



# Human papillomavirus: Beware the infection you can't see

**BACKGROUND** Genital human papillomavirus (HPV) is a common sexually transmitted infection. In the first 10 years of sexual activity, point prevalence rates approach 25% and the lifetime risk of acquisition of this infection may be as high as 80%. There are over 200 types of HPV, of which approximately 50 infect the genital area.

**OBJECTIVE** This article aims to discuss HPV detection and its role in cervical cancer development.

**DISCUSSION** The HPV types that cause genital warts do not cause cervical cancer. The subclinical types (especially types 16 and 18) are most frequently found in high grade epithelial abnormalities and therefore can potentially cause anogenital cancers. Human papillomavirus is a 'necessary but not sufficient cause for cervical cancer'. Most genital HPV infection is transient. Cervical cancer is actually a rare outcome of HPV infection. However, only 5% of women in developing countries have had a Pap smear in the past five years, and worldwide approximately 250 thousand women die of this disease every year. The role of HPV DNA testing has not yet been defined, but is no doubt a potential tool for the future. Meanwhile, international vaccine trials using HPV virus-like particles are taking place, and look promising.

Human papillomavirus (HPV) is a small nonenveloped double stranded DNA virus. Genital HPV infection (HPV-I) is very commonly sexually transmitted. The virus can induce a spectrum of genital disease from warts to cervical cancer. Exact prevalence rates of HPV in Australia are unknown, but in the USA it has been estimated that approximately 75% of the adult population has some evidence of being, or having been, infected with genital types of HPV<sup>1</sup> (Figure 1). Universally, the highest rates are found in young people between the ages of 18–28 years.<sup>2</sup> In fact, in the first 10 years of sexual activity point prevalence rates approach 25% (Figure 2), and the lifetime risk of acquisition

may be as high as 80%. Overall the prevalence in the sexually active population is thought to be approximately 20% depending on age.<sup>2</sup>

## Identification and diagnosis

Human papillomavirus can manifest in different ways; as a:

- clinically apparent infection visible to the naked eye as warts
- subclinical infection, which is unable to be seen to the naked eye, but becomes apparent in indirect ways through cytology or histology, and
- latent infection where the presence of the virus in the basal layers of the epithelium does not

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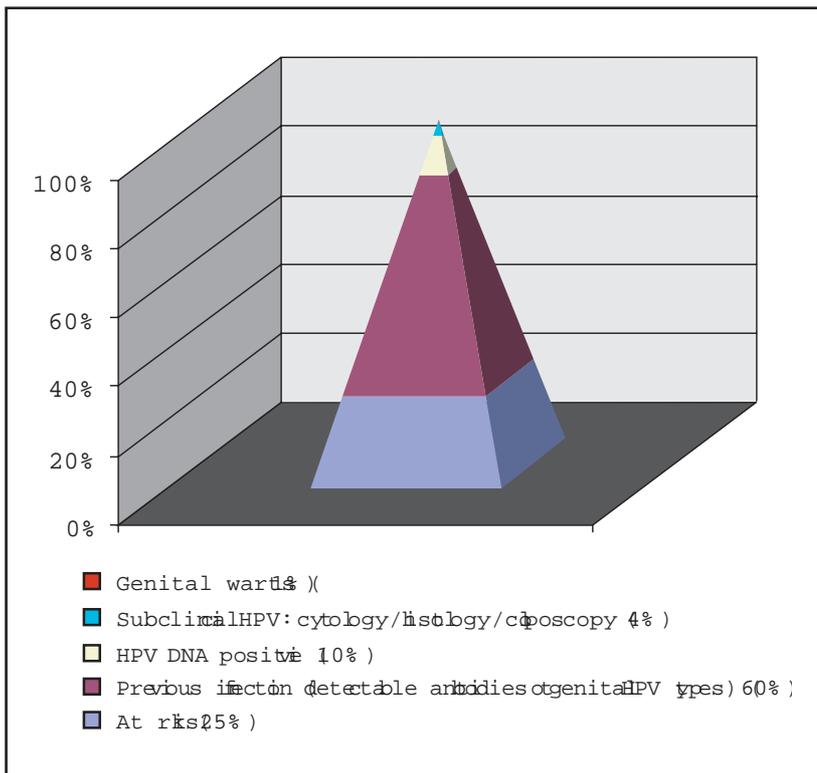


Figure 1. Manifestations of genital HPV-I in the adult population\*

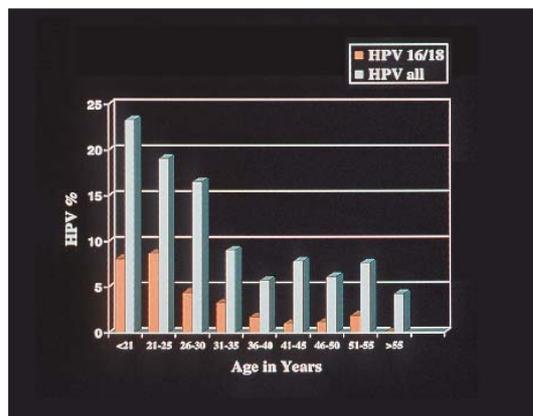


Figure 2. HPV prevalence by age group

cause any morphological changes in the infected tissue. Latent infection can only be detected by finding the presence of HPV DNA using an amplification technique such as polymerase chain reaction.

Over 200 types of HPV have now been identified, of which approximately 50 infect the anogenital area. Some of these types cause genital warts, including types 6, 11 and 42 etc. Genital warts are benign cellular outgrowths that are highly infectious and can be difficult to treat<sup>45</sup> (Table 1), but are essentially an aesthetic

problem, understandably associated with psychological morbidity. However, they do not cause cervical cancer.

The majority of anogenital HPV types cause subclinical infection, which is infectious, but invisible to the naked eye. This makes control of HPV-I difficult. The subclinical types (including types 16, 18, 31 and 33) are associated with high grade epithelial abnormalities (HGEA) and therefore potentially anogenital cancer.

The initial event in HPV-I involves epithelial trauma and the entry of the virus into the basal cell layer of the epithelium. Papillomaviruses multiply exclusively in the nucleus where they sit in a circular form next to the host cell DNA. Most HPV infection is transient (mean carriage rate of eight months for high risk types<sup>2</sup>) or becomes latent, possibly for life in some people. Containment may then depend on cell mediated immunity, but reactivation can occur.<sup>6</sup> In the development of most cervical cancers, the circular HPV DNA within the nucleus breaks and inserts itself into the host cell DNA. This is known as viral integration. If the host cell immunity breaks down, tumour suppressor genes may be inactivated allowing neoplastic changes to take place.

Human papillomavirus cannot be grown in culture. There are no sensitive or specific serological tests that can be used for diagnostic purposes. Electron microscopy for virions and immunochemistry for group specific antigens are relatively insensitive and nonspecific. So, until recently we depended upon the clinical observation of warts or upon indirect methods, such as cytologic or histologic effects, to make a diagnosis of genital subclinical HPV infection. Most laboratories adhere to strict criteria for such reporting but ultimately the 'diagnosis' is a subjective one and lacks sensitivity. In 2001, 778 women in Victoria had cervical biopsy following a cytological report suggesting the presence of HPV. Forty-one percent had normal biopsy findings.<sup>7</sup>

Recombinant DNA technology resulted in the first cloning and sequencing of DNA in 1980. Unlike typing schemes for other viruses (based on antigenic differences) HPV typing is based on the degree of DNA sequence homology. The subtype of infection can be determined only by DNA hybridisation. A new number is allocated to untyped DNA if it shares less than 50% homology with any of the known HPV types.

**Table 1. Summary of commonly used treatments for genital warts<sup>5</sup>**

Forms of treatment	Usage	Response rate	Recurrence rate	Advantages and disadvantages	Use in pregnancy
<b>Patient applied</b>					
Podophyllotoxin Condyline	External genital warts	45–82%	0–91%	Results may depend on patient compliance. Not for large (>10 cm <sup>2</sup> ) wart areas	No
Imiquimod Aldara	External genital warts	37–85%	13–19%	Immune enhancer. Most effective on moist warts. Less effective in men	No
<b>Provider administered</b>					
Cryotherapy	External anogenital, meatal, perianal or oral warts	60–97%	20–79%	Effective for moist and dry warts. Can be painful. Risk of over or under application	Yes
Electrocautery or diathermy	External anogenital or oral warts	35–94%	22%	Prompt wart free state, longer clinic visit, local anaesthetic mandatory	Yes

In the past few years the Digene Hybrid Capture II HPV DNA test has become available. This test has a nucleic acid hybridisation assay that depends upon chemiluminescent detection. It uses ribonucleic acid probes that are specific for the genomes of 13 viral types that are implicated in the pathogenesis of HGCA and invasive cancer (ie. 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Its potential clinical role is discussed below.

### Relationship between HPV and cervical cancer

Cervical cancer is the second commonest cause of cancer in women in the world (after breast cancer), accounting for approximately 470 000 cases and 250 000 deaths per annum.<sup>2,8</sup> Cervical cancer is the ninth commonest cancer in Australian women, and the eighteenth commonest cause of cancer death in women, accounting for 220 deaths in 1999.<sup>9</sup> The introduction of the Pap smear screening program in the 1960s, and in particular, the invigorated efforts over the past 14 years, has led to a significant drop in the incidence of cervical cancer from 14 per 100 000 women in 1985 to 7.14 per 100 000 women in 1999, and a decrease in mortality from 7.1 per 100 000 women in 1945 to 2.5 per 100 000 women in 1999. Among countries with comparable cancer registration systems, these are the second lowest age standardised rates seen.<sup>10</sup>

**Table 2. NHMRC recommendations for HPV changes suggested on a Pap smear\*<sup>16</sup>**

Pap smear report	Investigation	Management
HPV effect/ cell changes	Repeat smear at six monthly intervals. If HPV associated changes persist after 12 months, refer for colposcopy	If HPV confirmed, continue with six monthly smears until two negative reports are received. Repeat smear annually for two years then revert to two yearly screening

\*These guidelines are currently being updated

Of women who die from cervical cancer in Australia, 85% have either not had a Pap smear or have been inadequately screened in the previous 10 years.

Strong epidemiologic and molecular data now link HPV-I to cervical and other anogenital cancers.<sup>1</sup> Human papillomavirus DNA is found in 99.7% of cervical cancers and is recognised as the major cause of cervical cancer.<sup>11,12</sup>

However, cervical cancer is actually a rare outcome of infection with HPV. Most subclinical infection is transient. The International Agency for Research into Cancer noted that HPV is a 'necessary but not sufficient cause for cervical cancer'.<sup>13</sup> The majority of those infected

remain asymptomatic, and potentially infectious, but appear to either clear the virus with no ill effect or retain it in its latent nonreplicating form. In a minority of patients the infection persists, integration of the viral DNA into the host cell DNA may occur, cellular immunity breaks down, and additional cofactors (poorly understood but including smoking), aid the development of neoplastic disease. This process usually takes many years.

### The role of testing for HPV DNA

The Digene Hybrid Capture II HPV DNA test is becoming increasingly available in many parts of the country. It can be performed on a direct swab from the cervix (using a specifically designed kit) or on the fluid from a fluid based cervical cytological specimen. No rebate is available and the test currently costs approximately \$80.

The hybrid capture test is highly sensitive, but lacks specificity. Therefore, in a high prevalence population (women between the ages of 18–28 years) false positive results occur. Moreover, the test's usefulness resides in its determination of persistence of infection (longer than six months) in women over the age of 35 years (where prevalence rates are lower, and detection over such a period is more likely to represent continuing rather than new infection). If a 26 year old woman has a one-off positive HPV DNA test for high risk virus, it means very little: so will one in four of her friends. If a 35 year old woman has two positive tests over a six month period, she has a significant risk of developing a HGEA.<sup>14</sup> Table 2 lists NHMRC guidelines for women with HPV changes suggested on a Pap smear.

However, in utilising this test we want to be able to decrease rather than increase financial cost to the community and psychological morbidity to the individual. It would be good, for example, to decrease the number of colposcopies carried out annually on women in Australia. With that in mind, there are some suggestions for the test's use:

- as a triage test for women with repeated low grade epithelial abnormalities, ie. HPV, CIN-1 (positive: colposcopy; negative: repeat smear at designated interval)
- follow up of women post-treatment for HGEA, and
- in conjunction with cervical cytology for women over the age of 35 years to decrease the interval

of Pap smear screening (the negative predictive value of these two tests for the development of HGEA is 99.9%<sup>2</sup>).

As yet, the role of HPV testing has not yet been defined, but we need to be aware of it as a potential tool for the future.

### The future

Human papillomavirus related neoplasia is a largely preventable disease. Squamous cell carcinoma (which accounts for approximately 85% of all cervical cancers) is preceded by relatively well defined precursor lesions able to be detected on a Pap smear and amenable to treatment. But the success of a cervical screening program depends on a complex infrastructure which relies upon the organisational skills and resources of a developed country. It is estimated that only 5% of women in developing countries have been screened in the past five years.<sup>2</sup>

Vaccination against high risk HPV types may seem the answer. But how do you do this with a virus that does not cause viraemia, cell death, nor even a local inflammatory response?

In animal models, vaccination using only empty viral capsids (devoid of any DNA and therefore noninfectious) produces neutralising antibodies which are protective against the development of disease.<sup>2,15</sup> Recent trials using HPV-16 virus-like particles (VLPs) to vaccinate young antibody negative women have shown reduction in the incidence of both HPV-16 infection and HPV-16 related cervical intraepithelial neoplasia (CIN). However, because of the exquisite antigenic specificity of HPV capsid antigens, there is unfortunately no cross protection to other types. We need a vaccination cocktail that includes VLPs for at least HPV 16, 18, 31 and 45. This could potentially prevent 75% of cervical cancers.<sup>8</sup>

Phase 1 and 2 clinical trials of recombinant vaccines are currently underway worldwide. In the future, vaccination of teenagers before they commence sexual activity may prevent them from developing this disease. Until then, a woman's best protection against the development of cervical cancer is to have regular bi-yearly Pap smears.

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SUMMARY OF IMPORTANT POINTS

- Genital HPV-I is common. In the first 10 years of sexual activity, point prevalence rates approach 25%. The lifetime risk of acquisition may be as high as 80%.
- Approximately 50 HPV types can infect the genital area. The types that cause warts do not cause cervical cancer. The subclinical types (especially types 16 and 18) are those associated with HGEA and thus potentially anogenital cancer.
- HPV DNA is found in 99.7% of cervical cancers and is recognised as the major cause of cervical cancer.
- Most HPV infection is transient and cervical cancer is actually a rare outcome of infection with HPV.
- 85% of women who die from cervical cancer in Australia have either not had a Pap smear or have been inadequately screened in the previous 10 years.
- The Digene Hybrid Capture II HPV DNA test is highly sensitive, but lacks specificity. Therefore in a high prevalence population (women between the ages of 18–28) false positives occur.

Conflict of interest: none declared.

Resources

The 'Pap tests and the human papillomavirus (HPV)' booklet (Figure 3) can be ordered through: [www.papscreen.org](http://www.papscreen.org) or by calling The Cancer Council Victoria Helpline on 13 11 20. [www.hpv.org.nz](http://www.hpv.org.nz) [www.mshc.org.au](http://www.mshc.org.au)

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Figure 3. The 'Pap tests and the Human Papillomavirus (HPV)' booklet

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REPRINT REQUESTS

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