Human papillomavirus-associated head and neck cancer: oncogenic mechanisms, epidemiology and clinical behaviour

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Abstract

Human papillomavirus (HPV) is best known as the underlying cause of cervical squamous cell carcinomas and most cervical adenocarcinomas. Recently however, HPV has been implicated in the development of increasing numbers of oropharyngeal squamous cell carcinomas (OPSCC). This review begins by describing the basic biology of HPV-associated cellular proliferation and the ways in which this proliferation can become unregulated. It also considers points of difference between cervical and oropharyngeal neoplasia.

The incidence of HPV associated oropharyngeal cancers has increased dramatically over recent decades and HPV-positive now outnumber HPV negative OPSCC in many developed countries. The epidemiology of HPV-positive OPSCC will be reviewed, in conjunction with the demographics and risk factors.

Patients with HPV-positive OPSCC enjoy significantly better prognosis than patients with HPV-negative OPSCC, and treatment regimes specific to HPV-positive are being evaluated. This demonstrates the importance of correct recognition and diagnosis of HPV-positive tumours. The clinical behaviour of HPV-positive OPSCC will be described and current clinical trials summarised.

HPV is primarily a sexually transmitted infection, and the implications of this for patients and their families may need to be explored. The penultimate section focuses on the information needs of patients with HPV-positive OPSCC.

Primary and secondary prevention have been highly effective in reducing the incidence of cervical cancers. The final section discusses the potential of prophylactic vaccination and screening to prevent HPV-associated OPSCC.

Keywords HPV; papillomavirus; review; oropharyngeal; oropharynx; cancer

Introduction

Human papillomavirus (HPV) is a small DNA virus that infects human epithelial cells. In 1974 Harald zur Hausen proposed that HPV could contribute to the development of some cervical cancers. Almost 10 years later, his group isolated HPV type 16 DNA from a cervical squamous cell carcinoma. Further studies established that HPV16 DNA was present in a significant proportion of cervical cancers. By 1999, work in Jan Walboomers' laboratory in the Netherlands confirmed that HPV was present in nearly all cervical squamous cell carcinoma, and that HPV could be considered a "necessary but not sufficient" cause of cervical cancer.

Since anogenital HPV infection was first recognised, its incidence has increased markedly; most probably as a consequence of changes in sexual behaviour after the 1960s. This is reflected in England by the 922% increase in incidence of benign genital warts (caused by low-risk types of HPV) from 1972 (15820 cases) to 2009 (145875 cases). Similar increases have not been observed in incidence of cervical cancers, and this is attributable to organised cervical screening introduced in the UK in 1988. Even with screening however, approximately 2300 new cases of cervical cancer are diagnosed annually in England.[1] This highlights the need for additional preventative measures against HPV. Investigations conducted by Ian Frazer and Jian Zhou in Brisbane in the early 1990's led to development of prophylactic vaccines based on HPV Virus-Like-Particles (VLP). These vaccines currently prevent infection with HPV types 16 and 18 (present in >70% of cervical cancers). Nonavalent vaccines with potential to prevent >90% of cervical cancers are expected to be available soon. UK-wide vaccination of 12–13-year-old girls began in 2008 and has achieved >85% coverage of the target population. In the long term, this intervention will lead to substantial reductions in incidence of HPV-associated cancers. In many ways, the HPV story represents a real triumph for science in the battle against disease. However, as we have learned more about this virus, it has emerged that HPV-associated disease is not just limited to the ano-genital region. There has been a recent surge in interest in the biological and clinical significance of HPV in the upper aerodigestive tract.

Epidemiology: classification of HPV types

Papillomaviruses show a very high degree of species and tissue specificity. Classification of HPV types is based on DNA sequence and the genomes of more than 150 HPV types have now been completely sequenced. This has allowed delineation of five HPV genera (Alpha, Beta, Gamma, Nu and Mu). Many types of HPV, especially those of the Beta and Gamma genera, cause only asymptomatic infections in immuno-competent individuals and they complete their lifecycle without apparent disease. This allows stable maintenance of these viruses within the human population and suggests a finely tuned balance between replication and immune tolerance.

The most clinically significant group is the Alpha-papillomaviruses which include HPV types that infect cutaneous or mucosal sites. Cutaneous types include HPV2 and HPV57 which cause common warts, and HPV3 and 10 which cause flat warts. Mucosal types are sub-divided into high-risk and low-risk types depending on the strength of their association with carcinogenesis. Twelve HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) are defined by the World Health Organisation as being high-risk cancer-causing types, and a further eight types are regarded as possibly cancer-causing. Low-risk mucosal types include HPV6 and 11, which cause the

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majority of genital warts. The classification and life-cycle of HPV has recently been reviewed.[2] The clinical manifestations of HPV infection, and the most commonly associated types are shown in Table 1.

HPV oncogenic mechanisms

Nearly all of our knowledge of the mechanisms by which HPV causes cellular proliferation and neoplasia relates to infection in cervical cells. There are clearly some differences between the natural history of HPV infection in cervical cells and in oropharyngeal cells, and in the manifestation of HPV associated neoplasia in the two tissues. However, the fundamental molecular mechanisms by which HPV encoded proteins circumvent cell-cycle control are likely to be the same irrespective of tissue localisation. A remarkable feature of HPV oncoproteins is their multi-functionality; only the best characterised features of high-risk HPV oncoproteins are discussed here, a more comprehensive review can be found elsewhere.[3]

Most viruses infect a target cell and produce progeny virus within the initially infected cells. In contrast to this, new HPV virions are only produced once the initially infected cell has undergone mitosis and one of the daughter cells has differentiated. HPV does not encode proteins directly responsible for replication of its own DNA, but uses the host cell replication machinery instead. Hence HPV encoded proteins disrupt or usurp multiple cellular signalling pathways to maintain infected cells in a proliferative state that facilitates viral persistence and replication. The primary viral proteins responsible for disruption of the host cell cell-cycle, and most significant in oncogenesis, are the E7, E6 and E5 proteins, which act largely by overcoming negative growth regulation mediated by members of the Rb tumour suppressor family. Expression of these HPV encoded proteins is normally tightly regulated and restricted to specific stages of the viral life cycle. It is hence deregulation of viral gene expression that promotes carcinogenesis. Several mechanisms may underlie this deregulation of viral gene expression including viral integration, DNA methylation and growth in inappropriate epithelia.

Clinical manifestations and associated HPV types

Clinical manifestations	HPV types[a]
Plantar warts (verruca)	1, 2, 27, 57
Common warts	1, 2, 27, 57
Flat warts	3, 10
Epidermodysplasia verruciformis	5,8
Recurrent respiratory papillomatosis	6, 11
Genital warts	6, 11
Cervical intraepithelial neoplasia	6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Cervical squamous cell carcinoma	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Other genital carcinomas (vagina, vulva, penis and anus)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

[a] Only the HPV types most commonly reported for a particular manifestation are listed.

Table 1

The E7 oncoprotein

The E7 protein of high-risk (cancer-associated) HPV types is a small (13 KDa) protein localised primarily in the nucleus. It does not possess intrinsic enzymatic or DNA-binding activities, but functions by interaction with cellular factors such as Rb and related family members (Figure 1). Rb family proteins control the G1-S phase transition by regulating activity of the E2F family of transcription factors, which includes both transcriptional activators and repressors, and control expression of many genes involved in proliferation, differentiation, mitosis and apoptosis. In normal cells, Rb represses transcription from E2F dependent promoters by directly binding the E2F transactivation domain and recruiting chromatin modifiers, including histone deacetylases (HDACS), to promoter sequences. This repression is reduced in late G1, when Rb is phosphorylated by cyclin −dependent kinase (CDK) complexes, causing disassociation from E2F, and facilitating transcription of S-phase specific genes. This repression can also be alleviated by binding of high-risk HPV E7 to Rb, which disrupts the interaction with E2F, and targets Rb for ubiquitin-mediated proteosomal degradation. This results in constitutive expression of E2F-responsive genes, such as cyclin A and cyclin E, and promotes premature S-phase entry and DNA synthesis. Release of E2F also causes increased expression of p16 thereby setting up negative feedback of the former through the inhibition of CyclinD/CDK4 complex. E7 also affects expression of S-phase genes through direct interactions with E2F factors and with HDACs. It also directly inhibits key proteins that control cell-cycle progression, such as p21 and p27 which regulate activity of CDK2.

The E6 oncoprotein

In most cells, the disruption of the cell cycle caused by E7 proteins would result in accumulation of p53 tumour suppressor protein and consequent cell-cycle arrest. To prevent this, the E6 proteins of high-risk HPV types have evolved several mechanisms to interfere with p53 function. E6 is a small (18 kDa) protein with predominantly nuclear localisation, which recruits the cellular E3 ubiquitin ligase E6-associated protein (E6AP) to a complex with p53, resulting in p53 ubiquitinylation and proteosomal degradation. Furthermore, E6 proteins can bind directly to p53 and block transcription by interfering with its DNA binding activity. E6 also inhibits the activity of histone acetyltransferases which would normally acetylate and stabilise p53. Together, these mechanisms substantially reduce the cellular p53 response; although some residual p53 activity remains and can still be activated in response to DNA damage and other cellular stresses. This may be relevant to the improved clinical response of HPV-positive OPSCC relative to HPV negative patients i.e. mutation of the p53 gene may confer a more complete phenotype. The evolutionary significance of this p53 blockage is to enable productive viral replication, but it is obviously highly significant for carcinogenesis, as in HPV infections of prolonged duration (and in both cervical and oropharyngeal disease, persistent HPV infection may precede diagnosis by several decades), abrogation