THEME

Gynaecological malignancies

Pap test update

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BACKGROUND

2006 was an eventful year in the area of screening to prevent cervical cancer. New screening guidelines were introduced nationally in July, and in November the Australian Government agreed to fund one of the human papillomavirus (HPV) vaccines, Gardasil, under the National Immunisation Program.

OBJECTIVE

This article discusses the cervical screening program and the Pap test in the era of HPV vaccination.

DISCUSSION

With the introduction of a vaccine to prevent the acquisition of significant genital HPV types, many practitioners will be questioning the continuing need for the Pap test. But for those women who have missed out on the vaccine, the Pap test will still play a crucial role in preventing the development of cervical cancer, and the vaccinated cohort will need to continue screening in some form as the vaccine does not cover all the HPV types responsible for anogenital cancer.

While cervical cancer affects around 500 000 women internationally each year leading to 250 000 deaths,[1] Australia has the second lowest incidence and the lowest mortality rate for this disease in the world.[2] Since the introduction of the National Screening Program in 1991 we have seen a decrease in the incidence of and mortality from cervical squamous cell cancer by around 60%.[3–5] In Australia, about 700 women are diagnosed with cervical cancer each year, with around 240 deaths; 85% of these women have either not had a Pap test in the past 10 years or have been inadequately screened, and 75% are over the age of 50 years.[6] Adenocarcinoma now accounts for around 20% of cases of cervical cancer and the incidence has not dropped despite the (otherwise successful) Pap test screening program.[5]

During 2006 the *Guidelines for the management of asymptomatic women with screen detected abnormalities*[7] were introduced (incorporating indications for the 'high risk' human papillomavirus [HPV] DNA [Digene] test) in July, and in November, the Australian Government agreed to fund one of the new HPV vaccines (Gardasil) as part of the National Immunisation Program.[8] This is truly an exciting time to be involved in the area of screening to prevent cervical cancer.

The new guidelines

The new guidelines were ratified in 2005 and introduced nationally in July 2006 (*Table 1*). There are six new areas of change:

- new terminology
- management of women with low grade changes detected on cytology
- management of women with low grade changes confirmed on biopsy
- management of women with glandular changes detected on cytology
- management of women with normal endometrial cells on cytology*, and
- follow up of women with confirmed high grade changes on cytology.

* Recommendation: normal endometrial cells on Pap tests of postmenopausal women need not be reported.

New terminology

Under previous guidelines there were five major categories of reports:

- negative
- low grade abnormalities
- high grade abnormalities
- inconclusive, and
- unsatisfactory.

To have a clearer understanding of the management of Pap test abnormalities, the new guidelines ask practitioners to think in terms of the two different types of cells in the cervix: squamous and glandular. With this in mind, the

major headings have been reorganised and reduced to four:

- negative
- squamous
- glandular, and
- unsatisfactory.

Squamous changes occur at the squamo-columnar junction, where the columnar cells change or transform or metaplase into squamous cells. These changing cells are particularly vulnerable to infection with HPV. The Pap test is designed to pick up these cellular changes. Squamous changes can be either:

- low grade squamous intraepithelial lesions (LSIL), or
- high grade squamous intraepithelial lesions (HSIL).

Significant changes (HSIL, previously called cervical intraepithelial neoplasia CIN 2/3) can be successfully treated to prevent progression to squamous cell cervical cancer.

Glandular changes are cellular changes originating from columnar epithelium found higher in the endocervical canal. Glandular changes (usually reported on a Pap test as possible adenocarcinoma) are also caused by HPV (often type 18) but are not easily detected on a Pap test as the cells may be too high or too deep in the canal. The new guidelines recommend that a woman with glandular changes on her smear should be referred for colposcopy, where possible to a gynaecologist with expertise in malignancy, or to a gynaecological oncologist.

Management of LSIL

Under the previous guidelines low grade abnormalities included a number of subheadings, each of which had a different recommendation. These were:

- nonspecific minor changes (repeat 12 monthly with no colposcopic endpoint)
- HPV effect (repeat every 6 months, and if changes are still present at 12 months, refer for colposcopy), and
- CIN 1 (refer for colposcopy).

The new guidelines have simplified this markedly by bringing these three subheadings together as one – LSIL: low grade squamous intraepithelial lesions. The recommendation for an LSIL Pap test is to repeat the test in 12 months.

Underscoring the development of the new guidelines is our understanding of the role that HPV plays in the cause and development of cervical cytological changes and, potentially, anogenital cancer (including cervical cancer).

Natural history of HPV

There are around 200 different types of HPV, classified according to DNA sequence. About 40 types specifically infect the anogenital area.[1,9] These HPV types spread through genital skin-to-skin contact. The genital types are divided into 'low risk' and 'high risk' according to their association with and ability to cause anogenital cancer. 'Low risk' types include types 6 and 11, responsible for approximately 90% of genital warts.[10] These types do not cause anogenital cancer. There are 15 'high risk' HPV types, of which types 16 and 18 are the most important, being responsible for about 70% of cervical cancers worldwide and 80% of cervical cancers in Australia.[10]

Table 1. Recommendations (for asymptomatic women)[7]

Results	Action
Negative	Repeat smear 2 years
LSIL	Repeat smear 12 months
HSIL/glandular changes	Colposcopy
Unsatisfactory	Repeat 6–12 weeks

Human papillomavirus enters the skin through tiny micro-abrasions. Once it has entered, it remains confined to the surface epithelium, entering the nuclei of the basal cells. An acute HPV infection does not cause viraemia; nor cell death or local inflammation. In fact, HPV relies on the replication of the basal cells and their own transformation and ultimate exfoliation for its own replication and ability to spread. Natural HPV infection hides itself well from the body's immune system.

Exfoliated cells are collected from the surface of the cervix when a Pap smear is taken. In the Pap test, the cytologist examines the cells looking for certain features such as a dense or double nucleus or a high nuclear-cytoplasmic ratio that may indicate infection with HPV (*Figure 1*).

Human papillomavirus is an extremely common infection in the first 10 years of sexual activity. Estimated point prevalence for young sexually active people is between 20–25% and estimated longitudinal prevalence (and life time risk) is at least 80%.[3] The majority of this infection is not only subclinical, but transient, and for this reason

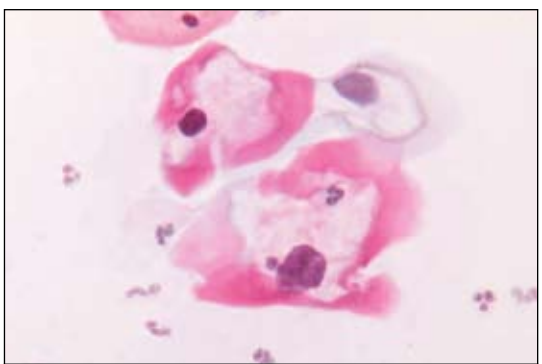

Figure 1. HPV infected exfoliated cells
Photo courtesy Gillian Phillips, Scientific Department, Victorian Cytology Service

genital HPV infection has been referred to as 'the common cold of sexual activity'.

When HPV enters the nucleus of the basal cells in the epithelium it usually sits next to the host cell DNA in what is known as 'episomal' infection. Most HPV infections of the cervix result in no cytological abnormality. But occasionally this episomal infection causes cytological changes that can be detected as LSIL. Close to 80% of these LSIL lesions regress within 12 months.[7] Progression from LSIL to HSIL is very uncommon, and if it does occur, takes on average around 7 years.[7]

Even infection with one of the 'high risk' types is usually transient. However, the circular DNA of these particular types very occasionally (and for reasons which are poorly understood) breaks and inserts itself into the host cell DNA. This is known as 'viral integration'. Integrated HPV infection is more likely to be persistent and associated with the types of cellular changes seen in HSIL lesions.

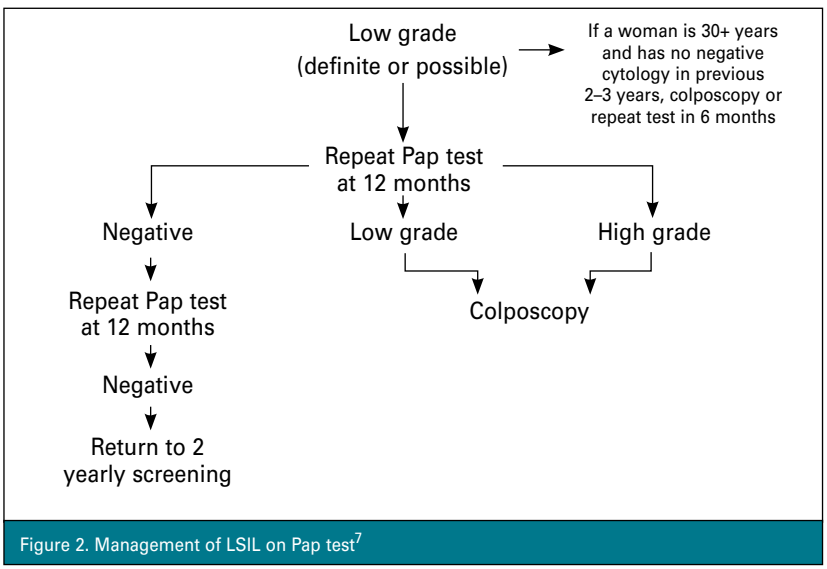

Figure 2. Management of LSIL on Pap test[7]

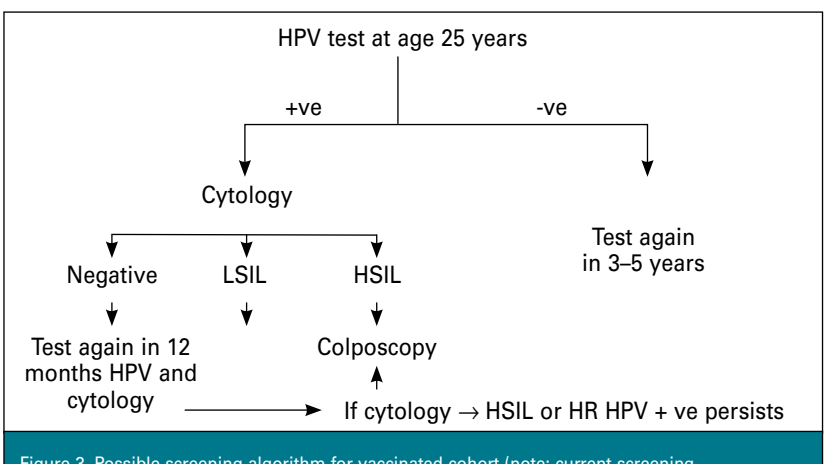

Figure 3. Possible screening algorithm for vaccinated cohort (note: current screening recommendations remain the same for both vaccinated and nonvaccinated women)
Source: Dr Marion Saville, Victorian Cytology Service

This understanding of the natural history of genital HPV infection informs our new guidelines. After an initial Pap test report of a LSIL, a woman is advised to have a repeat test in 12 months. This gives her a chance to 'clear' the infection. If, on repeat, the LSIL changes are still present, or if HSIL changes are detected, a colposcopy will be recommended. If LSIL changes are confirmed on biopsy, gynaecologists are now asked not to treat these lesions but to appreciate that as they are almost always caused by HPV, women can safely have a repeat Pap test in 12 months (*Figure 2*). HSIL confirmed on biopsy should be treated as previously.

HPV testing

The current recommended test for cervical HPV is the Digene HC (hybrid capture) II test which looks for 13 of the 'high risk' HPV types. The result is reported as either positive or negative for high risk types of HPV. Individual types of HPV are not separately identified. This test can be used as a 'test of cure' after the treatment of an HSIL. The woman should return to her gynaecologist for a repeat colposcopy and Pap test 4–6 months after treatment of an HSIL. If these are satisfactory, she can see her usual practitioner 12 months post-treatment for both a Pap and HPV test. These two tests should be done annually until the woman has tested negative on both tests on two consecutive occasions. When all four tests are negative the woman can return to the usual 2 yearly screening interval (*Table 2*).

HPV vaccine

The development of the HPV vaccine marks an exciting opportunity for the control of anogenital cancer internationally. In November 2006, the Australian Government approved funding of the Gardasil vaccine for females aged 12–26 years. Gardasil is a quadrivalent vaccine that protects against HPV infection with types 6, 11, 16 and 18. Types 6 and 11 cause 90% of genital warts; types 16 and 18 cause 70–80% of cervical cancer in Australia. Gardasil is given intramuscularly in a three dose schedule at 0, 2, and 6 months. It has been shown to provide 90–100% protection against persistent infection and cervical/genital disease due to HPV types 16 and 18.[10] Although approved for use in males aged 9–15 years, there is currently little data on vaccine efficacy in preventing genital warts or ano-genital cancer in males. Therefore, Gardasil will be put on the National Immunisation Program on an ongoing basis for girls aged 12–13 years to be delivered through schools with further funding for a 'catch up' program for females aged 13–18 years in schools, and women aged 18–26 years through their general practitioner.

How will the vaccine affect the screening program?

Pap test screening needs to continue into the foreseeable future, but the program will inevitably change. We anticipate that in Australia over the next few decades cervical cancer will decrease by 80%, vulval cancer by 50%, vaginal cancer by 50%, and genital warts by 90%. Histologically confirmed HSIL will decrease by around 50%, and there will be significantly fewer abnormal Pap test reports. In the meantime, older, unvaccinated women will need to maintain regular Pap tests. The vaccinated cohort, although protected against the HPV types that cause 70–80% of cervical cancer, are still vulnerable to infection with other high risk types and will therefore still need to be monitored. A current topic of discussion is what type of screening test might be most appropriate for these women. The HPV Digene HC11 test is extremely sensitive in its ability to detect viral HPV DNA, but at present lacks positive predictive value for the development of significant cervical lesions in a young population (under 30 years of age) because infection in this age group is so common. However, once the vaccinated cohort reach their 20s, we can anticipate a precipitous fall in the amount of HPV 16 and 18 infection. This means that a positive HPV test in this age group attains significance. One suggested model is that we could commence screening at the age of 25 years with an HPV test. If that test is negative, a repeat test could be performed 3 years later. If positive, the woman could have cervical cytology and be followed up accordingly (*Figure 3*).

Conclusion

Australia is renowned internationally for its successful cervical screening program. Our incidence and mortality rates are, along with Finland, the lowest in the world. The development of national guidelines and the establishment of state registries during the 1990s, along with strict laboratory quality control measures and media and educational assistance from state Cancer Councils, has made Australia a leader in the prevention of this disease.

However, the 21st century has brought exciting developments. The most recent guidelines, acknowledging our increased understanding of the role HPV plays in ano-genital disease, were ratified in 2005 and implemented in July 2006. They have simplified and improved the management of a woman with an abnormal Pap test. Incorporated into these guidelines is the use of testing for HPV DNA of 'high risk' types at the cervix. Professor Ian Fraser, who played a seminal role in the development of the HPV vaccine, was awarded 2006 Australian of the Year.[11] The Australian Government approved the use of Gardasil under the National Immunisation Program to commence in 2007. The future looks promising.

Table 2. Post-treatment of high grade lesions[7]

A woman who has had treatment for HSIL should have a colposcopy and cervical cytology at 4–6 months post-treatment. Cervical cytology and HPV typing should be done at 12 months post-treatment and annually until the woman has tested negative by both tests on two consecutive occasions. When all four tests are negative as indicated below, the woman can then return to the usual 2 yearly screening interval

Time since treatment	Pap test	Colposcopy	HPV typing
4–6 months	✔	✔	
12 months	Negative		Negative
24 months	Negative		Negative

Summary of important points

- The new guidelines have simplified and streamlined the management of an abnormal Pap smear.
- The Pap test screening program will inevitably need to be revised with the advent of the HPV vaccine.
- Women (vaccinated or unvaccinated) should continue to have regular Pap tests. The current screening recommendations are the same for all women irrespective of HPV vaccination status.
- The new vaccines prevent infection with 'high risk' HPV types 16 and 18, but as these types cause only 70–80% cervical cancers, screening will need to continue in some form.

References

1. Garland SM. Human papillomavirus update with a particular focus on cervical disease. Pathology 2000;34:213–24.
2. International Agency for Research on Cancer. Available at www.dep.iarc.fr.
3. Mitchell HS. How much cervical cancer is being prevented? Med J Aust 2003;178:17.
4. Farnsworth A, Mitchell HS. Prevention of cervical cancer. Cancer screening. Med J Aust 2003;178:16.
5. Australian Institute of Health and Welfare. Cervical Screening in Australia 2002–2003. Canberra: AIHW Cat. No. CAN26.
6. Victorian Cervical Cytology Registry. Statistical report 2001, p 15.
7. Screening to Prevent Cervical Cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. National health and Medical Research Council. National Cervical Screening Program, 2005.
8. Government funds Gardasil Media Release, Tony Abbott MHR Minister for Health and Ageing, 29 November, 2006.
9. Heley S. Human papillomavirus: beware the infection you can't see. Aust Fam Physician 2003;32:311–5.
10. National Centre for Immunisation, Research and Surveillance of Vaccine preventable Diseases. Human papillomavirus vaccines for Australians: information for GPs and immunisation providers. NSW: University of Sydney, September 2006.
11. Australian of the Year Wins Grants to Further Develop Cancer Vaccine. NHMRC Ministerial Media Release, 31 May 2006 (ABB075/06).

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