Genital human papillomavirus infection in Hong Kong

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This review traces the history of genital human papillomavirus infection and documents its discovery as a venereally transmitted infection. The strong links of human papillomavirus to ano-genital malignancies—particularly carcinoma of the uterine cervix—are outlined. DNA hybridization testing has enabled various subtypes to be identified, some of which are associated with certain malignancies. This new technology has also shown that male transmission of human papillomavirus is important and some men are vulnerable to cancer from the infection. Methods for treating human papillomavirus lesions are discussed. The role of cervical cytological screening in preventing cervical cancer is detailed and cervical cytology, despite the advent of DNA technology, is still the key to preventing cervical cancer. This should be encouraged in Hong Kong which, unfortunately, has an unacceptably low screening rate. Because of changing sexual behaviour, human papillomavirus infection is reaching epidemic proportions worldwide and the infection rate in Hong Kong is probably much higher than was previously thought. The medical profession and the public need to be aware of the consequences of this infection.

HKMJ 1996;2:80-88

Key words: Papillomaviruses; Tumor virus infections; Genital diseases, female; Genital diseases, male; Neoplasms; Vaginal smears

Introduction

Genital warts are a heterogeneous group of lesions which range from the conspicuous condylomata acuminata to subclinical lesions which require magnification to be seen. They are all caused by human papillomavirus (HPV) infection and are one of the most common sexually transmitted diseases. Human papillomavirus infection also has a strong association with the subsequent development of ano-genital cancers, the most common of which is cervical cancer. Hence, HPV infection is an important disease, but compared with human immunodeficiency virus (HIV) infection, it has received much less attention in Hong Kong. This is an oversight which needs to be addressed because the HPV-associated cancers can be prevented, whereas full blown acquired immunodeficiency syndrome (AIDS), despite medical intervention, is invariably fatal. Thus the effective and simple measures which can prevent the potentially serious results of HPV infection deserve much greater attention from both medical practitioners and the general public. Although this review examines in detail the links between HPV infection and cervical cancer, other clinically important lesions are also discussed.

Venereal transmission of genital warts

Genital warts is not a new disease and was known to the ancient Greeks and Romans who mistakenly thought the lesions were found only in homosexuals. This premise proved to be wrong as HPV infection is widespread among heterosexuals. Genital warts was also thought to be a marker of promiscuity and this assumption has proven to be correct. In Europe during the 15th century, when there were epidemic outbreaks of syphilis, despite heightened interest in sexually transmitted diseases, genital warts was grouped in with gonorrhoea and syphilis and all were thought to be due to 'venereal poisons'. A later view was that genital warts was a manifestation of syphilis but gradually it was accepted that this was a separate disease entity, although a link with gonorrhoea persisted and a common 19th century term was 'gonorrhoeal warts'. However, with the isolation of the gonococcus organism in
1879, the connection was dropped. Physicians in the 19th century thought genital warts could be due to "irritation of the epithelium by various agents such as dirt, decomposed smegma, and genital discharges". The idea that both common and genital warts were caused by the same 'parasite' was popular at the turn of the 19th century and some limited experiments were performed by inoculating extracts of common warts into the genital area as well as the reverse. The results supported the idea that the two lesions were due to the same virus and this was the basis of the 'unitary' theory. The supporters of this theory suggested that genital lesions were due to the accidental transfer of viruses from warts on the hand to the genital area. This idea was widely accepted and prevailed for many years, although a venereal transmission was supported by a minority of investigators.

Despite a venereal transmission being suspected by the ancient Greeks and Romans, proof was not established until comparatively recently. A group of American soldiers on active duty during the Korean War who had sexual intercourse with indigenous women while overseas became infected with HPV and developed penile warts. When the troops returned to their home base in the United States of America they infected their spouses and HPV lesions became manifest four to six weeks after sexual intercourse had taken place. On clinical examination, characteristic condylomata acuminata were found on the penis and vulva.

**Diversity of human papillomavirus lesions**

Human papillomaviruses are very small, measuring 50 to 55 nm in diameter, and belong to the *Papovaviridae* family. They have a circular double-stranded DNA genome and a molecular weight of 5 x 10^6 daltons. The capsid shows icosahedral symmetry and is composed of 72 individual protein subunits. The HPV's are epitheliotropic and, in infected cells, the virion is located in the cell nucleus. Seen through the electronmicroscope, the viral particles have a typical geometric honeycomb appearance. The viral particles in common warts were only demonstrated as recently as 1949. Some HPV-associated lesions are uncommon, such as laryngeal warts and epidermodyplasia verruciformis. The latter occur in a rare autosomal recessive condition in which affected individuals have multiple flat skin warts which have an extremely high rate of conversion to squamous carcinoma on exposure to UV light.

Viruses similar to HPV infect animals and an important breakthrough in the understanding of HPV and its role in neoplasia was made by Shope when he induced skin papillomas in cottontail rabbits. Shope inoculated the animals with a cell-free filtrate containing viruses prepared from papillomas obtained from other cottontail rabbits. Observations on highland cattle with viral-induced oesophageal papillomas which underwent malignant transformation after feeding on bracken fern also helped to establish the link between viruses and cancer. It was postulated that the fern had both immuno-suppressive and oncogenic roles.

With the advent of DNA hybridization techniques and the more sensitive procedure of polymerase chain reaction (PCR) amplification, it has been possible to identify the various HPV types found in lesions at different anatomical sites. More than 70 HPV subtypes have been reported. The ubiquitous common warts, often found on the fingers, are caused by HPV types 1, 2, 4, 26, 27, 29, 41, and 57; laryngeal papillomas are due to HPV types 6, 11, and 30; whilst those associated with genital warts in both men and women are HPV types 12, 16, 18, 30, 31, 33, 35, 45, 51, and 58. These viruses have been further categorised into two main groups. In the first group are HPV types 16, 18, and 30, 31, 33, 35, 45, 51, and 58. These have been designated high-risk viruses because the lesions in which they are found, especially those on the cervix, have a substantial risk (relative risk 8 to 11) of progressing to a pre-cancerous lesion and later to overt malignancy. The second group consists of the low-risk subtypes and include HPV types 6, 11, 42, 43, and 44. These are associated with benign genital warts and various papillomas of the skin and mucous membranes and present little risk of malignancy.

It is widely accepted that most cancers of the cervix begin as pre-invasive neoplastic cellular changes in the covering squamous epithelium. These cellular alterations have been termed cervical intraepithelial neoplasia (CIN) and three grades—CIN I, CIN II, and CIN III—are described; they roughly correspond to the old terminology of mild, moderate, and severe dysplasia-carcinoma in situ, respectively. The recently introduced Bethesda classification has only two categories of abnormality, low grade squamous intraepithelial lesions (LSIL) which includes HPV and CIN I lesions, and high grade squamous intraepithelial lesions (HSIL) which incorporates both CIN II and CIN III lesions. A substantial number of CIN III or HSIL lesions have the potential to progress to invasive carcinoma. Although HPV DNA testing can identify CIN cases due to high-risk viruses, there is currently no method which identifies with certainty those lesions which will progress to cancer. This means...
that once a high grade CIN diagnosis has been established treatment and close followup are mandatory.

Other ano-genital lesions, such as Bowen’s Disease and Bowenoid papulosis, both essentially carcinoma in situ, are often associated with the high-risk viruses and frequently progress to invasive carcinoma. As well as HPV type, additional factors which may be required for malignant transformation are viral load and transcription of the E6 to E7 region of the high-risk HPVs. Tumourgenesis is thought to be due to double inactivation of the two anti- oncogene products, p53 and pRB, and this may involve two oncogenic pathways. Firstly, there is deregulation of proto-oncogenes and cellular replication and secondly, there is failure to eliminate cells that have DNA damage by apoptosis.

Other co-factors, either endogenous or exogenous such as hormones, deranged immunity, smoking, and radiation may also be important in the induction of malignancy in the HPV-infected squamous cells. Smoking is an independent risk factor for cervical cancer—the cervical mucous of smokers has high levels of nicotine and cotinine and these substances may have a transforming effect on HPV-infected cells and give rise to malignancy. Additionally, smoking may enhance HPV infection by reducing the number of Langerhan’s cells in cervical epithelium. But the exact mechanism of how HPVs cause cervical cancer is still waiting to be delineated although some of the pieces in the puzzle are beginning to fall into place.

A global problem

It has been estimated that worldwide there are 30 million new cases of HPV infection each year. In many developed countries, HPV infection is reaching epidemic proportions, especially among younger women. A recent Swedish study showed that one-third of women aged 25 years and younger who attended a clinic for contraceptive advice had a history of HPV infection. In the United Kingdom and the United States of America, the most common viral venereal disease is due to HPV infection. One US study showed that 46% of young women attending the University of California’s Health Service were positive for HPV.

The dramatic upsurge in HPV infection appears to be due to a more permissive society and the availability of effective non-barrier methods of contraception. It has been convincingly demonstrated that the chances of acquiring HPV infection are greatly increased when there is a history of multiple sexual partners and promiscuity of the partner. The following hypothetical—but not rare—scenario illustrates the ease with which viruses may be acquired from a huge human reservoir. If an individual has five different partners, and if each partner also has five partners and this sequence is repeated in an exponential manner, then it is possible for a person to have exposure to a reservoir of viruses from an enormous number of people. A study which used PCR technology to assess HPV infection of the cervix and vulva showed that women with one partner had a positive HPV detection rate of 21% whereas women with 10 or more partners, had a rate more than three-fold of 69%.

It has been suggested that the passage of HPV through many individuals may result in the emergence of a more aggressive virus which is better able to transform cells and is a more effective carcinogen. When women who had cervical smears positive for HPV infection were followed up for a period of six years it was found that they had a 15.6 times greater risk of developing a lesion in the severe dysplasia-carcinoma in situ category compared with women with no cervical smear abnormality. Further finding was that women younger than 25 years were especially at risk of developing a premalignant cervical lesion. Figure 1 is a colpophotograph showing the cervix of a 25-year-old woman with an exophytic HPV lesion and a circumferential CIN III lesion. Human papillomavirus type 16 was detected in both lesions.

Hong Kong experience

Accurate information on the incidence of cervical HPV infection in Hong Kong is not available. In the experience of the author, many of the cervical smears examined at the Prince of Wales Hospital cytology laboratory have evidence of HPV infection and this is also likely to be the experience of other Hong Kong hospi-
tal laboratories. However, Hospital Authority laboratories in general do not evaluate cervical smears from population screening programmes and their experience cannot accurately reflect the incidence of HPV infection in the general population.

One local retrospective study which analysed 108 388 smears obtained from women attending Government Outpatient and Family Planning Clinics during a three-year period (1986 to 1988) showed that only 54 (0.05%) of cervical smears had evidence of HPV infection. The rate was two to three times lower than that for Canadian and American women. In this study an overwhelming majority (99%) of the cervical smears were from women older than 30 years. There were a number of reasons why the number of HPV-positive cervical smears in this study was low. A major factor was that many of them were from women having repeat cervical smear tests and another important reason was the small number of young women in the survey, only 1% of whom were younger than 30 years. Data from overseas indicates that women in the 20- to 24-year age group have the highest incidence of HPV changes.

Another retrospective Hong Kong survey analysed 288 810 smears from 184 591 women evaluated by the cytology laboratory of the Hong Kong Anti-Cancer Society and Hong Kong Family Planning Association. Of the abnormal cervical smears, 842 (0.46%) had HPV changes either alone or in conjunction with CIN changes. Subsequently, 459 patients had biopsies and 179 (46%) had CIN and concurrent HPV changes, a figure similar to that reported in Western countries. Although this study had subjects as young as 16 years old, the mean age was 37 years and, once again, many (36%) were repeat specimens.

It is interesting to record that one study concluded that HPV infection was low because Chinese people had a more conservative attitude towards sex and promiscuity was uncommon. Although this conclusion may be valid for older women (99% of women in the study were older than 30 years) and also for the period when the study was carried out (1986 to 1988), it may not be valid for younger Chinese women in the 1990s. A 1995 survey of 1038 young Hong Kong people (age range 15 to 29 years) conducted by the Social Science Research Centre, University of Hong Kong, showed that young Chinese people have a very liberal attitude towards sex. The survey revealed that by the age of 19 years almost half of the respondents (46%) were sexually active. In the study, 40% of single men and 30% of single women said they had experienced sexual intercourse. Some participants reported being sexually active at a younger age, with 10% of males and 5% of females having had coitus by the age of 15 years and 5% when aged only 14 years. Other important findings were that 40% of respondents did not use condoms, although 55% were concerned about AIDS and more than half said they approved of premarital sex.

As the cervical smear screening rate in Hong Kong is very low, it is unlikely that any study to gauge the incidence of HPV infection by analysing cervical smears will yield reliable information. It has been suggested that fewer than one in three Hong Kong women have ever had a cervical smear. There is good evidence to indicate that young Hong Kong people are sexually active and sexual behaviour and attitudes are not as conservative as previously thought. Thus if many eligible women have not had a cervical smear test, especially younger women, then the true incidence of HPV changes remains to be established. It is likely that the incidence of HPV infection in Hong Kong is significantly higher than that reported and may even approach the incidence recorded for Caucasian women. Further clinical studies which are comprehensive and more representative of the local population will help to resolve this.

Human papillomavirus infection in men

The concept of a sexually transmitted male factor, such as an infectious agent, for cervical cancer emerged from the collective findings and observations of many researchers. Kessler observed that the wives of men previously married to women with cervical cancer had higher rates of both pre-invasive lesions as well as cervical cancer than did women without such partners. It was also noted that there was a high rate of cervical cancer among women with partners who had penile cancer. One investigation convincingly showed that the husbands of women with cervical cancer had more sexual partners than did the husbands of women free of disease. Husbands with wives who had cervical cancer were also more likely to have a history of genital warts and other venereal diseases. Another interesting observation was that women whose husbands regularly used condoms had a low rate of cervical cancer compared with those who did not use this method of contraception. This was further circumstantial evidence for the role of a male factor in the aetiology of cervical cancer. Subsequently, HPV has been identified in semen and in the prostate, suggesting that semen may be the route of transmission.

Information regarding HPV lesions among men is more limited than the data in females as the substantial body of knowledge regarding genital HPV relates to cer-
vical lesions in women. In men, genital warts may produce no symptoms, although some urethral warts may bleed, produce a discharge, or lead to urinary frequency. Large exophytic penile lesions are easy to diagnose but are uncommon. Most penile lesions are subclinical and without the application of acetic acid and examination with a colposcope the lesions are difficult to see. In uncircumcised men, the frenulum and the inner aspect of the foreskin are the most common site of lesions, whereas, in circumcised men, the shaft of the penis is often involved. A rare penile lesion is the giant condyloma or Buschke-Lowenstein tumour which can be very destructive and leads to fistula formation. Histologically, this lesion has the appearance of a verrucous carcinoma.

Penile cancer is an uncommon malignancy but HPV type 16 and to a lesser extent HPV type 18 have been detected in a significant number of tumours and this suggests that the viruses are involved. In one study using PCR, 37% (27/73) of the penile cancers had evidence of HPV infection and most had HPV type 16 present. An investigation into Brazilian men with penile cancer showed that of 53 cases, nearly half (49%) were HPV type 16-positive. A population-based case-control study from British Columbia and Washington State, US, looked at 110 men with penile cancer. In 67 cases where tumour tissue was available for study, 49% were HPV-positive. In the positive cases 70%, had either HPV types 16 or 18 DNA detectable.

Although peri-anal and anal warts are found in both sexes, they are particularly common in homosexual men where receptive anal intercourse is a major factor. These can be large and bleed or ulcerate. In addition, anal intraepithelial neoplasia (AIN) with later progression to carcinoma has been documented. In 120 Danish homosexual men with AIN, HPV-positivity was strongly linked to HIV-positivity and evidence of immunosuppression as judged by measurement of T lymphocyte subset markers. Another study using PCR showed that 85% of anal cancers were HPV-positive and both HPV types 16 and 18 were detected. It has been suggested that AIN is increasing significantly among HIV-positive men and data from the United States also show a sharp rise in anal cancer among these males.
Cytological diagnosis

In the past it was not uncommon to encounter cases of dysplastic lesions of the cervix which were identified on cervical smears and confirmed by biopsy which spontaneously regressed without treatment. A proportion of these cases were undoubtedly HPV lesions. That HPV lesions could be mistaken for cervical dysplasia is not surprising as a widely respected cytological textbook of the time commented on the marked similarities between HPV lesions and carcinoma in situ. Prior to 1952, cervical HPV lesions were thought to be uncommon and only a few cases were reported in the world literature. Some lesions were described as papillomas and the rarity of the condition is not surprising as the overwhelming majority of cervical HPV cases are subclinical.

Ayre, the designer of the wooden scraper still widely used for obtaining cervical smear samples, alluded to a possible viral origin of so-called ‘halo cells’ in lesions which later progressed to cancer. The term ‘koilocytopic atypia’ was coined by Koss and Durfee for the cells seen in cervical smears obtained from flat lesions that resembled skin warts because the cells had a hollow or empty appearance. Despite these observations and the suggestion that these ‘halo cells’ might represent viral cytopathic changes it was not until some years later that the link was finally established.

An important development was the delineation of the cytological features of HPV cervical lesions simultaneously by researchers in Canada and in Finland. These investigators described the cytological features which are now accepted by pathologists as pathognomonic for HPV lesions. In addition, the colposcopic and histological appearances of the various clinically detectable HPV lesions were reported. Another important observation was that the florid exophytic condylomata acuminata were not a common lesion on the cervix. The most common lesions are subclinical, small, and inconspicuous, and difficult to see with the naked eye. However, they can be readily seen with a colposcope after the application of 5% acetic acid.

Clinical features

During sexual intercourse, a small abrasion of the epithelium permits the HPV to gain entry into the basal cells which regularly undergo mitotic division to replace cells which are continuously shed from the surface layers. Eventually, the infected cells migrate to the surface and are manifest as dyskaryotic and dyskeratotic cells and koilocytes. All these cytopathic cells are readily seen in cervical smears. The interval between exposure and the appearance of lesions varies and ranges from three weeks to eight months (mean, 2.8 months). The healing of epithelial damage may enhance viral replication and this is observed clinically when recurrent HPV lesions develop at the laser ablation margins following treatment. In men, many lesions are subclinical and the HPV types are identical to those found in their female partners. After infection, an individual can respond in a number of ways, including early regression with elimination of the HPV, persistence, fluctuation, progression, late regression, and recurrence.

![Florid exophytic condyloma acuminata on the cervix of a 25-year-old woman who had experienced intermittent postcoital bleeding for two years (x 5)](image)

Although most information has come from clinical observations of genital HPV infection in women, the pattern may be similar in males. A study which followed a group of women with genital HPV lesions (mean follow-up of eight years) found that 65% of the cases underwent spontaneous regression and 14% of the subjects had developed carcinoma in situ—a lesion with a substantial risk for progression to invasive cancer. The state of an individual’s cell-mediated immunity may also determine what happens to HPV lesions. This is illustrated when cell-mediated immunity is temporarily altered in pregnant women in whom genital warts can increase markedly in size. Similarly, patients with AIDS, renal transplant recipients, and those with Hodgkin’s disease have a higher incidence of HPV infection because of their altered cellular immunity.

The use of condoms has been promoted as a result of the AIDS epidemic and, when used properly, condoms will provide considerable protection against many sexually transmitted diseases. However, condoms may not provide total protection against HPV which is transmitted by skin-to-skin contact during intercourse. When
condoms are used it is still possible to transmit viruses which are present in lesions or have colonised the skin around the vaginal introitus (Fig 6) and pubic area in a woman or the skin at the base of the penis, scrotum, and pubic areas of the man. In men, HPV lesions can be found at many sites, including the penis, scrotum, around the anus, and in the urethra or bladder. As lesions are small, and invisible to the naked eye, it is common for individuals to be totally unaware that they have genital warts. As these small lesions do not produce symptoms, a sexual partner can be unknowingly infected. In the cervix, vagina, penis, and other areas, the skin surrounding any lesion may also be colonised by HPVs.

Fig 6. Small exopytic lesions on the vulva of an 18-year-old woman after application of 5% acetic acid and examination with a colposcope (x 10)

In women, the most serious complication of HPV infection is the very high risk for the subsequent development of cervical cancer. As mentioned, vulval and vaginal warts can enlarge during pregnancy because of transient immune changes and large lesions may even obstruct delivery. If warts are very extensive, there is a slight risk of infecting an infant during delivery but rarely is an elective caesarian section needed. The rapid regression of these warts after termination of pregnancy or after parturition is well documented. Laryngeal papillomas can be found in some young infants and may be a consequence of infection acquired during passage through an infected birth canal. In adults, lesions may develop in the mouth after oral sex.

The role of molecular diagnosis

Some authorities have advocated the use of routine PCR testing and have argued that by identifying patients with high risk HPV, such as types 16 and 18, more intensive treatment and surveillance can be provided. Such testing may have a role to play in managing patients with low grade CIN. These lesions have minimal microscopic changes and can be difficult to diagnose even for expert pathologists. When a panel of experienced pathologists were given 100 cervical biopsies to evaluate, the agreement was good for high grade CIN lesions but for low grade CIN there was poor inter-observer correlation. If these low grade CIN or equivocal lesions are HPV DNA-negative for high-risk HPVs then the chance of the patient developing a future malignancy would be extremely low. A positive result would be managed by referral for colposcopy and biopsy and more intensive follow up. Similarly, in cases where the cervical smear is equivocal for CIN and HPV infection, the more objective DNA test could be valuable. Thus HPV DNA testing provides objectivity to a subjective diagnosis. However, there is also a negative aspect to DNA testing. The anxiety level in some women will be increased when they learn they are harbouring a high-risk HPV and there is a danger of developing a cancer in the future. Hence, adequate counselling and support services are essential to help allay fears. Finally, if DNA testing is embarked upon, it is imperative that laboratory standards are high for there is no scope for error when the physical and mental health of a woman is at stake.

Treatment of lesions

In many individuals, genital warts disappear over time without treatment, but there is a substantial risk of further and more extensive lesions developing. In women with cervical, vaginal, and vulval lesions, once a diagnosis has been established by means of a cervical smear test supplemented with colposcopic examination and biopsy, treatment can be commenced. Methods used include cryotherapy, electrocautery, laser vaporisation, the application of podophyllin solution, 50% to 100% glacial tri-chloroacetic acid, or fluorouracil. If lesions are extensive, several treatments may be needed and should be carried out under anaesthetic, both to facilitate treatment and for patient comfort.

A new treatment involves interferon which consists of glycoproteins with antiviral, immunomodulating, and anti-proliferative activities. Interferon can either be injected into individual lesions or given by intramuscular injection for a systemic effect, but the results have been variable. Unfortunately, all currently available methods of treatment have high recurrence rates. Therefore, regular monitoring with cytology and clinical examination is essential after the completion of treatment. The use of HPV DNA testing has already been alluded to and may assist in the management of some patients.
The question of what to do with the male partner is unclear. Few clinics exist to routinely diagnose and treat men with subclinical genital HPV lesions. Large lesions present no diagnostic problem and excision and ablative techniques described for women are appropriate. Whether or not subclinical lesions (Fig 3) require treatment is still uncertain as detection requires colposcopy, and unlike cervical cytology which is widely used among women, such a screening technique is not available for men. Treatment may decrease the pool of virus available for transmission during sexual intercourse. Homosexual men with AIN need close surveillance and appropriate intervention when indicated. A more difficult problem is the management of women and men who are HPV carriers and have no detectable lesions. In some individuals, the virus will clear after a period of time but in others, there is persistence of the carrier state. The development of a vaccine against HPV would be a major breakthrough but the biggest hurdle to overcome is the lack of suitable in vitro systems for HPV replication.64

Summary

Although the HPV viruses most commonly give rise to harmless skin lesions, genital lesions need close monitoring as significant numbers may progress to carcinoma. Women should have regular cervical smears. For men, the danger of cancer is much lower, but there is good evidence linking penile and anal cancers to HPV infection. Condoms provide some protection and limiting the number of sexual partners is a more prudent option. Even though genital warts were known to the ancient Greeks and Romans, and despite dramatic advances in medicine, HPV infection remains a significant health care problem.

The Hong Kong medical profession should actively promote greater use of the cervical smear test as this will allow the detection of lesions which have the potential to progress to cancer. With appropriate treatment, cancer is prevented, and all sexually active women need to be encouraged to have regular cervical smears. The current rate of cervical smear testing in Hong Kong is unacceptably low (30%) and this is inadequate for an area which has sufficient well-trained doctors, a good medical service, and a burgeoning economy. Conversely, in China, good regional cervical screening programmes have been in operation since 1957.65

Although the risk for serious disease is substantially greater in women, the impact of HPV in men is still not fully known and this is an area which merits further clinical research.

References