Human papillomavirus (including vaccination)

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Abstract

Human papillomavirus (HPV) is responsible for 99.7% of cervical cancer. Worldwide, cervical cancer causes more deaths than any other cancer, almost two per minute. Over 200 types of HPV have been identified. HPV is transmitted by skin-to-skin contact. Most HPV infections are cleared by the immune system; persisting infections can cause intra-epithelial neoplasia and invasive disease. Prophylactic HPV vaccines have been developed and prevent disease caused by the included HPV types. Current vaccines could prevent 70–75% cases of cervical cancer. The UK, in 2008 added HPV vaccination to the national immunization programme. The vaccines are safe and well tolerated. It is likely that the benefits will be seen over a 15–20 year period. Tests for HPV have been developed and are being evaluated as to their possible role in clinical practice. Research is ongoing regarding therapeutic HPV vaccination and improving prophylactic vaccines to prevent more cases of cancer.

Keywords cancer screening; cervical intra-epithelial neoplasia; human papillomavirus; papillomavirus vaccines; uterine cervical neoplasms

Background

Human papillomavirus (HPV) is a small, double-stranded DNA virus containing only eight genes. It has the capability, however, to cause disease at a number of different sites in the body. Within the female genital tract, the most common association of HPV is with cervical cancer and its precursor, cervical intra-epithelial neoplasia (CIN). HPV also causes vulval, vaginal and anal intra-epithelial neoplasia (VIN, VAIN, AIN), which, although less common than CIN all have the potential to develop into invasive disease at these sites. In males, as well as anal disease, HPV causes penile intra-epithelial neoplasia (PIN) and penile cancer. HPV in both sexes also causes benign genital warts. HPV can also cause disease away from the genital tract: it can cause disease on the skin, and the mucous membranes of the head and neck where it is the causative agent of 3% mouth cancers and 12% oro-pharyngeal cancers.

As long ago as 1842, Rigoni-Stern observed that cervical cancer was found in married women and almost never in celibate women; but we had to wait until the 1970s to identify the true aetiology. During the 1960s and 70s evidence suggested that the likely aetiology was a sexually transmitted infection and studies were done on almost all known infective agents at the time. In 1974 a review of the research by Stafl and Mattingly suggested that an environmental factor, possibly a virus, caused atypical metaplasia of cervical columnar epithelium, which could progress to cancer. In 1976 and 1977 several teams found HPV within the nuclei of abnormal squamous epithelial cells and Harold zur Hausen hypothesized that HPV was an important aetiological factor in cervical cancer. The following 30 years saw a huge expansion in HPV research leading to the knowledge we have today. In 2000 Munoz reviewed the epidemiological evidence indicating 99.7% of cervical cancers were caused by HPV.

Worldwide cervical cancer is the second commonest cancer in women, although it causes more deaths than any other cancer in the developing world. It is estimated that there are at least 500,000 new cases of invasive cervical cancer a year worldwide and over 274,000 deaths, meaning that every 2 min somewhere in the world a woman dies of the disease. Over 80% of cervical cancer cases occur in the developing world, which is least equipped to deal with the problem. However, it is not just a disease of developing countries; in the UK, approximately 1000 women still die annually from cervical cancer or almost three a day, despite an effective cervical screening programme.

HPV virology

Viral structure

The double-stranded DNA of HPV is circular in nature, containing only eight genes, also known as open reading frames (ORFs). It's a relatively small virus, approximately 55 nm in diameter. There are three regions within the genome: a relatively large, regulatory region that controls viral replication and some DNA transcription; then an early (E) and late (L) region. There are six ORFs within the early region (E1, E2, E4, E5, E6, and E7) and two ORFs in the late region (L1 and L2).

The early region genes are expressed when the virus infects the host cell. They code for functions that allow the infection to become established: E1 and E2 are required for, and control viral replication and also maintain the circular viral genome. E4 interacts with the host cell proteins causing instability, allowing the release of viral particles. E6 and E7 are the disease forming genes, or oncogenes that may cause a neoplastic change within a normal cell. They are thought to modify the cell cycle so as to retain the differentiating host keratinocyte in a state that allows amplification of viral genome replication and consequent late gene expression. They do this by targeting and inhibiting the tumour suppressor proteins of the host cell: p53 and retinoblastoma (pRB).

The late region of the genome, the L1 and L2 ORF encode for the capsular proteins that encapsulates the viral DNA to make the whole viral particle or virion.

HPV types

The standard virological classification of HPV includes genera of which there are 16 different groups. The alpha papillomavirus genera contain all the HPV types that cause ano-genital disease.

Over 200 HPV types have now been described. The gene sequence of the L1 region encoding for the protein coat is used to classify the HPV type. A greater than 10% difference needs to be observed in order to define a new HPV type.

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The HPV types can be sub-divided into groups depending on their oncogenic risk. In 2003 Munoz described high risk (HR) and low risk (LR) groups.

High risk HPV types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Low risk types include HPV 6, 11, 42, 43 and 44.

High risk HPV types 16 and 18 account for approximately 75% of cervical cancers worldwide and low risk HPV types 6 and 11 account for 90% of genital warts.

Infectious life cycle

HPV with its simple genome, is unable to produce DNA polymerase and requires the host cell to permit viral replication. As an epitheliotrophic virus HPV infects only epithelial surfaces, targeting parabasal and basal cells. To access these cells a break in the surface epithelium is required, often caused by mild trauma. A possible reason for cervical disease being the most prevalent of HPV-related disease is that the transformation zone with its immature, metaplastic cells is a relatively easy target for the virus.

If the infected, basal epithelial cell is mitotically active then the HPV will be reproduced and may remain in the host cell at a relatively low copy number of approximately 100 genomes per cell. This is known as **latent infection**. Latent infection does not present clinically.

Latent HPV infection may progress to **productive viral infection**, where high numbers of viral particles are produced. The reasons for this are not well understood, however the early genes promote the amplification of viral DNA. As the host cell matures, reaching the epithelial surface, the late genes encode the protein capsid and the completed virion is formed. The infected squamous cell on reaching the epithelial surface is shed (desquamation) and with the help of the E4 ORF the large number of new viral particles is released.

Carcinogenesis

When a normally replicating cell becomes damaged the host response is to induce tumour suppressor proteins, p53 and retinoblastoma (pRB). These proteins have the ability to cause programmed cell death or apoptosis to keep cellular division under control and remove damaged DNA.

It is the E6 and E7 genes that give HPV the ability to transform a normal squamous cell into a neoplastic one. It is thought that integration of the HPV DNA into the host DNA has an important role in carcinogenesis. When the circular viral genome breaks to allow integration, E6 and E7 gene expression is increased due to loss of the E2 ORF, which normally maintains regulatory control of oncogene transcription. HPV E6 and E7 inhibit the action of p53 and pRB and therefore damaged cellular DNA is allowed to continue to replicate bypassing the usual control mechanisms. This uncontrolled replication of abnormal DNA results in genetic instability and eventually leads to cancer.

Natural history of disease

As previously noted, cervical cancer was thought to be caused by a sexually transmitted infection since the 19th century, but it is only relatively recently that HPV has been identified as the causative agent.

HPV infections are transmitted via skin-to-skin contact (including genital skin), not just sexual intercourse. HPV infection is endemic in the sexually active population. Peak exposure to HPV is following sexual debut in the late teens and early 20s, with a prevalence of 20–60%. Approximately 80% of sexually active women will have been infected with HPV by the age of 50. Therefore HPV infection should not be seen as a sign of a patient's or their partner's promiscuity or infidelity.

Epidemiological studies have shown that most (90%) infections with HPV are transient and do not cause significant disease. Studies have shown that following infection 50% of women will test negative at six months, 70% negative at one year and 80–92% will be negative at two years. The infection is cleared by the body's immune response.

Transient infection is much less likely than persistent infection to cause high-grade CIN. Transient infection may cause low grade CIN (CIN1) prior to clearance of the virus by the body. Approximately 50–60% of CIN1 will resolve without treatment within two years.

Persistent viral infection, particularly with high risk HPV types such as HPV 16 and 18, increases the risk of high-grade CIN (CIN2 or 3) and cervical cancer. High-grade CIN can still regress to normal without treatment, though the rates of regression are not well documented due to current management being to treat rather than observe these lesions.

Persistent infection causing high-grade CIN, if left untreated may progress to cervical cancer. Studies done in the 1980s, which now would be unethical, showed that 22–27% of untreated high-grade CIN progresses to cancer within 20 years with an annual risk being approximately 1–2% per year.

Overall 5% of high risk infections progress to cervical cancer in an unscreened population of women whereas in a screened population the risk is 1–2%.

Immunocompromised patients such as those with HIV, or those on immunosuppressive medication e.g. transplant recipients, are more at risk of persisting infection and high-grade CIN.

Prophylactic HPV vaccination

The current mainstay of management of cervical HPV infection in the UK is through secondary prevention by cervical screening and treatment of CIN. The aim being to pick up and treat CIN before it progresses to invasive cancer. Should cervical cancer be diagnosed, it is managed by the multidisciplinary gynaecological oncology team.

Attending cervical screening and any subsequent referral for further investigation or treatment is associated with a large degree of anxiety, in addition to the morbidity relating to the procedures themselves. It would be preferable to prevent initial HPV infection and hence the development of any subsequent disease (primary prevention). Prophylactic HPV vaccination offers the opportunity for primary prevention of HPV-related disease.

Vaccine development

The host uses both the innate and adaptive immune systems to react to HPV infection. The innate immune system, also known as the natural, or non-specific immune system is already in place prior to the viral insult. The innate system includes the natural barrier produced by the skin and mucous membranes which function to contain the infection whilst the adaptive (acquired/specific) immune system is activated. The humoural immune response to HPV infection can be to either the early or late proteins which both act as antigens. The antibody response to the early proteins, made by the virus during replication is usually weak. The late proteins that code for the viral capsid induce the strongest and most consistent antibody response.