CLINICAL REVIEW

Human Papillomavirus (HPV)-associated Oral Cancers and Treatment Strategies

N. Sathish[1], X. Wang[2], and Y. Yuan[3]*

Abstract: *Human papillomavirus (HPV) is known to be associated with several types of human cancer, including cervical, vulvar, vaginal, penile, anal, and head-and-neck cancers. Among these cancers, HPV-associated head-and-neck cancers, inclusive of oropharyngeal squamous cell carcinoma (OSCC) and oral cavity squamous cell carcinomas (OCSCC), have recently risen dramatically in men under 50 years old. Within 20 years, the percentage of HPV-positive OSCC in total OSCC went from less than 20% to more than 70% in the United States and some European countries. This article reviews the incidence trend and pathogenesis of HPV-associated head-and-neck cancers as well as current treatment modalities for the disease.*

Key Words: head-and-neck cancer, oropharyngeal squamous cell carcinoma (OSCC), treatment of head-and-neck cancers; HPV vaccine, oral pathology, oral neoplasia.

Introduction

Cancers are known to have a diverse etiology that includes infectious agents. Greater than 20% of the global cancer burden has an associated infectious etiology, with viruses accounting for about 15% of the total human cancers (zur Hausen, 2006; McLaughlin-Drubin and Munger, 2008). A diverse range of viruses is implicated in these cancers, which originate in different regions of the body, including the liver, genital regions, and the oral cavity, to name a few. A significant proportion of the viral cancers arises from the oral cavity (Mesri *et al.*, 2010; Leemans *et al.*, 2011; Rautava and Syrjänen, 2012; Tsao *et al.*, 2012). The viral agents associated with oral cancers include: (1) human papillomavirus (HPV)-associated with head-and-neck squamous cell carcinoma (HNSCC) (Leemans *et al.*, 2011; Rautava and Syrjänen, 2012), (2) Epstein Barr virus (EBV)-associated with nasopharyngeal carcinoma (NPC) (Tsao *et al.*, 2012), and (3) Kaposi's sarcoma-associated herpesvirus (KSHV) associated with oral Kaposi's sarcoma (KS) (Ganem, 2006; Mesri *et al.*, 2010).

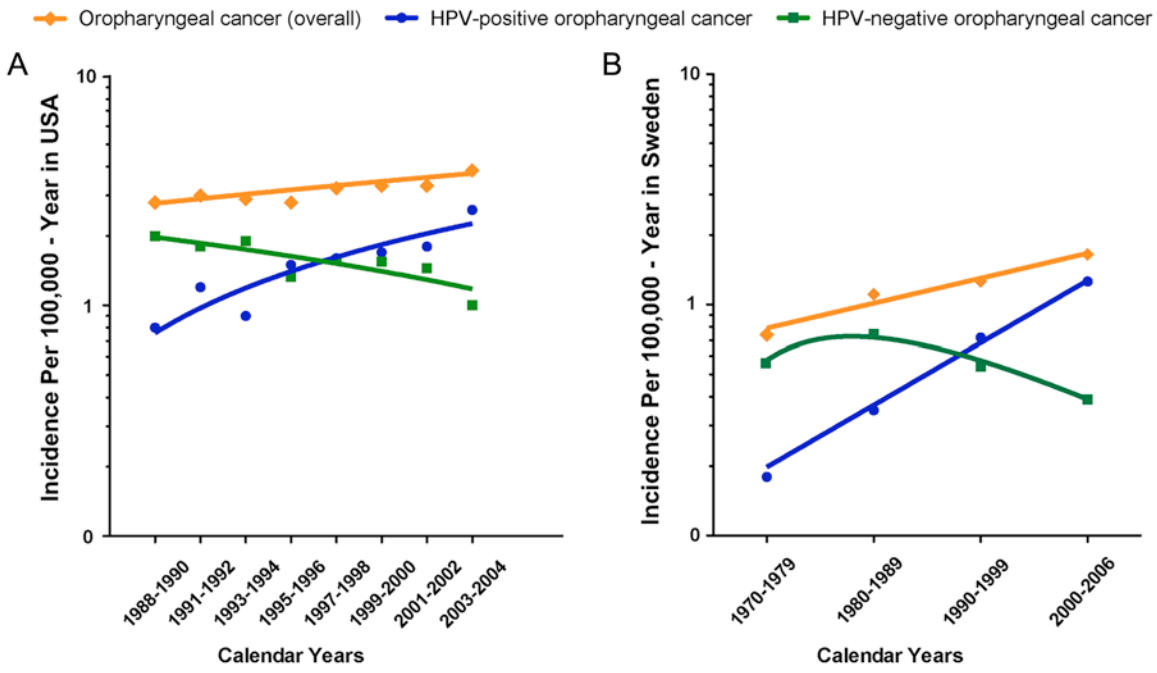
HPV has been found to be associated with several types of human cancer, inclusive of cervical, vulvar, vaginal, penile, anal, and head-and-neck cancers (zur Hausen, 2002). Among these cancers, the incidence of HPV-associated oropharyngeal squamous cell carcinoma (OSCC) has risen dramatically in men under 50 years old. Within 20 years, the percentage of OSCC that was HPV-positive went from less than 20% to more than 70% in the United States and some European countries. To halt the incidence trend and ultimately eradicate HPV-associated cancers, there is an urgent need to raise awareness of the alarming increase of HPV-associated head-and-neck cancers, to encourage research for better understanding of the pathogenesis of HPV-associated head-and-neck cancers, and to call for novel and advanced therapeutic strategies for the treatment of the disease, especially HPV-target therapies.

HPV-associated Head-and-Neck Cancer Has Risen Significantly in the Last Two Decades

Head-and-neck squamous cell cancers constitute the sixth leading malignancy globally and arise primarily in the oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx (Kamangar *et al.*, 2006; Leemans *et al.*, 2011). Known etiological risk factors for these cancers include tobacco use and alcohol consumption (Leemans *et al.*, 2011; Rautava and Syrjänen, 2012). In the United States and some European countries, the overall incidence of head-and-neck cancers associated with the above etiological

DOI: 10.1177/0022034514527969. [1] Department of Biological Sciences, Indian Institute of Science Education and Research (IISER) Bhopal, Bhopal - 462023, Madhya Pradesh, India; [2] Institute of Human Virology, Sun Yat-sen University, Guangzhou, 510081, China; and [3] Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; *corresponding author, yuan2@pobox.upenn.edu

Figure 1.
Incidence rates of HPV-positive oropharyngeal carconomas and HPV-negative oropharyngeal carcinomas **(A)** in the United States during 1988 to 2004 and **(B)** in Stockholm, Sweden, between 1970 and 2006.



risk factors has declined in the past two decades, consistent with the decrease in tobacco usage in these regions. By contrast, a rapid rise in the incidence of HNSCC, especially oropharyngeal squamous cell cancer (OSCC) involving the tonsil and the base of the tongue, has been noticed in men younger than 50 years of age with no prior history of tobacco usage and alcohol consumption (reviewed in Marur *et al.*, 2010). These cancers were found to be specifically associated with HPV infection. In the United States, HPV prevalence in oropharyngeal cancers increased at the rate of 7.5% *per* year, so the proportion of HPV-positive OSCC rose from 16.3% during 1984 to 1989 to 71.7% during 2000 to 2004 (Fig. 1, left panel) (Chaturvedi *et al.*, 2011). Similarly, increases in the incidence of HPV-associated OSCC have also been reported in many European countries, including Finland, Sweden, the Netherlands, and the United Kingdom. Based on the Sweden Cancer Registry, the incidence of HPV-positive OSCC doubled each decade during 1970 to 2007, having reached 90% of total OSCC in recent years (Fig. 1, right panel) (Näsman *et al.*, 2009).

There are over 140 HPV types that can be divided into two categories, high-risk oncogenic types and low-risk non-oncogenic types. The high-risk type 16 constitutes the most prevalent HPV type globally, being detected in almost 60% to 80% of head-and-neck cancers. However, high-risk type 18 was found in 34% of oral cavity squamous cell cancers and 17% of laryngeal squamous cell cancers (rarely in HPV-positive OSCC, 2.8%) (Kreimer *et al.*, 2005; Zandberg *et al.*, 2013). The HPV-associated HNSCCs manifest different clinical and biological characteristics in comparison with the HPV-negative HNSCCs. In addition, patients with HPV-positive HNSCCs have a favorable prognosis in comparison with those with HPV-negative HNSCCs, and mutations associated with tumor suppressor genes like p53 are relatively infrequent in the former (Leemans *et al.*, 2011; Rautava and Syrjänen, 2012; Zandberg *et al.*, 2013).

Although it has been established that HPV infection has increased the incidence of head-and-neck cancer in the United States and some European countries, a great many ambiguities exist pertaining to the epidemiological characteristics of these cancers: (1) The increased incidence of HPV-associated head-and-neck cancers could be attributable to changes in sexual norms, such as increased oral sex practices and more oral sex partners (Schwartz *et al.*, 1998; Kreimer *et al.*, 2004; Smith *et al.*, 2004; Gillison *et al.*, 2008). However, HPV-positive OSCCs are also documented in patients reporting very few oral sexual partners, with almost 8-40% of the patients reporting never having had oral sex. Thus, oral sex may not be the only significant attribute, and sexual behavior as well as other factors must be further evaluated. (2) Traditional risk factors, such as alcohol consumption and tobacco use, may still have a significant impact on HPV-associated oropharyngeal cancers, since around 10-30% of these cancers occur in patients who smoke or consume alcohol. Thus, the contributions of these risk factors in the etiogenesis of HPV-associated oral cancers cannot be undermined, and a possible synergy of HPV infection and traditional etiological factors should be investigated. (3) The plausible reasons for the increased incidence of HPV-

associated oropharyngeal cancers in men, with no substantial rise among women, are unclear. It is thus not known if any other biological factors contribute to the increased incidence in men or if a prior HPV infection in the cervix protects a woman from infection of oral squamous epithelium by HPV. These questions need to be addressed by further investigations.

Pathogenesis of HPV-associated Head-and-Neck Cancers

HPV is a non-enveloped double-stranded DNA virus. Its DNA genome encodes 8 genes, divided into two classes, the early (E) and the late (L) genes (Fig. 2). The early genes include E1, E2, E4, E5, E6, and E7, which are important for viral genome replication, while the late genes, L1 and L2, encode the major capsid and the minor capsid proteins, respectively (Leemans *et al.*, 2011; Rautava and Syrjänen, 2012; Zandberg *et al.*, 2013).

High-risk types of HPV are known to be unequivocally associated with cervical neoplasia, with the mechanisms of viral pathogenesis well-understood (reviewed in Burd, 2003). The pathogenesis of HPV-associated HNSCC is thought to be very much similar to that of cervical cancer. Infection of the oral squamous epithelium with HPV could result in either a productive life cycle closely coupled with progressive differentiation of the epithelial cells, culminating in virion generation and egress, or a transformative life cycle resulting in transformation of the growth-arrested differentiated cells into actively proliferating cells (Doorbar, 2005; Moody and Laimins, 2010; Rautava and Syrjänen, 2012).

Productive Life Cycle of HPV

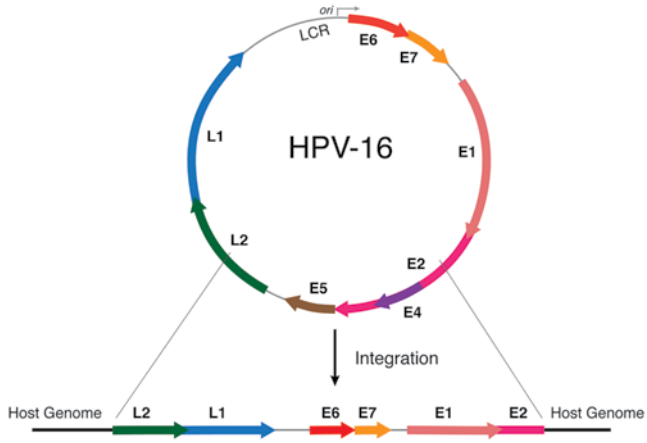
The productive life cycle of HPV initiates with HPV infection of undifferentiated basal squamous epithelial cells of the oral cavity subsequent to a trauma or erosion, resulting in the delivery of the viral DNA into the host cell nucleus (Syrjänen, 2004). The viral genomes maintain themselves as low copy numbers autonomously replicating the episome, the replication of which is coupled with that of the host cellular chromosomal replication during the S phase of the cell cycle (Doorbar, 2005; Hamid *et al.*, 2009). A few viral early genes, including E1 and E2, ensure replication of the viral genome through the engagement of the host cellular replication machinery components (Rautava and Syrjänen, 2012). The HPV E1 protein is a DNA helicase/ATPase for viral DNA replication (Hughes and Romanos, 1993). The HPV E2 protein is pivotal to the viral life cycle and has well-characterized functions in transcriptional regulation, initiation of DNA replication, and viral genome maintenance. There are many E2-binding sites (E2BS) in the HPV genome. E2 participates in the initiation of viral DNA replication by binding with E1 helicase and loading it at the replication origin (Mohr *et al.*, 1990). The E2 protein activates or represses transcriptional processes by recruiting cellular factors to the viral genomes or blocking their binding sites (reviewed in McBride, 2013). The E2 protein also suppresses the transcription of E6/E7 genes that encode proteins with oncogenic properties (Androphy *et al.*, 1987). Blockade of the E6/E7 expression by E2 helps the virus escape immune surveillance. Furthermore, the E2 protein interacts with the E7 protein and inhibits E7-induced pRb degradation and cell transformation (Gammoh *et al.*, 2009; Wang *et al.,* 2012). In addition, the E2 protein is able to tether HPV genomic DNA to the mitotic chromosome to maintain the episomal HPV genome in the host cell (You *et al.,* 2004). Thus, HPV E2 plays a pivotal role in maintenance of the productive viral life cycle and the suppression of transformation.

The final steps in the productive life cycle of HPV are characterized by the expression of the viral L genes followed by assembly into the viral capsid, encapsulation of the viral DNA, and release of the mature infectious virions. The viral progeny synthesis is confined to the terminally differentiated cells in the upper layers of the epithelium (Doorbar, 2005; Rautava and Syrjänen, 2012).

Transforming Life Cycle of HPV

The E6/E7 of high-risk HPV are major viral oncogenes, which play roles in the transformation of growth-arrested differentiated epithelial cells

Figure 2.
The organization of HPV-16 episomal genomic DNA. The HPV genome encodes 6 non-structural proteins (E1, E2, E4, E5, E6, and E7) and 2 structural proteins (L1 and L2) and contains a transcriptional and replication control region (long control region, LCR). In HPV-associated cancer cells, the HPV genome is frequently integrated into the host cell chromosome, and the circular viral DNA is often opened within the open reading frame (ORF), E2. Parts of E2 and the adjacent ORFs (E4, E5, and part of L1) are regularly deleted after integration. In some cases, viral transcription spanning the ORFs E6 and E7 are flanked to a host cellular promoter and up-regulated by the cellular promoter.



into actively proliferating cells (Doorbar, 2005; Hamid *et al.*, 2009; Rautava and Syrjänen, 2012). High-risk HPV E6/E7 are able to induce aberrant cell cycles and proliferation by interacting with several tumor suppressors and cyclin-dependent kinase inhibitors. E6 in combination with a cellular ubiquitin ligase, the E6-AP, binds to the tumor suppressor protein p53, targeting it for ubiquitination and proteosomal degradation. Destabilization of p53 culminates in the down-regulation of p53 and mediated effects, including: (1) decreased transcription of p21, a cyclin-dependent kinase inhibitor (CDKI), resulting in the initiation of the S phase of the cell cycle in the differentiated epithelial cells; (2) deregulation of DNA damage repair and cellular senescence; and (3) inhibition of the pro-apoptotic functions of p53 (Finzer *et al.*, 2002; Hamid *et al.*, 2009; Moody and Laimins, 2010; Leemans *et al.*, 2011; Rautava and Syrjänen, 2012). In addition to the promotion of cell proliferation, HPV E6 also plays a carcinogenic role by promoting immortalization of primary human cells. E6-mediated ubiquitination and degradation of p53 (above) manifest as deregulated cellular proliferation and progressive telomerase erosion. This erosion is markedly inhibited through the ability of HPV E6 to induce expression of hTERT and to interact with the telomerase complex, resulting in telomerase activation and cellular immortalization (Klingelhutz *et al.,* 1996; Liu *et al.*, 2009).

HPV E7 interferes with the functionality of the tumor suppressor protein pRb by preferentially binding to the hypo-phosphorylated form of pRb. This form of pRb associates with the eukaryotic transcription activator family E2Fs, inhibiting their functions. With HPV E7 binding to the E2F-binding domains of pRb, the association of E2Fs with pRb is markedly reduced, allowing E2Fs to be relieved from the repression effect of pRb. Deregulated E2Fs induce the transcription of several downstream genes that collectively mediate the onset of the S phase of the cell cycle (Finzer *et al.*, 2002; Hamid *et al.*, 2009; Moody and Laimins, 2010; Leemans *et al.*, 2011; Rautava and Syrjänen, 2012). In addition to binding and degrading pRb, E7 targets other cellular proteins that are relevant to cell-cycle progression. E7 is known to interact with p21 and target it for ubiquitin-proteosomal degradation, resulting in initiation of the S phase of the cell cycle (Rautava and Syrjänen, 2012). Furthermore, E7 has also been reported to interact with the transcriptional co-activators p300, CBP, and pCAF with its amino-terminal domain (Cahill *et al.*, 1999; Huang and McCance, 2002; Avvakumov *et al.*, 2003). The binding of E7 with its carboxy-terminus to histone deacetylase is necessary for the viral life cycle and contributes to transforming activities of the E7 protein (Longworth and Laimins, 2004). In addition, both E6 and E7 are known to activate the Wnt signaling pathway, resulting in protection of β-catenin from the phosphorylation and proteosomal degradation of GSK-3β, in turn bringing about the transcription of cyclin D1, which initiates the G1 phase of the cell cycle (Rampias *et al.*, 2010).

E5, a membrane-associated protein, is also being increasingly implicated in HPV-mediated cellular transformation. HPV E5 is known to delay the internalization and degradation of several receptor tyrosine kinases, including EGFR. A reduced recycling of EGFR results in its constitutive activation, manifesting as: (1) activation of the mitogenic activated protein kinase (MAPK) pathways, allowing for progression of the cell cycle beyond the G1 into the S phase; (2) activation of the phosphatidyl inositol-3-kinase (PI3K)-Akt/protein kinase B (PKB)-mediated anti-apoptotic pathway and proliferative pathway; and (3) activation of COX-2, promoting the induction of vascular endothelial growth factor (VEGF), known to promote angiogenesis (Straight *et al.*, 1993; Rautava and Syrjänen, 2012). Moreover, E5 enhances the onset of the cell-cycle S phase through down-regulation of both of the CDK inhibitors, p21 and p27 (Rautava and Syrjänen, 2012).

Overall, it becomes evident that the combined effects of the principal HPV oncogenes, E6, E7, and E5, lead to an induction of cell-cycle progression of the otherwise growth-suppressed differentiated oral squamous epithelial cells, resulting in deregulated proliferation, loss of apoptosis, genomic instability, transformation/immortalization, and, eventually, progression to cancer.

Integration of High-risk HPV into the Host Chromosome Is an Important Step in Carcinogenesis

Although high-risk HPV E6 and E7 are potent oncogenic proteins, their oncogenic properties are generally restricted in the presence of the E2 protein. E2 is a replication and transcription factor and is known to suppress the transcription of E6 and E7 genes (Bernard *et al.*, 1989; Romanczuk *et al.*, 1990; Tan *et al.*, 1994). In addition, it is reported that E2 can inhibit the oncogenic activities of E6 and E7 by direct protein interaction with E6 and E7, respectively (Grm *et al.*, 2005; Gammoh *et al.*, 2009; Wang *et al.,* 2012). Thus, it appears that the balance of E2 and E6/E7 activities determines if the virus is in the productive life cycle or the transforming life cycle. Interestingly, in most cases of HPV-positive squamous cell carcinoma, both cervical cancer and head-and-neck cancer, the HPV genomic DNA is found to be integrated into the host cell genome, which is always associated with the interruption of the E2 open reading frame and the loss of E2 protein (Fig. 2) (Schwarz *et al.,* 1985; Smotkin and Wettstein, 1986; Lace *et al.,* 2011). The integration of the HPV genome and deletion or disruption of E2 gene lead to the deregulated expression of E6 and E7 in cervical cancer and possibly head-and-neck cancer as well. In addition, the integration can also lead to high expression of E6/E7 proteins through transcription of stable chimeric virus-cell mRNA in cervical and head-and-neck cancers (Jeon *et al.,* 1995; Lace *et al.,* 2011). Therefore, integration of high-risk HPV into the host chromosome is an important step in the progression of carcinogenesis.

Antagonization of Host Immune Responses by HPV

A persistent HPV infection is one of the known risk factors for HPV-induced cellular transformation, with

such a scenario possible only through potent subversion of the host immune responses. Hence it is not surprising that HPV interferes with both the host innate and adaptive immune responses through multiple mechanisms (reviewed by Kanodia *et al.*, 2007).

The interferon (IFN)-associated pathway is the first line of host defense against viral infection. HPV has evolved mechanisms to avoid or antagonize this antiviral response. It has been observed that premalignant lesions of patients non-responsive to INF-α treatment have higher levels of E7 mRNA in comparison with those from patients responsive to the treatment (Arany *et al.*, 1995). The mechanism by which E7 inhibits the IFN-α pathway is that E7 interacts with interferon regulatory factor 9 (IRF-9) and prevents its nuclear translocation, thereby inhibiting the formation of the interferon stimulation gene (ISG) transcription complex on ISG promoters (Barnard *et al.*, 2000). E7 also interacts with IRF-1 and thereby inhibits IRF-1-mediated activation of the IFN-β gene (Park *et al.*, 2000). The E6 protein interacts with IRF-3, thereby inhibiting IFN-β production (Ronco *et al.,* 1998). E6 is also reported to interfere with JAK-STAT activation and inhibit IFN-α-associated signaling (Li *et al.,* 1999).

In adaptive immune responses, T-cell immunity is important in the control of HPV infection and HPV-induced warts and tumors. HPV can block the antigen recognition and activation of T-cells through dysregulation of antigen-processing and -presenting machinery. E5 and E7 have been implicated in the disruption of antigen presentation, thereby helping the virus to escape detection and destruction by cytotoxic T-cells (Georgopoulos *et al.,* 2000; Ashrafi *et al.,* 2002). Viral immune evasion facilitates the persistence of HPV infection, which, in turn, increases the risk of the development of HPV-mediated malignancy.

Treatment of HPV-associated Head-and-Neck Cancer

Although HPV-associated head-and-neck cancers manifest different clinical and biological characteristics in comparison with the HPV-negative subset, including better prognosis, there is no evidence to indicate that treatment is different from that with other cancers arising in this area. For patients with early-stage HPV-positive HNSCC, a single-modality treatment by either surgery or radiation is sufficient, as documented by a favorable prognosis in these patients. Radiation therapy is more commonly used, but surgery is preferred in selected cases—for example, for tonsillar cancers that are now often HPV-related. Minimally invasive techniques such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have been used in carefully selected early oropharyngeal cancers, with excellent oncologic and functional outcomes (Genden *et al.*, 2011). For locally advanced cancers, surgery could be combined with adjuvant radiation therapy, especially in scenarios with the concomitant presence of additional risk factors, including positive surgical margins, bone erosion, lymphovascular involvement, and extracapsular lymph node extension. However, care needs to be exercised to ensure that a combination approach as described above is not used for cancers localized to critical areas in the oral cavity, since the involvement of surgery could result in impairment of the normal functioning of that area. This is exemplified in a scenario where, in tumors localized to the larynx, surgical resection of the tumor could definitely result in speech impairment in the patient. In these conditions, only non-surgical approaches are favored; thus, a concurrent chemo-radiotherapy with high-dose cisplatin is widely administered to patients with advanced laryngeal cancer, resulting in localized control of the tumor with preservation of the larynx. Therapies encompassing concurrent chemo-radiation have been shown to result in significant decreases in rates of local-regional recurrence and death, though the occurrence of distant metastases was not reduced (Pignon *et al.,* 2009).

Treatment for the survival of patients with distant metastasis has always been a challenge. Systemic chemotherapy has been shown to decrease the risk of distant metastasis associated with HNSCC. A randomized phase III trial for the treatment of patients with HNSCC compared the efficacy of induction chemotherapy involving docetaxel plus cisplatin and fluorouracil (TPF) with that of induction chemotherapy involving cisplatin and fluorouracil (PF). In total, 501 patients (either with stage III or IV disease with no distant metastases) were randomized to PF *vs.* TPF therapy, and the responding patients received an additional 7 weeks of concurrent chemo-radiotherapy with carboplatin. Patients who received TPF induction chemotherapy with additional chemo-radiotherapy had a significantly longer survival than did patients who received PF induction chemotherapy with chemo-radiotherapy (70.6 *vs.* 30.1 mos) (Posner *et al.*, 2007). Thus, induction chemotherapy with TPF has become a standard treatment modality for HNSCC patients.

Experimental Targeting Therapy

More than 90% of head-and-neck cancers express EGFR, with high levels of expression of EGFR being associated with poor prognosis (Chung *et al.*, 2006). This is not surprising, given the effects of EGFR in promoting cellular proliferation and angiogenesis while inhibiting apoptosis. Thus, EGFR has been identified as a potentially useful candidate that could be used as a therapeutic target in the treatment of HNSCC and several other malignancies. Further, administration of a humanized mouse anti-EGF-R IgG1 monoclonal antibody (Cetuximab), in combination with radiotherapy, has been documented to improve loco-regional control and overall survival in patients with locally advanced HNCCS (Bonner *et al.*, 2006). Yet another study has witnessed increased survival times (median of 10.1 mos) in HNSCC patients treated with a combination of Cetuximab and platinum-based chemotherapy compared with patients treated with chemotherapy alone (a median survival time of 7.4 mos) (Vermorken *et al.*, 2008). The

U.S. Food and Drug Administration (FDA) has now granted approval for the use of Cetuximab in combination with either radiation therapy (RT) or in combination with platinum-based therapy plus 5-fluorouracil (5-FU) for the treatment of locally or regionally advanced HNSCC and recurrent loco-regional and metastatic HNSCCs, respectively.

FDA-approved HPV vaccines, Gardasil® and Cervarix®, are highly effective in preventing infection with HPV types 16 and 18 (Gardasil® also prevents infection with HPV types 6 and 11). HPV vaccines have been shown to reduce HPV prevalence among young women and prevent HPV-associated cervical cancer (Markowitz *et al.,* 2013). Gardasil® is now recommended for both males and females. However, the efficacy of HPV vaccine in reducing oral HPV infection and the incidence of HPV-positive HNSCC has not been documented, and further research is required to address this question. In addition, HPV-targeted therapies for HPV-associated head-and-neck cancers are being explored, including the immunotherapy ADXS-HPV, which is designed to target cells expressing the HPV gene E7 and is currently being evaluated in a clinical trial for HPV-associated head-and-neck cancers.

Concluding Remarks

HPV-associated HNSCC has become a significant global burden. It has been predicted that the number of HPV-positive HNSCC patients will surpass those with cervical cancer by 2020 (Chaturvedi *et al.,* 2011). This could be prevented if urgent actions are taken, including raising public awareness about HPV-associated head-and-neck cancers and promoting research on the pathogenesis of HPV-associated cancers and novel therapeutic strategies to treat them. Many significant questions need to be addressed.

First, although the pathogenesis of HPV-associated cervical cancer has been intensively investigated, little is known about biology of HPV-associated OSCC. Although the oncogenicity of HPV in oral neoplasia is thought to be broadly similar to that of cervical neoplasia (Gillison *et al.,* 2013), the comprehensive understanding of HPV-positive OSCC will lead to novel strategies to prevent and treat HPV-positive OSCC. For example, prior to the onset of invasive oropharyngeal carcinoma, does any pre-cancerous lesion exist, and can it be detected? This could be very useful in identifying and following up individuals at high risk for OSCC.

Second, in addition to oropharyngeal cancer, high-risk HPV has also been detected in other types of oral cancers. High-risk HPV has been identified in oral cavity squamous cell carcinomas (23.6% of 2,642 cancer specimens) and laryngeal squamous cell carcinomas (24% of 1,435 cancer specimens) (Kreimer *et al.*, 2005). However, it is not clear if HPV infection is a significant risk factor for these head-and-neck cancers, other than oropharyngeal cancer.

Third, HPV-associated head-and-neck cancers manifest different clinical and biological characteristics in comparison with the HPV-negative cancers arising in this area. Patients with HPV-positive OSCC have better prognostic outcome (*e.g.*, 5-year survival rate) than those with HPV-negative OSCC. This suggests that treatment modalities for these two subsets of OSCC need to be different to achieve optimal results. Novel therapeutic strategies for each subset of OSCC might emerge on the basis of a comprehensive understanding of the mechanisms underlying the differences in survival rates. In particular, HPV-targeted therapies and drugs are anticipated to be revealed and used in the treatment of HPV-associated head-and-neck cancers. Furthermore, new biomarkers for particular OSCC subtypes need to be identified that may contribute to enhancement of the efficacies of subset-specific therapies.

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