Cervical screening and human papillomavirus

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BACKGROUND

Cervical screening in Australia has been successful in reducing the incidence and mortality of cervical cancer. Human papilloma virus (HPV) is a common sexually transmitted infection and an integral agent in the development of cervical cancer.

OBJECTIVE

This article discusses cervical screening, HPV infection and counselling women with low grade abnormalities on cervical cytology.

DISCUSSION

For most women, detectable HPV infection is transient and subclinical. While HPV is a precursor to cervical cancer, this is a rare outcome of HPV infection. Minor abnormalities on cervical cytology reflecting acute HPV infection are common. Women with low grade Pap test abnormalities require reassurance and education about the prevalence and natural history of HPV.

Early detection and treatment of cervical cell abnormalities reduces the risk of cervical cancer development. Papanicolaou tests (Pap tests) have been available in Australia since the 1960s and a national cervical screening program commenced in 1992.[1]

In New South Wales in the 10 years from 1993–2002, the age standardised incidence rates of cervical cancer declined by 48% and mortality fell by 49%.[2] An estimated 61.9% of women aged 20–69 years had a Pap test in 2001–2002.[3] For more on screening for the prevention of cervical cancer refer to *Table 1*.

Routine cervical screening provides the opportunity to take a brief sexual history and consider testing for STIs (particularly chlamydia) if appropriate.

HPV and cervical cancer

Epidemiology of HPV infection

Up to 75% of women will become infected with human papillomavirus (HPV) at some stage in their lives,[4] usually in the first few years after becoming sexually active.[5] Most infections are subclinical[4] and transient,[6] with the immune system clearing detectable virus in time. Median duration of detectable HPV infection has ranged from 8–17 months in studies.[6–8] High risk HPV persist longer on average than low risk HPV.[6,8] Women with certain genetic and immune system cofactors may be more likely to have persistent high risk HPV infection and are at increased risk for cervical cancer.[5]

The pathogenesis of cervical cancer has become clearer as techniques for detecting HPV DNA have improved. Human papillomavirus infection is an important precursor for cervical cancer development, but HPV infection does not inevitably lead to cervical cancer.[5,7] Human papillomavirus DNA has been detected in at least 95% of cervical cancers,[5] with HPV16 and HPV18 being the most commonly isolated types.[9]

Over 200 types of HPV have been identified.[10] High risk HPV types such as HPV16, 18, and 31 are considered oncogenic. They are associated with cervical cancer and abnormal cervical cytology. Low risk HPV types such as HPV6 and 11 are infrequently detected in cervical cancer. They are associated with genital warts and low grade abnormalities on cervical cytology.[8]

HPV infection and cervical cytology

Low grade abnormalities on cervical cytology represent acute HPV infection.[11] While abnormal cervical cytology is a common manifestation of HPV infection,[12] it is not an invariable consequence of it.[11] Koilocytes, nuclear atypia, delayed maturation, hyperkeratosis and parakeratosis are all suggestive of HPV infection.[5] Studies have shown that 22–33%

of women who test positive for HPV develop abnormal cervical cytology within several years.[9,13,14] This risk increases with persistent HPV infection and smoking.[13]

Low grade squamous intraepithelial lesions

The Australian Modified Bethesda System 2004, classifies 'HPV effect' and 'cervical intraepithelial neoplasia 1' (CIN1) as low grade squamous intraepithelial lesions (LSILs).[11] This new terminology allows Australian data to be compared with international research. Also, by grouping 'HPV effect' and CIN1, it removes a subdivision that was not found to be clinically meaningful or reproducible.[11] In 2002, 1.9% of New South Wales Pap tests were reported as showing HPV changes,[3] and 4.7% were classified as either 'mild atypia' or CIN1.[3]

Counselling women following abnormal cervical cytology

Counselling about HPV

Women with abnormal cervical cytology require education about HPV. Discussion about HPV prevalence and natural history is appropriate, with emphasis on how common the infection is, and reassurance that cervical cancer is a rare outcome of HPV infection.

McCaffery et al[15] found that women expressed anxiety, confusion and stigma about HPV as a STI. Some women associate an abnormal Pap test result with promiscuity – probably a result of lay awareness of cervical cancer risk factors including multiple sexual partners and early age of first sex.[16]

Determining when HPV acquisition occurred is not possible, and the patient or her partner may have been infected many years previously (an important point for women in long term relationships where issues of fidelity and trust may arise). The value of partner notification is unclear, as there is no treatment for men unless they are in the estimated 1% of the population who develop visible warts.[17]

Use of condoms following a low grade abnormality on a Pap test (or clinical genital wart infection) is controversial.[18,19] Condoms probably do not prevent infection with HPV, and as HPV infection is likely to be 'shared' by a couple by the time it is diagnosed, condoms may not offer significant benefit. However, a meta-analysis on the effect of condom use on HPV infection concluded that condoms may prevent the progression of clinical warts and Pap test changes.[20] More research in this area is needed so that women can be provided with accurate and consistent information.

Table 1. Screening for the prevention of cervical cancer

Screening has been defined as testing carried out on apparently well people to identify those at risk of a disease or disorder.[23] Cervical cancer screening with cytology provides the opportunity for early effective intervention and has reduced morbidity and mortality

Conventional Pap test

The conventional Pap test has been used for over 50 years and there have been no significant changes in this time to its preparation or interpretation.[24] Its biggest limitation is its sensitivity. Repeat Pap tests are required to achieve satisfactory sensitivity levels.[25] Pap tests are less adept in detecting adenocarcinoma than squamous carcinoma.[26] Clinician and community anxiety about false-negative tests have contributed to the introduction of newer tests including liquid based cytology and HPV testing

Liquid based cytology

Use of liquid based cytology (or 'thin layer' testing) involves collecting cervical cells in a liquid vial. A machine filters cells from the liquid, removes any extraneous matter and transfers cells onto a slide. Cells are distributed as a single layer making interpretation easier for cytotechnologists. Liquid based cytology has lower rates of unsatisfactory samples,[27] and is more sensitive[24] than a conventional test, but specificity is probably lower[28,29]

HPV testing – the role in cervical cancer screening

The purpose of HPV testing is to detect the presence of high risk HPV types associated with cervical cancer. HPV testing is very sensitive and is considered a useful tool for predicting which women with a history of high grade squamous intraepithelial lesions (HSILs) are at greatest risk for recurrence.[11] The NHMRC recommends women treated for HSILs are initially followed up with a Pap test and colposcopy at 4–6 months.[11] Cervical cytology plus HPV testing should then be performed at 12 months post-treatment and annually thereafter until both tests are negative on two consecutive occasions. Women may then be advised to return to the routine screening interval for cervical cytology

HPV testing could also be used in women with LSILs to predict who is at increased risk of developing high grade abnormalities (or to reassure women who test negative to high risk HPV types). NHMRC guidelines do not currently recommend HPV testing in this circumstance. While women can be offered HPV testing at their own expense, it is important to note testing positive for high risk HPV may exacerbate patient anxiety and testing negative does not change recommended management

Cuzick et al[30] have proposed a potential new approach to cervical cancer screening, suggesting HPV testing could be used as a primary screening approach for women aged 30 years and over, with Pap tests reserved for women who test HPV positive. Screening women less than 30 years of age for HPV is not recommended, as with the high prevalence of HPV and low incidence of cervical cancer, the specificity of the test is low

HPV vaccines

It is anticipated HPV vaccines will become commercially available in the near future,[10] with prophylactic and therapeutic vaccines being trialled worldwide. An effective vaccine could potentially reduce the number of Pap tests women require in a lifetime and lower cervical cancer incidence and mortality. Cost effectiveness, safety and parental acceptance will be critical to its success as a widespread public health initiative

Discussing low grade abnormalities

Women with low grade abnormalities on Pap tests need explanation and reassurance. A Swedish study surveyed women who had a Pap test reported as 'mild dysplasia' approximately 5 years earlier and found 30% reported the result affected everyday life from the time they learnt the result to subsequent investigation.[21] Women with abnormal cervical cytology should be re-called to discuss their result.

As the majority of low grade changes resolve spontaneously without treatment[22] – especially in young women – it is important to avoid creating undue anxiety. Explanation could include reassurance that minor changes on Pap tests are common, usually transient and require surveillance. Low grade changes are not necessarily 'precancerous', and the word 'cancer' needs to used with care.

Women may be advised that the reduced screening interval for a subsequent Pap test is to ensure that any further problems can be treated promptly. At the time of writing, the latest (unpublished) National Health and Medical Research Council recommendation stated that asymptomatic women aged 30 years or over with an index Pap test report of LSIL and without a history of negative tests in the preceding 2–3 years should be offered either immediate colposcopy or a repeat test in 6 months.[11] Other asymptomatic women with an index Pap test report of LSIL are advised to have a repeat test in 12 months. If this repeat test shows either LSIL or high grade changes, the woman should be referred for colposcopic assessment. If the repeat test is negative, the next test should be done in a further 12 months. If this is negative, the woman may return to having her Pap tests at the routine screening interval.[11]

Conclusion

Australia's national cervical screening program has successfully reduced cervical cancer incidence and mortality. Human papillomavirus is a STI and an important precursor to cervical cancer. The majority of sexually active women acquire HPV at some stage, and it is important to minimise the morbidity associated with its common and usually benign manifestation of a low grade abnormality on a Pap test.

Summary of important points

- HPV is a common STI with up to 75% of women becoming infected during their lifetime.
- HPV infection is an important precursor for cervical cancer development.
- Cervical cancer is a rare outcome of HPV infection.
- Most detectable HPV infections are transient and asymptomatic.
- Low grade cytological abnormalities on cervical cytology reflect acute HPV infection.
- Low grade changes on Pap tests (especially in young women) usually regress spontaneously.
- Few women understand the role of HPV infection in cervical cancer, and education about HPV is required when discussing any abnormal Pap test result.

Conflict of interest: none declared.

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