Human Papilloma Virus-Induced Head and Neck Cancer

Dennie V Jones*, Houman Fekrazad M and Julie E Bauman 1

1Division of Medical Oncology, University of Kentucky Markey Cancer Center, Lexington, KY, USA
2University of New Mexico Cancer Center, Albuquerque, NM, USA
3University of Pittsburgh Center Institute, Pittsburgh, PA, USA

Abstract

Head and neck cancers are a common spectrum of diseases, accounting for over one-third of a million deaths worldwide each year, and over 11,000 annual US deaths. Most head and neck cancers have traditionally been diagnosed in older males who abuse tobacco and/or alcohol. With increasing public awareness of the dangers of tobacco exposure and excessive alcohol intake, the incidence of many subgroups of head and neck cancer is now decreasing in the West. However, over the past several decades, the rates of carcinomas of the tonsil and base of tongue are increasing, and are affecting a different demographic group consisting mainly of younger, nonsmoking, males. These lesions are caused by infections with the same high-risk human papillomaviruses (HPV) genotypes as those responsible for cervical cancer and other anogenital neoplasms. These HPV-induced head and neck cancers differ in their biology and prognosis from those neoplasms induced by tobacco or ethanol. Understanding the biology of these lesions will allow for the development of selective preventive and treatment strategies, and better outcomes, for this subpopulation of patients.

Keywords: Cancer; Oropharynx; Human Papilloma Virus (HPV); Tumor suppressor gene; Vaccine

Introduction

Head and neck cancers are a common spectrum of diseases, accounting for over one-third of a million deaths worldwide each year, and over 11,000 annual US deaths. This has typically been thought of as a disease related predominately to lifestyle choices, specifically to heavy exposures to tobacco and alcohol, and as such, has been diagnosed more in older males than in females. With increased public education efforts aimed at reducing smoking and moderating alcohol consumption, the incidence of many subgroups of head and neck cancer is now decreasing in the United States. However, over the past couple of decades, the demographics of at least a subset of head and neck cancer are radically shifting, with increases in the rate of predominantly oropharyngeal carcinomas in younger, nonsmoking, males. These lesions are caused by infections with the same high-risk human papillomaviruses (HPV) responsible for cervical cancer and other anogenital neoplasms. These HPV-induced head and neck cancers exhibit a different biology and prognosis from the “traditional” head and neck cancer. Learning the biology of these lesions is allowing for a better understanding of head and neck cancer in general, and will allow for the development of selective preventive and treatment strategies for this subpopulation of patients.

Epidemiology

Head and neck cancers are a common malignancy. According to data from the American Cancer Society, oropharyngeal and laryngeal malignancies will be diagnosed in approximately 52,600 patients in the United States in 2012, and will be responsible for 11,500 deaths [1]. Globally, squamous cell carcinomas of the head and neck cancers are the sixth most commonly diagnosed malignancies, and account for 350,000 deaths annually [2,3]. Most head and neck cancers are squamous cell carcinomas which are derived from the mucosal surfaces, though salivary gland carcinomas, sarcomas, and other less common lesions are reported. In most subsites, men outnumber women by at least a 2:1 ratio. The majority of head and neck cancers are caused by exposure to alcohol and tobacco products, and they commonly occur in patients in their 60s or 70s [4-6]. In the United States, at least, the decrease in tobacco use has led to a reduction in some of the demographic groups with head and neck cancer. Simultaneously, there has been an increase in head and neck cancer in patients who are younger than 45 that has been reported worldwide, a pattern mirrored in the US [5-15]. This increase is being driven in tumors which are associated with human papillomavirus (HPV) infection, as the incidence of those tumors which is not associated with HPV is decreasing [15,16]. Most of the increase over the past several decades has occurred in tonsillar and base of tongue carcinomas, where an increase in the incidence of 2% to 4% per year has been recorded in multiple patient groups in the Surveillance, Epidemiology and End Results (SEER) database from 1973-2001; more recent data indicates that the incidence of oropharyngeal carcinomas has increased more rapidly over the past decade [15-20].

HPV has been found in roughly a quarter of squamous cell carcinomas of the head and neck at all anatomic subsites [21]. While most HPV-associated head and neck cancers occur in the oropharynx (the tonsils and base of tongue), HPV has been detected in laryngeal and oral cavity carcinomas at lower frequencies [21,22]. Similar to head and neck cancers which are not related to HPV infections, HPV-related neoplasms are more commonly found in males. In developed nations, HPV is associated with up to 93% of all oropharyngeal carcinomas with HPV genotype 16 predominating [15,21,23].

Moreover, the incidence of HPV-associated oropharyngeal cancers is dramatically increasing over the past several decades [23-25]. It is unclear if HPV found in non-opharyngeal sites within the head and neck is a causative factor in the development of neoplasia, as opposed to...
to HPV which is found in oropharyngeal malignancies, which is transcriptionally active and not found in surrounding non-neoplastic tissues [26].

Though there is less data specific to head and neck cancers, most of which are caused by an oncogenic HPV infection similar to cervical and penile cancers, HPV-related head and neck cancers are related to sexual behavior [27,28]. HPV-associated oropharyngeal cancers were more prevalent in patients with a higher number of lifetime partners with either oral sex or vaginal sex, and the risk of HPV-related head and neck cancer is increased in those who have a prior diagnosis of HPV-related anogenital malignancies, and in the male partners of women with HPV-induced cervical neoplasia [29,30]. Oral HPV is rare in children, including those born to women with genital HPV infections, but incidence levels rise to young adulthood, where nearly 5% of all healthy young adults have evidence of HPV in their oral cavity and oropharynx [31,32]. In a cross-sectional study in the United States, 7% of adults aged 14-69 carried oral HPV infection including 1% HPV genotype 16. Males demonstrated significantly higher prevalence, with a bimodal age distribution peaking between ages 25-34 and 55-64. It is not possible at present to determine who may clear their infection as opposed to whose infection will lead to significant sequelae, though HIV co-infection and tobacco abuse may lead to persistence of the infection [33]. In common with cervical cancer, the most common genotype observed in oropharyngeal cancer is HPV-16 which comprises more than 90% of cases. HPV genotype 18 DNA has been detected in malignancies from multiple head and neck sites as well, though at a substantially lower frequency; similar to HPV-16 there is a predilection for the oropharyngeal and laryngeal subsites, though the detection of HPV DNA is not the equivalent to the virus being transcriptionally active and functioning as a causative agent in the development on the malignancies from each non-opharyngeal subsite. HPV serotypes 6 and 11, both of which are associated with cervical cancer (along with HPV-18), are more commonly associated with recurrent respiratory papillomatosis [34].

**Molecular Biology**

There are over 100 known members of the HPV family. These viruses infect and produce tumors in epithelial and mucosal surfaces, though most infections tend to be latent. Most clinically apparent infections lead to benign warts. Of all of the known genotypes, HPV-16 and HPV-18 are considered high risk as infections with either lead to intraepithelial lesions which have a high oncogenic potential. Genotypes HPV-6 and HPV-11 are considered low risk as infections and either tends to cause condylomata or papillomata which are far less likely to undergo malignant degeneration. Papillomaviruses are highly species-specific, and are incapable of infecting other species even under artificial circumstances. They also tend to be site specific, with a high degree of predilection for the anatomic site, though there is overlap.

Papillomaviruses lack an envelope, and are composed of a protein coat of 72 subunits (capsomeres) which contains an 8 Kb circular, double-stranded DNA genome. The genome is arranged in three regions: a 1 Kb non-coding Long Control Region which contains the elements which regulate gene function and viral replication; the Early Region (ER), which codes for six genes of which several are associated with cellular transformation and viral replication; and the Late Region (LR), which contains the two genes which code for the capsid proteins.

Within the cervix, papillomaviruses enter the epithelial layer through an area of local breakdown, such as a wound or laceration and infect the cells of the basal layer, which are the only cells capable of division. The viral DNA is normally maintained as a low-copy-number circular plasmid within the nucleus, however, high-risk HPV (HPV-16 and HPV-18) are able to integrate into the host genome [35]. As the cell differentiate and migrate through the epithelium, viral replication is triggered, and is most efficient in terminally-differentiated cells where the virus replicates to a high copy number in cells at or near the epithelial surface [35,36]. Viral replication is confined to the nucleus, leading to considerable nuclear atypia. The LR genes are produced only in terminally differentiated cells, and the virus is released as the epithelial cells are shed [35]. The process of viral replication itself alters the appearance of the epithelium, giving rise to the formation of warts and papillomata. Even though terminally-differentiated epithelial cells are normally incapable of DNA synthesis, the E6 and E7 proteins allow for the replication of DNA. The E6 protein of high-risk HPV binds to ubiquitin ligase, E6-associated protein (E6AP), which then ubiquitinates the p53 tumor suppressor protein, leading to its degradation [37-41]. p53 participates in the recognition and repair of damaged DNA by the induction of cell cycle arrest at the G1/S and G2/M checkpoint; it activates DNA repair proteins, but if the DNA damage is too extensive then leads to activation of apoptosis, or programmed cell death. The E6-E6AP complex also binds to and ubiquitinates the prapoptotic protein BAK, leading to its destruction and inhibition of programmed cell death [42]. The E7 protein of high-risk HPV binds to the cullin 2 ubiquitin ligase complex to ubiquitinate the retinoblastoma protein, Rb1, leading to its inactivation and degradation [43,44]. Rb1 also prevents cells from progressing through the G1/S checkpoint [45]. Rb1 functions as a growth suppressor when it binds to the E2F protein, which directly prevents E2F-mediated progression through the cell cycle [46-51]. The RB1/E2F proteins form part of a complex which subsequently recruits histone deacetylase to modify the chromatin to reduce the transcription of factors responsible for DNA synthesis [52]. The E7-mediated destruction of Rb1 also allows the transcription of the cyclin dependent kinase inhibitor p16INK4A [53,54]; elevated levels of p16INK4A are now considered as an indicator of HPV-mediated carcinogenesis. The E6 and E7 proteins interact with a variety of additional cellular targets [55,56], including the Rb-related proteins p130 and p107, and the cyclin-dependent kinase inhibitors p27Kip1 and p21Cip1 [57-60], and the Seven-In-Absence-Homologue-1 of the WNT signal transduction pathway; leading to increased levels of beta catenin and increased nuclear accumulation of beta catenin and gene activation through the T-cell factor/lymphoid enhancer factor family of transcription factors [61]. Silencing of the expression of the E6 and E7 genes in HPV-positive oropharyngeal cell lines leads to decreased viability and increased apoptosis. Interestingly, the E5 protein may also have a limited role in carcinogenesis. Early in the infection, the E5 protein supports cellular proliferation though activation of the colony stimulating factor 1, epidermal growth factor, and platelet derived growth factor beta receptors [62,63]. The E5 protein does not appear to bind directly to the EGFR, but rather increases its recycling to the cell surface, leading to increased EGFR signaling, with increased AKT and ERK 1/2 phosphorylation and vascular endothelial growth factor expression [64-67]. However, the E5 gene is often deleted during integration into the host genome, and as a result it is thought not to be essential to the later stages of carcinogenesis [63].

**Biologic Behavior and Prognosis**

As previously noted, HPV-related head and neck cancers demonstrate a predilection for the base of tongue and tonsil. In a pattern similar to cervical cancer, HPV-mediated head and neck cancers
display a loss of p53 and Rb1 function through decreased protein levels, though the genes themselves are unaffected; in contrast, non-HPV-induced, tobacco-related head and neck cancers often harbor p53 mutations which render the protein nonfunctional. Additionally, HPV-related head and neck cancers have elevated levels of p16INK4A due to the loss of Rb1 function, while those lesions caused by tobacco abuse have low or absent p16INK4A levels. Patients with HPV-associated head and neck cancers are less likely to have abused alcohol or tobacco, and are approximately five years younger than those with tobacco-related head and neck cancers. Similar to tobacco-related disease, HPV-related head and neck cancer demonstrates a male predilection [15,68-70]. In addition to the preponderance of an oropharyngeal primary site, HPV-induced lesions are more likely to be poorly differentiated (60%-77% vs. 24%-27%) [55].

The mere presence of HPV DNA in a lesion does not imply a role for HPV in the etiology of the disease; rather, the HPV must be transcriptionally active. As such, evaluating for the presence of HPV DNA and using p16INK4A expression as a biologic surrogate for transcriptionally-active HPV, three distinct subtypes of lesion have been revealed: Class I, lacking both HPV DNA and p16INK4A expression; Class 2, with HPV DNA present but still lacking p16INK4A expression; and Class 3, which are tumors which contain both HPV DNA and demonstrate elevated levels of p16INK4A expression [68,71]. These distinctions are prognostically significant: the 5-year overall and 5-year local recurrence survivals are markedly better for Class 3 lesions when compared to Class 1 and Class 2 lesions: the 5-year overall survival is 79% vs. 18%-20%, respectively, while the 5-year disease-free survival is 75% vs. 13%-15%, respectively [71]. While this study was small, all three groups were balanced for treatment strategies, with the majority in each group utilizing primary radiotherapy versus surgery with or without post-operative radiotherapy; only 9% of each group received chemotherapy. Thus, the differences in outcomes were more likely to be due to inherent biologic differences as opposed to the impact of varied treatment strategies. Multiple studies have noted that HPV-induced oropharyngeal carcinoma has a much better prognosis than tobacco induced oropharyngeal carcinoma [26,72-78]. Similar results have been noted in HPV-induced carcinoma of the pharynx and supraglottic larynx [79]. The cause is unclear but may be related to an enhanced radiosensitivity or a lack of field cancerization [76,79]. It is not yet clear that such tumors are also more sensitive to chemotherapy with targeted therapies such as cetuximab, or standard cytotoxic agents such as cisplatin, when administered as single modality, though patients with HPV-associated head and neck cancers have superior outcomes when chemotherapy is administered concurrently or as both induction therapy and concurrently with radiation therapy [78,80,81]. It appears that the presence of an active HPV infection as the etiology of the malignancy has no impact upon the toxicities of the regimen experienced [7].

Future Directions

The incidence of HPV-associated head and neck cancer, particularly oropharyngeal cancer, is increasing. At present, there is no strategy for screening, and the incidence rate is still low enough that any screening program would, in all likelihood, not be cost-effective. However, the two genotypes that are most closely associated with head and neck cancer are also most closely associated with cervical cancer; prophylactic HPV vaccines have been developed in an effort to reduce the incidence of anogenital neoplasms, it is possible that such vaccines may also lead to a reduction in the incidence of HPV-related head and neck cancers. One of the approved vaccines, Cervarix® (GlucoSmithKline) protects against HPV-16 and HPV-18, while the second vaccine, Gardasil® (Merck) is directed against HPV-6, -11, -16, and -18. Both vaccines raise high levels of neutralizing antibodies, and have been shown to reduce the incidence of persistent HPV16 and HPV-18 infections, as well as grade 2-3 cervical intraepithelial neoplasia [82-84]. It is expected that this will be accompanied with a fall in cervical cancer rates over the next two decades, owing to the latency period between infection and the development of clinical neoplasia. It is hoped that the vaccines may also reduce other HPV-induced neoplasms such as head and neck cancers.

A second strategy is to investigate modifications of treatment regimens for those with HPV-induced head and neck cancers (Class 3 lesions). As noted, the toxicities of treatment, while considerable, are no different than those experienced by those who have non-HPV-related disease while undergoing the same treatment. Yet the outcomes are clearly superior. Thus it is possible that patients with HPV-induced disease may be able to obtain the same level of clinical benefit to regimens of lesser intensity, and thus lower levels of short and long-term toxicity. Such modified regimens are currently being designed and evaluated in clinical trials.

Conclusions

High-risk human papillomaviruses are associated with a clinical subgroup of head and neck cancers that differ in terms of demographics, clinical presentation, as well as prognosis. Continued investigation into the molecular pathogenesis of such lesions will lead to a greater appreciation of not only these lesions, but has broader implications for the understanding for a variety of malignancies, which may lead to the development of more effective, and less toxic therapies. Furthermore, despite the association with a substantially-improved prognosis, there are still a substantial percentage of patients with HPV-induced head and neck cancers whose disease persist or recur and will lead to death. Clearly, much work still needs to be done. At present, head and neck cancers are treated identically regardless of the etiology, though it may be possible to modify treatment regimens to better fit the cause and underlying molecular biology. In common with those head and neck cancers that are not related to HPV infections, both types of tumors may be preventable, either by avoiding tobacco exposure (which is already leading to a reduction in the incidence of non-HPV-related head and neck cancers), or potentially through a vaccination program. Continued efforts in these areas will provide more agents to prevent and combat these lesions.

References


