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REVIEW

HPV-related head and neck squamous cell carcinoma: An update and review

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Review

This is a review of human papilloma virus (HPV)-related head and neck squamous cell carcinoma (HNSCC). The epidemiology, pathology, clinical features, and risk factors of HPV-related HNSCC are discussed. HPV vaccines are also discussed.

Contents

Introduction 204
Human papilloma virus 204
Epidemiology 204
Anatomical sites 205
Risk factors 205
Diagnostic techniques 205
Microscopic features 206
Immunohistochemical stains 208
p16 IHC stain 209
HPV studies 209
PCR 209
Hybrid capture II 209
DNA in situ hybridization 209

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RNA in situ hybridization 210
Clinical importance 210
Prognosis 210
Treatment implications 210
HPV vaccine 211
Cervarix 211
Gardasil 211
Gardasil 9 211
Summary 212
Funding sources 212
Conflict of interest 212
References 212

Introduction

High-risk human papillomaviruses (HPVs) cause a distinct pathologic, clinical, and epidemiologic subset of head and neck squamous cell carcinoma (HNSCC).[1,2] Excluding skin neoplasms, cancers of the head and neck most often arise within the upper aerodigestive tract. With the exception of salivary gland tumors and thyroid carcinomas, the majority of these cancers are squamous cell carcinomas (SCCs) that originate in the oral cavity, oropharynx, hypopharynx, and larynx. A growing body of literature has described the role that HPV plays in the tumorigenesis of HNSCC, particularly occurring in the oropharynx.[1,3-7]

Human papilloma virus

HPVs are small, icosahedral, and non-enveloped viruses. They contain a circular, double-stranded DNA genome with 6800 to 8000 base pairs coding for early (E) and late (L) functioning proteins. Early proteins regulate a variety of processes including viral DNA replication (E1 and E2), viral RNA transcription (E2), and cytoskeleton reorganization (E4). Further, E5, E6, and E7 are the major stimulators of proliferation, although only E6 and E7 are responsible for malignant transformation.[8] Additionally, late proteins, including L1 and L2, make up the structural component of the viral capsid.

HPV is a ubiquitous virus that relies on the proliferative capacity of basal epithelial cells in order to produce infection and subsequent viral synthesis. Therefore, infection typically occurs when micro-laceration of the skin or mucosa gives the virus access to the basal epithelial layer. During infection, the HPV genome integrates into the host chromosomal DNA, leading to the disruption of the E2 gene and, subsequently, the inability to express late genes.[9] Loss of E2 then leads to an up-regulation of the E6 and E7 genes and an increase in expression of the E6 and E7 proteins. This change causes a disruption of the cell cycle and can eventually lead to genomic instability. Next, the infected cells divide and the virus spreads laterally. Following entry into the suprabasal layers during maturation of the infected cells, late viral genes are activated, viral DNA is replicated, and capsid proteins are formed. Finally, viral particle formation is completed and the particles are released at the surface, exposing additional tissue to potential infection.[8]

E5, E6, and E7 have proliferation-stimulating activity; E6 and E7, however, are the oncogenes that play a primary role in malignant transformation. E6 inhibits the tumor suppressor activity of P53 and E7 inhibits activity of RB (retinoblastoma) protein. Interestingly, only E6 and E7 of high-risk HPV types can immortalize human cells.[8,10,11] These findings essentially define these high-risk HPVs as oncogenic.

HPV can be classified according to its affinity to infect oral/anogenital mucosa (α-papillomaviruses) or skin (β- and γ-papillomaviruses);[12] these viruses are more commonly classified into low-risk and high-risk HPV types according to their oncogenic potential to promote malignant transformation in host cells, however.[13] Low-risk HPVs, most commonly types 6 and 11, are associated with common warts,[14] anogenital warts, oral squamous papillomas, and recurrent respiratory papillomas. [15,16] High-risk HPVs are associated with precancerous lesions and carcinomas of cervical, vulvar, vaginal, anal, penile, and head and neck squamous cell carcinoma. High-risk HPV genotypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82; types 16 and 18 are the most common and cause the majority of oropharyngeal cancers in both men and women.[16] More specifically, some have suggested that oropharyngeal and oral cavity squamous cell carcinoma are most strongly associated with HPV 16, accounting for 90% and 96% of cases, respectively.[17] HPV 33 is the most common HPV detected in sinonasal tract HPV-related carcinoma with adenoid cystic-like features, followed by HPV 16 and HPV 35.[18]

Epidemiology

Up to 80% of HNSCCs arising in the oropharynx have been shown to be associated with HPV, and the total number of HPV-positive HNSCCs are rising.[2,19,20] One study showed