Anticipation of the Impact of Human Papillomavirus on Clinical Decision Making for the Head and Neck Cancer Patient

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KEYWORDS

• Human papillomavirus • Clinical decision making • Head and neck cancer • Patient • Survival • Prognosis

KEY POINTS

- Human papillomavirus (HPV) is a common sexually transmitted infection that is the cause of a distinct subset of oropharyngeal cancer (OPC) rising in incidence in the United States and other developed countries.
- This increased incidence, combined with the strong effect of tumor HPV status on survival, has had a profound effect on the head and neck cancer (HNC) discipline.
- The multidisciplinary field of HNC clinicians is in the midst of re-evaluating evidence-based algorithms for clinical decision making, developed from clinical trials conducted in an era when HPV-negative cancer predominated.
- This article reviews relationships between tumor HPV status and gender, cancer incidence trends, overall survival, treatment response, racial disparities, tumor staging, risk stratification, survival post disease progression, and clinical trial design.
- Elucidation of the causal role for HPV in HNC has already altered the understanding of risk factors for HNC, and we anticipate a time in the near future when it will have a tremendous impact on clinical decision making.

INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted infection that is the cause of a distinct subset of oropharyngeal cancer (OPC) rising in incidence in the United States and other developed countries. This increased incidence, combined

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with the strong effect of tumor HPV status on survival, has had a profound effect on the head and neck cancer (HNC) discipline. The multidisciplinary field of HNC is in the midst of re-evaluating evidence-based algorithms for clinical decision making, developed from clinical trials conducted in an era when HPV-negative cancer predominated. This article reviews relationships between tumor HPV status and gender, cancer incidence trends, overall survival, treatment response, racial disparities, tumor staging, risk stratification, survival post disease progression, and clinical trial design. Elucidation of the causal role for HPV in HNC has already altered the understanding of risk factors for HNC, and we anticipate a time in the near future when it will have a tremendous impact on clinical decision making.

HUMAN PAPILLOMAVIRUS BIOLOGY

HPVs are small, nonenveloped, double-stranded DNA viruses of approximately 8000 base-pairs in size that have a distinct tropism for human epidermal and mucosal epithelium.[1] More than 150 HPV types, distinguished by viral sequence variation, have been isolated from humans to date. Most infections spread by direct human-to-human contact are asymptomatic. Viruses with low oncogenic potential, called low-risk types, may cause benign hyperproliferation of the epithelium that manifests as skin warts, genital warts, or oral papillomas. The viral genome encodes early proteins that promote viral maintenance in the infected cell nuclei and viral replication (E1, E2, E4, E5, E6, and E7). Late proteins L1 and L2 encode the viral capsid proteins.

HPV types are classified as oncogenic or "high-risk" based on case-control studies demonstrating significant associations with cervical cancer.[2,3] High-risk types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66. However, HPV types 16 and 18 are accountable for approximately 70% of cervical and greater than 90% of noncervical cancers (eg, vaginal, vulvar, penile, anal) caused by HPV, including HNCs. The transforming ability of high-risk HPV types has been attributed to myriad functions of the classic viral oncoproteins E6 and E7,[4] which disrupt regulation of cellular replication and differentiation to facilitate viral replication. HPV E7 oncoprotein disrupts control of the G1 to S phase of the cell cycle through interactions with pRb family members (p105, p107, p130),[5] and HPV E6 prevents apoptosis by inducing degradation of p53.[6,7] HPV16 E6 and E7 expression is sufficient to immortalize human keratinocytes, but insufficient for malignant progression. HPV E6 and E7 promote genomic instability,[8] leading to secondary genetic events necessary for malignant progression. However, these secondary events remain poorly defined.

Early in infection, HPV genomes replicate as extrachromosomal elements in the nucleus. The frequency of viral integration increases with severity of precancerous lesions,[9] and most cervical cancers harbor HPV integrants.[10] The literature suggests approximately 20% to 48% of HPV-positive OPC have HPV integrants,[11–13] but the sensitivity of assays used to detect HPV integrants in these studies has been called into question. HPV integration imparts genomic instability and a selective growth advantage on infected cells.[14–18] Enhanced expression and stabilization of viral oncogene transcripts[17] and disruption of the viral repressor HPV E2 contribute to such clonal selection.[19]

Until recently, insertional mutagenesis has not been widely accepted as a functionally important consequence of HPV infection.[10] However, Akagi and colleagues[20] recently reported a striking association between HPV integrants and focal host alterations in genomic structures, frequently disrupting the expression and function of cancer-associated genes. Subsequently, HPV integration was associated with copy