Human papillomavirus (including vaccines)

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Abstract

Human papillomavirus (HPV) is responsible for 99.7% of cervical cancer. There are over 200 types of HPV, and much is now known about the virus, including its life cycle, the function of its proteins and the mechanism by which the neoplastic transformation of keratinocytes occurs. The causal relationship between HPV and anogenital neoplasia has been confirmed by epidemiological evidence. Several methods of HPV detection have been proposed, and studies are ongoing to examine whether these tests might be incorporated into a cervical screening programme. The observation that HPV-related disease is more common in immunosuppressed patients has led to research into the host response to HPV and the development of vaccinations. Although consistent clinical responses have not been seen with therapeutic vaccination, trials of prophylactic vaccination have shown encouraging results. Public knowledge regarding the causal link between HPV and cervical neoplasia is poor and will provide a challenge for vaccination programmes.

Keywords cancer of the cervix; cervical intraepithelial neoplasia; human papillomavirus; papillomavirus vaccines

Human papillomavirus

Human papillomavirus (HPV) is responsible for 99.7% of cervical carcinoma, the second most common cancer to affect women worldwide. Although the incidence of cervical cancer is decreasing in countries with screening programmes, it is increasing in developing countries, where incidence figures often equate with mortality. HPV is also implicated in some cancers of the vulva, vagina, anus and head and neck.

The papillomaviruses are small, intracellular DNA viruses and are ubiquitous in nature. They affect many animals and are both species- and tissue-specific. HPV types infecting mucosal surfaces are divided into two groups: low-risk (LR) types that cause anogenital warts, and high-risk (HR) types that can cause anogenital neoplasia. HR types are capable of integrating into the host cell genome and produce two oncoproteins, E6 and E7, which interfere with normal cell cycle control and ultimately lead to malignant transformation of the host cell.

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HPV types

At least 200 HPV types have been recognised, based on a greater than 10% dissimilarity in the L1 region of the genome. Thirty-eight types have been isolated from genital lesions. The types that are found in anogenital warts and other non-malignant conditions have been designated as LR. Types 6 and 11 are the most common LR types, found in approximately 90% of warts; also included are types 40, 42, 43 and 44. HR HPV types are associated with anogenital neoplasia and have been reported in 99.7% of cervical cancers worldwide, HPV types 16 and 18 accounting for 70–75% of cervical cancers. Other types that have been classified as HR include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. Multiple HPV infections can be found co-existing within the same lesion.

Viral structure

The viral particle consists of a non-enveloped protein capsid, containing the circular, double-stranded viral genome. HPV has eight genes, known as open reading frames (ORFs), which encode for functional viral proteins. The genome can be divided into three regions: a long control region, and an early and a late region. The late (L) ORFs code for the capsid proteins that are produced late in the virus life cycle. The early (E) region codes for regulatory functions engaged in genome persistence, DNA replication and activation of the lytic life cycle.

Function of viral proteins

The viral proteins are named after their encoding ORF. A summary of the key functions of each protein is given in Table 1. E2 is a transcriptional repressor of E6 and E7. The loss of this ORF during viral integration in anogenital neoplasia results in an upregulation of E6 and E7 expression. E6 and E7 are oncoproteins and cause reduced levels of the tumour suppressor proteins p53 and retinoblastoma protein (Rb), respectively. The two viral capsid proteins L1 and L2 are encoded by ORFs within the late region.

Summary of the key functions of proteins encoded by human papillomavirus (HPV)

Open reading frame	Protein functions
E1	Viral replication
E2	Regulates viral transcription and replication
E4	Interacts with cytoskeletal proteins
E5	Down regulation of MHC class 1 molecules
E6	Oncoprotein, binds to tumour suppressor protein p53
E7	Oncoprotein, binds to tumour suppressor protein retinoblastoma (Rb)
L1	Major viral capsid protein
L2	Minor viral capsid protein

Table 1

Life cycle

HPV can produce infection that may be latent, productive or progressive to malignancy.

HPV only infects the basal epithelial cells and it therefore requires access to these cells for infection to occur. The squamocolumnar junction of the cervix and anal canal provides access to basal cells of the squamous mucosa. Oestrogen stimulation during puberty, pregnancy and from the combined oral contraceptive pill results in the squamocolumnar junction of the cervix being found further out on the ectocervix (a state described as an 'ectropion') and presents a greater surface area available for infection. In the vulva and vagina, viral access to basal cells may be permitted by small abrasions in the squamous epithelium.

Productive infection

The HPV genome does not encode for a DNA polymerase, and the HPV life cycle is therefore dependent on manipulation of the host DNA machinery for DNA synthesis. In the basal layer of the epithelium, the viral genome replicates in conjunction with host cellular DNA at low copy number. As the cell progresses toward terminal differentiation, an induction of viral DNA replication occurs at high levels, with an increase in the viral genome from 20–50 copies per cell to around 10 000 copies per cell. This productive stage of the infection occurs in the suprabasal layers of the epithelium. An activation of viral late gene expression follows, leading to an assembly of infective viral particles in the superficial layers of the epithelium. Late gene expression is restricted to terminally differentiated epithelial cells in these layers, where the L1 and L2 proteins package the replicated HPV genome DNA into infectious virion. Viral particles are then released as the upper layer of the epithelium desquamates.

Progressive infection and carcinogenesis

The DNA from HR types of HPV has the potential to integrate into host cell DNA. Integrated HPV DNA is found in invasive cancers and to a lesser extent in high-grade intraepithelial lesions. The site of integration into the host genome is variable, in contrast to the site at which the viral genome breaks, which is remarkably constant. The E2 ORF is almost invariably disrupted during integration, removing the inhibition of E6 and E7 expression.

When cellular DNA is damaged, the cell cycle is usually halted at checkpoints in the cell cycle, allowing for DNA repair or apoptosis (programmed cell death). HR HPV oncoproteins E6 and E7 can disrupt these checkpoints by targeting cell regulatory proteins, particularly p53 and pRb (see Figure 1 below). Following HPV DNA integration, the viral proteins' ability to disrupt the normal control of host cell replication can lead to immortalisation and malignant transformation.

Natural history of HPV-associated anogenital intraepithelial neoplasia

In addition to the establishment of the biological mechanisms by which HPV causes anogenital neoplasia, there is also a wealth of epidemiological evidence supporting the link between HPV and anogenital cancer. Neoplasia is detected most often in the cervix, although the vulva, vagina, perianal region and anal canal may also be affected. Anogenital intraepithelial neoplasia (AGIN) is a collective term used to include cervical (CIN), vulval (VIN), vaginal (VAIN) and anal (AIN) intraepithelial neoplasia.

Infection with HR HPV has been shown to be very common, with a lifetime risk of acquiring HPV of approximately 80%. It is particularly common in young women, with prevalence rates between 25% and 40% in women at 20 years old, falling to less than 10% in women over 40 years old. It is not known whether HPV detected in older women represents new or latent infection. Transient infection is the most likely outcome of HPV infection, with only 9% still infected at 2 years. This is particularly true for young women and infection with LR types. Longer median clearance rates have been reported for HR-type infections (approximately 12 months) compared with LR types (6 months).

Persistent infection with type-specific HPV precedes the development of cytological abnormalities. Reported time scales for the development of high-grade cytological abnormalities following infection with HPV are very variable: in a cohort of adolescents the time of highest risk was 6 months, and in a cohort with a median age of 35 years, the range was 7–12 years.

Prior to developing invasive disease, spontaneous regression of intraepithelial neoplasia may occur. This occurs more commonly in lower-grade disease. The spontaneous regression of low-grade cervical disease appears to be common, with rates of 55% reported. As high-grade disease is usually treated, the precise rate of spontaneous regression is not known, although it has been reported. For the same reason, the exact rate of progression to invasive disease is also unknown, although it is thought to be of the order of 30% over 20 years, or 1–2% per year. A number of factors appear to increase the likelihood of progression of HR HPV infections to cervical cancer. These include smoking, radiotherapy and oestrogen. Impaired host cellular immunity also increases the risk from HR HPV and is considered below. A model of the natural history of HR HPV infection is shown in Figure 1.

Host response to HPV and AGIN

Although most HPV infections are transient, persistent infection can lead to neoplastic disease. The observation of spontaneous

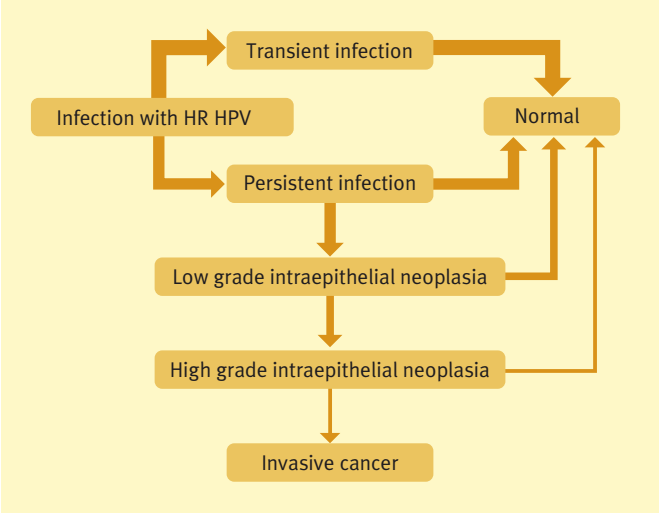

Figure 1 Model of natural history of high-risk human papillomavirus (HR HPV) infection and anogenital neoplasia.