Papillomaviruses (PVs) are ancient viruses — stable, ubiquitous, and evolutionarily well adapted to their hosts. They belong to the family Papillomaviridae with members in every vertebrate species. PVs have fascinated virologists for over a century, from early transmission experiments which showed that sterile cell-free filtrates could transmit skin and genital warts, to the recognition in the 1930s that transfer of cottontail rabbit papillomavirus to domestic rabbits resulted in malignant tumours.

Mid 20th century, human papillomaviruses (HPVs) were of interest clinically only to dermatologists and 'venereal disease' physicians where hand warts, plantar verrucae and genital warts contributed hugely to outpatient clinics (Fig. 1). The incidence of genital warts, as for other STDs, increased dramatically between the 1950s and the 1970s, as a consequence of greater sexual freedom. About 20 years ago, an association between HPV and malignant transformation was shown in cervical cancer and, inevitably since then, interest in HPVs has escalated exponentially. While the first international PV meeting in Lyon in 1975 had around 30 participants, the 20th International Papillomavirus Conference in Paris in October 2002 attracted over 600 worldwide PV researchers.

PVs are small icosahedral viruses (Fig. 2), with a supercoiled DNA genome approximately 8 kb in length and organized into two ‘late’ and six or more ‘early’ genes. Over 100 potential types have been identified and new types are being proposed every year. HPVs infect both squamous and mucosal epithelium, with around 30 types known to infect anogenital epithelium. Different clinical pictures are mirrored by the clustering of HPV types by molecular phylogenetic analysis. They can be segregated into non-oncogenic, cutaneous types; low risk types (LR-HPV) associated with external genital warts and mild cytological abnormalities; and high risk types (HR-HPV) with the potential to progress to severe abnormalities and cancers. The most common cutaneous types are HPV1–4, genital warts are most often associated with HPV6 and 11 and the five most common HR-HPV types in cervical cancers are HPV16, 18, 31, 33 and 45.

Most people will experience HPV infection at some stage in their lives, generally in childhood for cutaneous types (hand and plantar warts) and in early adulthood by sexual transmission. The chance of developing an HPV infection during life has been estimated at 80–85%, with a large proportion of women having been infected by age 30. However, active HPV16 infection has also been shown in the buccal mucosa of primary school children. Furthermore, in a study we carried out on schoolgirls aged 11–12 in Edinburgh, at least 7% had antibodies to HPV16. Surely such children are not all sexually active! Several studies have shown a few cases of cervical HPV infection in virginal women. Thus, while there is no doubt that most genital HPV infection is transmitted sexually, transmission from other sites is also possible.

Like many other virus infections in healthy individuals, most (around 80%) of HPV infections clear spontaneously, sometimes with the development of specific neutralizing antibodies which protect against
reinfection. In the remaining 20%, HPV infection persists, but regression of milder premalignant lesions is common and is associated with clearance of virus. Further infections with different types is of course possible, particularly for women with continued exposure through higher numbers of sexual partners. Only a very small number of persistent infections progress to cervical cancer.

Cervical cancer (Fig. 3) is the second most common malignancy in women worldwide. It can take many years to develop, but the pre-cancerous stages (called cervical intraepithelial neoplasia (CIN)) are detectable by cytological changes and are readily treated. A causal role for HR-HPV has been clearly shown from both epidemiological and experimental information. Not only are HR-HPV types found in 99% of cervical cancers worldwide, but viral DNA is integrated into the host genome in at least two out of three cancers. The transforming genes E6 and E7 of HR types are transcriptionally active, interact with cellular tumour suppressor genes p53 and pRB and disrupt cell cycle control. In contrast, E6 and E7 of LR-HPV types do not show these oncogenic properties.

Inevitably, the traditional factors associated with STDs, such as age at first intercourse, multiple sexual partners, increased parity and presence of other STDs have been extensively investigated as co-factors in cervical cancer. In addition, behaviours such as smoking and oral contraceptive use and genetic and other factors such as socio-economic status have been studied. Although many may appear to increase risk, the only independent variable, other than HR-HPV, directly associated with cervical cancer is smoking.

It is not HPV "acquisition", however, which is associated with cervical cancer, but HPV "persistence" and this occurs in only a tiny minority of infections. In this sense, HPV does not act as a typical STD, where infection is linked to a socially unacceptable level of sexual activity. Detecting persistence of HR-HPV infection will help identify women at greatest risk of developing cervical cancer, yet we do not understand what causes persistence in these few. It is not simply their sexual behaviour, but more probably a genetic predisposition with inadequate immune responses and uncontrolled cellular activity. We must not stigmatize women with cervical cancer because we consider they have had an STD when we cannot determine what else makes this minority different from most healthy women. The development of cervical cancer must be seen as a rare complication of a common infection acquired many years previously.

**Cervical screening**

Most people are aware of the media attention which has been given to ‘missed’ cases of cervical cancer, despite the existence in the UK of a population-based National Cervical Screening Programme using cytology. The public does not understand the limitations of ‘screening’ programmes and in cancer screening the issues are much more emotive. Cervical screening aims to detect cervical epithelial cell changes that precede the development of cancer in, and is based on, the premise that early
Further reading


detection and treatment of pre-malignant changes will prevent progression to invasive disease. The problem is that conventional screening uses 50-year old technology which on its own has probably outlived its usefulness. It has a sensitivity of only 50–70 % and in a recent audit in Scotland, 50 % of women with cervical cancer had actually had a negative smear within 5 years. There is therefore an urgent need for better identification of women at high risk.

There are two further major problems with current screening methods. First, up to 10 % of smears can be inadequate and must be repeated. The introduction of new automated methods of cytological preparation (liquid based cytology, LBC) will address this issue. In our Edinburgh studies we showed that LBC reduced the inadequate smear rate to less than 1 % and was at least as sensitive as conventional smears.

Second, 5 % of smears are reported as borderline (inconclusive) and referred for colposcopic examination if persistent. This is wasteful of resources since around 60 % will be within normal limits. The addition of HR-HPV testing would identify women most at risk and ensure treatment is targeted towards those who need it most. HPV cannot grow in cell culture, so we are dependent on molecular tests, using nucleic acid hybridization with or without amplification. These include a commercially available screening test (Hybrid Capture Assay, hc2, produced by Digene Corporation) used in a number of large-scale trials both for primary screening and triage of borderline and mild abnormalities, and several, as yet in-house, genotyping assays based on PCR followed by hybridization with type-specific probes. This allows detection of multiple types and distinguishes persistence from reinfection.

But herein lies the dilemma. There are no other cancer screening programmes which use a test which detects an apparent STD. How then can we introduce HPV testing to a cervical screening programme? Perhaps we will need to find surrogate biomarkers or look first for genetic polymorphisms which appear to be associated with greater host susceptibility to disease. I believe it would be better to educate the public about the nature of HPV infection and remove the stigma of HPV as an STD. HR-HPV tests can be easily linked into LBC screening protocols for selected groups of women, such as those with borderline abnormalities. For countries without organized cytology screening, HPV testing would be a more efficient starting point with a higher sensitivity for detecting high grade disease. This is already being trialled within Central and South American countries.

In the USA where individual healthcare needs are considered, cervical cytology with local excision of any suspicious lesions is carried out annually by medical practitioners themselves and healthcare teams need to be more informed and dissociate themselves from the old view of HPV as an STD.

Conclusions

There is an urgent need to increase public understanding of the way in which cervical cancer develops and to get rid of the perception that cervical cancer is a sexually transmitted disease. There is also an urgent need to educate women themselves in the ubiquity and natural history of HPV infection. Education leaflets are woefully inadequate, often written by academics or professionals with great knowledge, but set at a reading level beyond that of many of the women they address. A recent study of more than 20 HPV leaflets showed that all required a reading level 1.5 standard deviations above average ability to comprehend them. Finally, medical practitioners themselves and healthcare teams need to be more informed and dissociate themselves from the old view of HPV as an STD.

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