety percent are squamous cell histology with the remainder comprised of adenocarcinoma, muco-epidermoid, and adenoid cystic histologies; these latter types are seen mostly in salivary glands. Thyroid tumors are typically considered separately as an endocrine tumor and managed differently. Tumors of the brain and central nervous system and lymphomas of the head and neck are also considered separately. With those exclusions, the common anatomic sites of HNC include the oral cavity, nasal cavity, and pharyngeal cavity with sub-sites defined for nasopharynx, oropharynx, and hypopharynx, and the laryngeal-epigottic region (considered part of the hypo-pharynx).

The commonly associated causes of squamous cell carcinoma of the head and neck (HNSCC) have been tobacco use in all forms and excessive alcohol consumption. In addition, some viral etiologies have been defined including the Epstein Barr virus (EBV) and its association with nasopharyngeal cancers (NPC) and, in recent years, the Human Papillomavirus (HPV) and its correlation with oropharyngeal cancers (OPC), especially the base of tongue and tonsillar regions.

The HPV-associated cancers present with a different clinical phenotype compared with the non-HPV counterparts. Smoking remains a strong risk factor for all HNSCC. Over 80% of HPV+ OPC cancer patients are smokers; however, an OPC developing in a non-smoker is more likely to be HPV+ than negative, [2]. HPV+ patients typically present at a younger age, and, while men are still more likely to be affected, women with HPV-associated cancer are increasing more than HPV-negative counterparts. Histologically, these tumors are more likely to show basaloid squamous features ("jigsaw puzzle" appearance) with minimal to no keratinization.HPV can be demonstrated with immunohistochemical (IHC) techniques for the p16 protein expression or by the more sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) for the HPV-16/18 DNA, [3-5].

This inaugural issue of the Journal highlights epidemiology and prevention. HPV infection and its association with cancers of the anogenital area and more recently oropharynx is a perfect example of a potentially preventable disease. First described in its association with cervical and anal cancers, HPV is a DNA herpes-virus that is known to be transmitted sexually. In 2000, Dr. Maura Gillison, an Oncologist at Johns Hopkins, published the findings of research she was doing with microbiologist Dr. Kerti Shah which demonstrated HPV-positive tissue in 25% of oropharyngeal cancer patients in their registry at the time. Furthermore, they concluded that HPV-associated OPC is a distinct type of cancer that starts deep in the tonsil tissue with HPV DNA present in the tumor-cell nuclei but not normal tissue, has fewer p53 mutations than HPV-negative cancer, has less association with smoking and alcohol consumption and has better survival rates, [6]. In 2007, Dr. Gillison and Dr. GypsyamberD'Souza of Johns Hopkins School of Public Health published the results of a seven-year population study in approximately 300 participants that showed that HNC patients were 15 times more likely to harbor HPV than people without, [7]. Since then, the number of cases have increased with most recent estimates are that approximately 60% of OPC are associated with HPV. At the same time, HPV-associated cervical cancer rates have plateaued, possibly due to introduction of a vaccine although world-wide vaccination rates are variable. According to the International Agency for Research on Cancer (IARC), recent evidence suggests that the vaccine will also prevent development of OPCand may even impact disease response and survival in already-infected individuals who do develop cancer [8].

Epidemiology of HPV induced oral cancer is felt to be related to oral transmission and infection through oral-genital sexual contact. Reports of various sexual practices such as "deep oral" kissing have been described but confirmatory epidemiology is less supportive. Dr. D'Souza and colleagues presented preliminary data from the ongoing HOTSPOT (HPV Oral Transmission Study in Partners Over Time) study at the American Society of Clinical Oncology annual meeting in 2013 showed that monogamous partners of HPV-associated OPC patients had a rate of infection of only seven percent, comparable to the general population [9].

Thus, the risk of transmission through close contact is still uncertain in some epidemiologic circles. HPV is felt to cause cancer by integrating into normal host DNA, then binding with E6 and E7 binding proteins and causing degradation or suppression of p53 tumor suppressor gene, but not mutation of p53 which is the more common finding in HPV-negative HNC associated with heavy tobacco and alcohol use.

HPV-associated HNC tends to have a better prognosis than the non-HPV counterparts. A number of studies have shown better response to treatment, longer disease-free survival (DFS), and less development of metastatic disease [10-13]. As a result, de-intensified treatment approaches utilizing less chemotherapy and adjusted radiotherapy fractionation protocols have been studied with early data suggesting that most patients have as good an outcome as their more aggressively treated counterparts but with less toxicity (short term mucositis and long term xerostomia and feeding tube dependence). However, not every patient fares well with a de-intensified approach and current clinical trials are stratifying patients into risk groups based on tumor size, surgical margins, number of lymph nodes involved, and presence of nodal extra-capsular spread (ECS).

Despite the more favorable prognosis, some patient groups still do poorly. Recent evidence suggests that African-American patients with HPV-positive OPC have a poorer outcome and worse survival than their white counterparts [14]. Various reasons such as socio-economic status and access to care are cited; however, epidemiologic differences may play a role and are, yet to be defined. In the Central Savannah Richmond Area (CSRA), a twenty county area in northeastern Georgia and South Carolina spanning the Savannah River, the rate of OPC cases has steadily risen over the past decade. Tumor Registry data from the Georgia Regents University Cancer Center (GRU-CC) in Augusta, GA, which sits in the middle of the CSRA documented nine cases of cancers of the base of tongue, tonsils, or oropharynx in 2002, compared with 28 cases in 2012.Realizing that precise description of primary anatomic sites in tumor registry data for HNC is potentially inaccurate, these cases which specifically detailed sites as noted none the less suggest an increasing trend. A majority of these cases (over two-thirds) were in African Americans which exceed that expected based on population demographics for the region (35% according to 2010 US Census Bureau statistics).

Regardless, the issues noted above underscore the seriousness and severity of HPV-associated cancers, both cervical andoropharyngeal. Whether the percentage of OPCs that are HPV+ represents an emerging epidemic or simply better molecular testing is debatable but clearly continued epidemiologic research is critical to identify factors responsible; from population-based factors to viral pathogenesis and oncogenesis. Education regarding the potential benefit and safety of HPV vaccination programs need to reach those communities most affected. Cost effectiveness of a successful vaccination program with reduced cervical cancer is obvious and may likely extrapolate to OPC as well. This is an area ripe for further research to understand the molecular basis of HPV carcinogenesis which will help not only with potential treatments but also prevention. One fascinating area of study is the interaction of HPV with E6-binding protein; the result of this combination has been shown to degrade p53 tumor suppressor gene, [15]. Researchers have looked for ways to block this process. Xie and colleagues reported that CH1iB, a small molecule inhibitor of the CH1 binding domain of E6-p300 could block HPV's degradation of p53, resulting in "reactivation" of p53 and enhanced tumor suppressor activity, [16]. Yan and colleagues at GRU-CC have isolated Activating Transcription Factor III (ATF3) and demonstrated in-vitro that this compound can block the HPV-E6 binding, [17]. Unfortunately, ATF3 by itself is not pharmaceutically stable to be used clinically; however, research to influence its expression is currently on-going and translational studies are being developed.

These and other studies provide encouraging evidence that treatment of HPV-associated OPC is imminent; however, much work needs to be done and the incidence of the disease is not yet decreasing. With the long latency period for HPV-OPC after infection, it is likely that we will continue to see an increasing number of cases in the coming decades; however, like cervical cancer, hopefully with the increased education and use of the vaccine and the development of better treatments and prevention understanding we will see this deadly cancer plateau and even decline.

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