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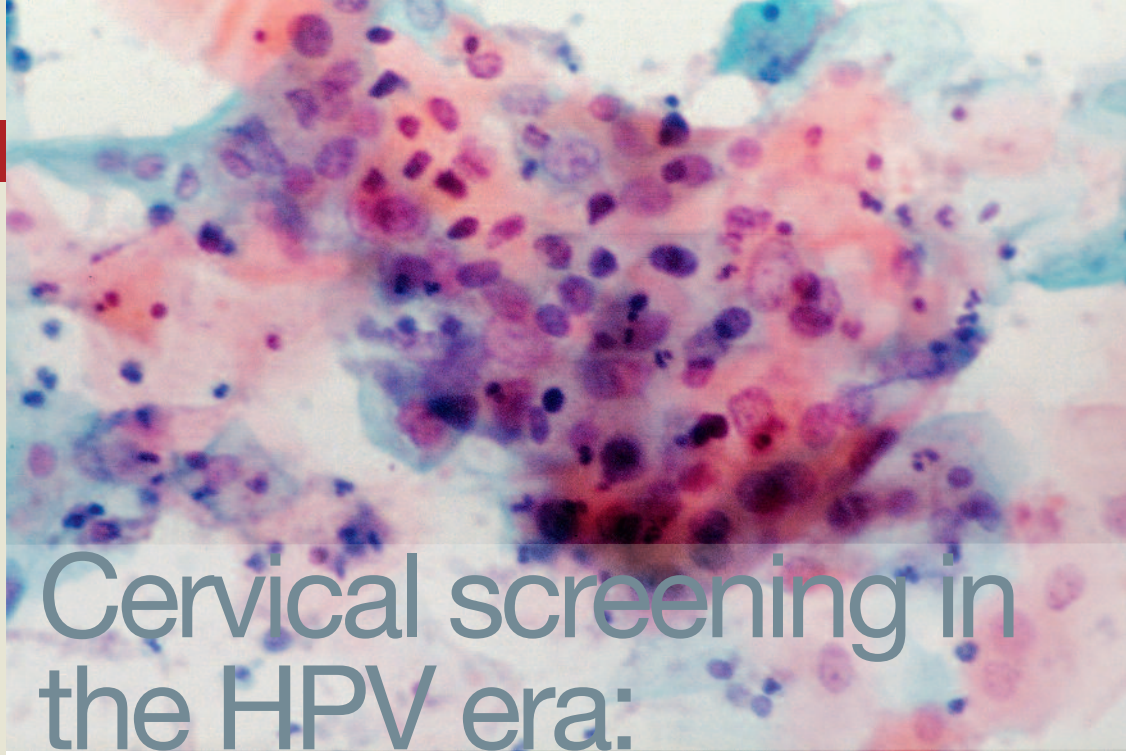

Cervical screening in the HPV era: don't ditch the Pap test!

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Key points

- The Pap test remains the cornerstone for the detection of premalignant HPV-related changes in the cervix, yet almost 40% of women in Australia remain unscreened.
- HPV infection is common, with 80% of women being infected with at least one genital type of HPV in their lifetime.
- Although HPV DNA testing is likely to play an increasingly significant role in cervical screening worldwide, it has no current role in the Australian screening program.
- The development of vaccines to prevent HPV infection has provided a primary prevention tool against cervical and other HPV-related cancers, such as anal and throat cancers.
- It is essential to continue performing Pap tests according to the recommended screening guidelines regardless of a woman's HPV vaccine history.

Despite ever increasing developments in our understanding of the role of the human papillomavirus (HPV) in relation to cervical cancer, the Pap test remains the cornerstone of our successful cervical screening program.

Australia has the second lowest incidence of cervical cancer in the world[1] as a result of the success of the National Cervical Screening Program introduced in 1991. In Australia in 2007, there were 739 new cases and 208 deaths from cervical cancer.[2] In 2007 to 2008, 3,599,919 women aged 20 to 69 years received cervical screening and 26,055 low-grade and 30,301 high-grade lesions were detected.[3]

However, there is certainly no room for complacency! In 2007 to 2008, the two-yearly screening participation rate was only 61.2%[3] and some groups of women remain under- or never-screened. Aboriginal and Torres Strait Islander women have a cervical cancer incidence that has been estimated to be more than double, and mortality rate five times, that of other women in Australia.[4] Other under-screened groups include women from non-English speaking backgrounds, women in rural and remote areas, lesbian and bisexual women and women with disabilities.

Hugely significant developments in our understanding of cervical cancer pathophysiology have occurred in the past decade. We now know that infection with human papillomavirus (HPV) is necessary, although not sufficient, for the development of cervical cancer, with more than 99.7% of cervical cancers testing positive for high-risk HPV DNA.[5] The Pap test detects premalignant cytological changes associated with HPV infection, and despite being used for more than 50 years it remains the cornerstone of the cervical screening program.

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DIFFICULTY LOCATING THE CERVIX?

- Raise the pelvis by placing a rolled towel or pillow under the buttocks to alter the cervical angle.
- Never continue to manipulate an opened speculum within the vagina.
- If it is still not visible then withdraw the speculum and palpate the position of the cervix before reinserting the speculum.
- Manage vaginal wall laxity by using a wider speculum or by placing a condom over the blades (cut off the end first).
- Check that the woman has not had her cervix removed!

WHO SHOULD BE SCREENED AND HOW OFTEN?

Any woman who has ever had sexual intercourse regardless of sexual orientation should be encouraged to have cervical screening. In Australia, the starting age for Pap testing is between 18 and 20 years, or two years after first intercourse, whichever is later. The nationally recommended screening interval for women whose previous Pap tests have never shown an abnormality is two years.

These guidelines have been in place for many years and it is likely that both age of initiation and screening interval for women in Australia will change in the future in line with new knowledge in this field.

Women who have had two normal Pap tests within the past five years can stop cervical screening at the age of 70 years. However, women over 70 years old who have not had recent Pap tests or request ongoing Pap test screening should still be screened.

Screening applies only to asymptomatic women. Women with postcoital or persistent intermenstrual bleeding require a diagnostic Pap test and further investigation irrespective of the result. Conditions such as malignancy and sexually transmissible infections must be excluded. Women with an abnormal looking cervix should be referred for colposcopy irrespective of the Pap test result.

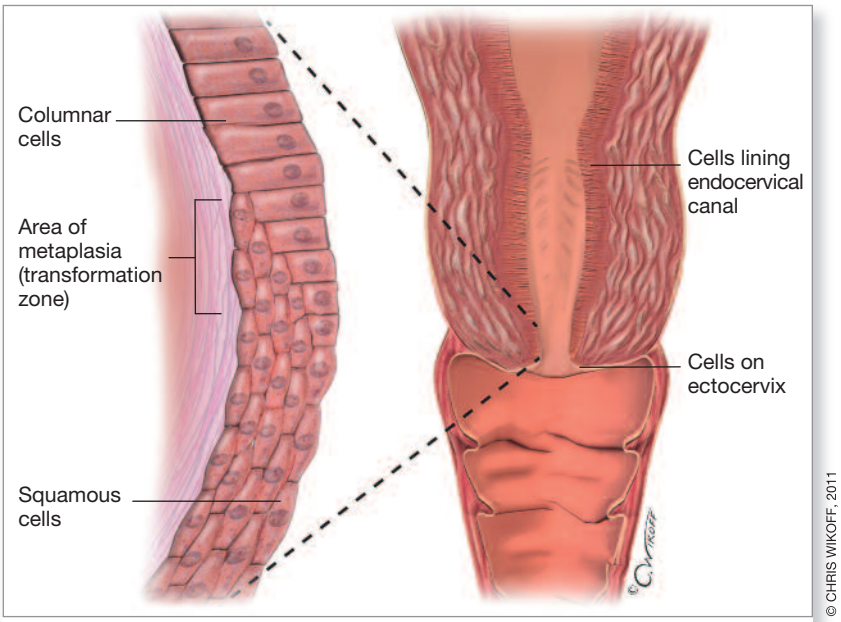


Figure 1. The transformation zone.

OVERVIEW OF THE PAP TEST

The Pap test involves sampling cells from the cervix. Women may feel anxious, fearful or embarrassed about the procedure. Using clear language is important when taking a history prior to the procedure. This will include information about previous tests (if any), as well as direct questions about any intermenstrual or postcoital bleeding. The procedure should be explained and verbal consent obtained before the woman's personal details are forwarded to the state- or territory-based Pap test register. This should be carried out each time a woman has a Pap test and this is an ideal time to recheck her contact details.

The woman should be encouraged to empty her bladder before asking her to undress below the waist. Privacy is essential and she should be able to undress behind a screen or curtain. A gown or cover sheet should be provided for use during the examination.

A bimanual pelvic examination at the time of a screening Pap test may help to locate the cervix if it cannot be visualised at the initial speculum examination (see the box on this page on difficulty locating the cervix).

Routine use of the bimanual pelvic examination in an asymptomatic woman at the

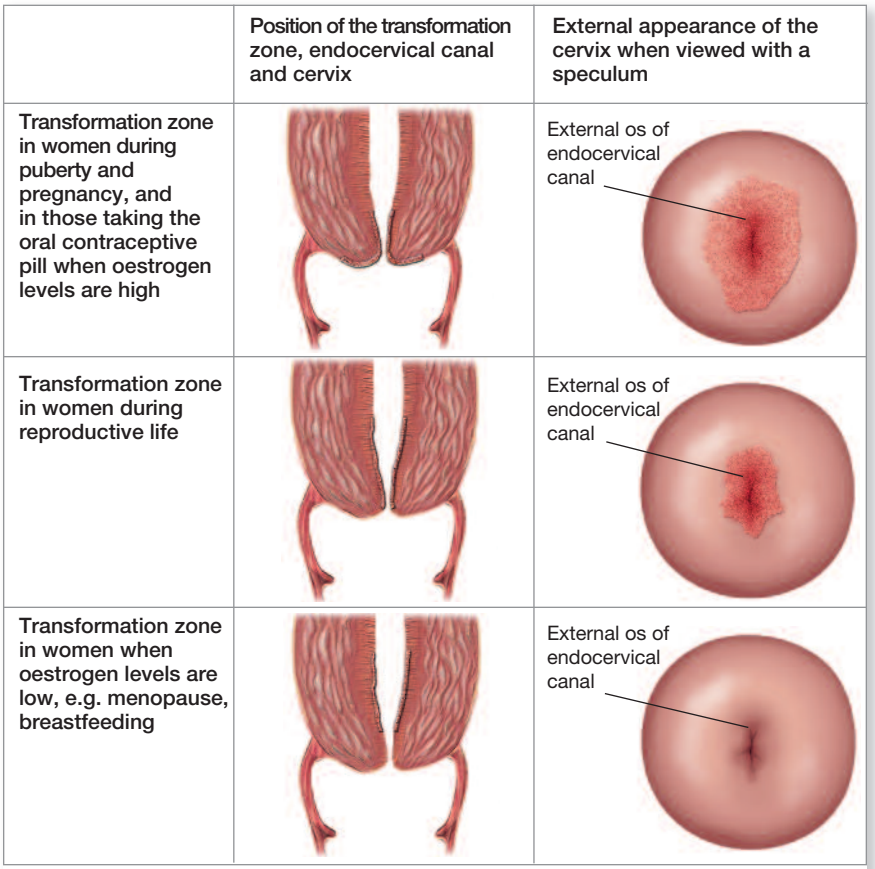


Figure 2. Cross-section diagrams of the transformation zone in women at different reproductive stages.

time of the Pap test is controversial. The bimanual pelvic examination, for example, is not indicated as a screening tool for ovarian cancer[6] and is considered an inaccurate test for detecting pelvic disease, even under ideal conditions.[7,8] That said, it can be argued that on an individual basis, a bimanual pelvic examination can lead to early diagnosis of pathological pelvic disease and that clinicians will only develop appropriate skills by regular practice.[9] Women should always be informed about the limitations of this examination so that they can make a decision about whether or not to have the examination performed.

Hand washing and gloves are essential and equipment should be prepared according to infection control policy guidelines. A good light source for visual inspection of the vulva, vagina and cervix should be ensured.

An appropriate-sized speculum should be chosen, with a small size for women having a first test and a longer, wider speculum for women with poor vaginal tone. Warm water can be used to lubricate a metal speculum, and a small amount of water-based lubricant is appropriate for the disposable plastic type.

Cells should be sampled from the squamocolumnar junction, also called the transformation zone. This lies between the single-layered columnar endocervical epithelium and the multilayered squamous epithelium of the vaginal ectocervix. This is the area most likely to develop squamous cell carcinoma of the cervix (Figure 1).

A healthy cervix is smooth and pink but when high oestrogen levels are present – for example, in young women, those who are pregnant or those using a combined oral contraceptive pill – the redder thinner columnar epithelium moves onto the vaginal portion of the cervix, known as ectopy or ectropion (Figure 2).

In postmenopausal women the transformation zone can retract up into the endocervical canal so the red columnar epithelium is often no longer visible with speculum examination. The transformation zone may be difficult or even impossible to sample but this is not thought to compromise the result.

Nabothian cysts and cervical polyps may also be visible at the cervix and the threads of an intrauterine device may also be seen.

An excellent resource for GPs of colour photographs showing the normal and abnormal cervix can be obtained online from Papscreen Victoria.[10]

WHICH SAMPLING IMPLEMENT TO USE?

There are a variety of sampling instruments for cervical screening (Figure 3), which are outlined below.

- **The cervical sampler broom.** This is generally the preferred implement; it can be used alone if the transformation zone is visible and should be rotated for three to five turns.
- **The endocervical brush (also known as cytobrush).** This is used to collect cells from the endocervix but should not be used as the sole implement; it is used in addition to the cervical sampler broom when the transformation zone is not seen (e.g. in postmenopausal women or if there has been treatment to the cervix); bleeding may occur so it should be used after the cervical sampler broom; it is rotated for a quarter turn and is not advised for use during pregnancy.

- **The combination brush.** This implement combines features of the cervical sampler broom and the endocervical brush; it is rotated for two turns and is not advised for use during pregnancy.

Spatulas are generally not preferred because their rigidity may make them less effective for collecting endocervical cells than the newer implements. If used they should be combined with the endocervical brush to maximise endocervical sampling and rotated for one to two turns. Wooden spatulas should be avoided.

The cellular material is transferred onto a glass slide (labelled in pencil because this is not dissolved by the fixative). The slide is sprayed with fixative within 30 seconds of slide preparation, air dried and placed in a slide case for transfer to the cytopathology service.

Figure 3. Examples of cervical sampling implements.

ROLE OF LIQUID-BASED CYTOLOGY

Liquid-based cytology (LBC) refers to methods of preparing cervical samples for the laboratory. In some countries it is used as an alternative to conventional cytology screening. Currently in Australia it can only be used as an additional test to conventional cytology, with any cells remaining on the sampling implement after preparation of the conventional slide being transferred to the liquid-based collection system. This is known as the 'split sample'.

Use of LBC has been controversial in Australia. Use of LBC technology appears to increase the detection rate of low-grade abnormalities and reduces the number of unsatisfactory smears.[11] However, the picture for high-grade lesions is more complex with two meta-analyses failing to show an advantage over conventional cytology;[12,13] whereas an Australian study using LBC with a computerised imager detected more cases of histological high-grade squamous disease than did conventional cytology.[11] A statement released in May 2011 by the Medical Services Advisory Committee concluded that both manual and automated LBC are safe and at least as effective as conventional Pap tests.[14] However, at present these new technologies are not considered sufficiently cost effective to be supported by public funding.

LBC may be useful if there are blood or inflammatory cells on the conventional slide, possibly obscuring the view of the cytologists analysing it. LBC removes these red blood cells and inflammatory cells and views the cervical cells. LBC

does not attract a Medicare rebate so it is important that women are informed about the cost of this additional test before making a decision to add this test to their conventional smear.

SCREENING IN PARTICULAR GROUPS

Pregnancy

Screening should be offered to all pregnant women if they have not had a Pap test in the previous two years and to any woman with abnormal cytology and/or a history of treatment of a cervical abnormality according to the national guidelines. Pap tests have not been associated with an increased rate of miscarriage and can generally be performed up to 24 weeks' gestation.[15]

Postmenopausal women

Postmenopausal women who are not taking hormone replacement therapy may benefit from a short course of a topical vaginal oestrogen preparation before their Pap test. Local oestrogenisation of the atrophic genital mucosa can improve the quality of the smear and anecdotally may make the examination more comfortable.

An Australian study has shown that a five night course of oestradiol pessaries reduces the chance of an atrophic smear in postmenopausal women.[16] The treatment can be commenced seven days before the appointment and stopped two days before the test to ensure the tablets do not interfere with interpretation of the test.

Women who have sex with women

Any woman who has engaged in HPV-risk sexual practice including genital to genital contact, orogenital contact, fingers or shared sex toy contact should have a regular Pap test.

After hysterectomy

Women who have had a hysterectomy for benign disease, have a normal screening history and whose cervical histopathology showed no neoplastic or premalignant change are at minimal risk of developing vaginal cancer. These women, in the absence of symptoms, do not require further Pap tests.[17]

Women who have had a subtotal hysterectomy in which the cervix has not been removed should continue to have Pap tests at the recommended screening interval.[17]

Women previously treated for pre-invasive or invasive cervical disease should be managed according to the directions of the treating gynaecologist. This may include obtaining vaginal vault smears from the suture line using several sweeping motions with either a cervical sampler broom or spatula. Most women diagnosed with vaginal intraepithelial neoplasia or vaginal cancer have had previous abnormal smears at hysterectomy.

The important message for women is to continue to have their Pap tests at the recommended screening interval regardless of their HPV vaccination history.

Reporting of cervical screening test results follows the Modified Bethesda System.[18] The management of screen-detected abnormalities in asymptomatic women is beyond the scope of this article but can be accessed at the National Health and Medical Research Council website (see: www.nhmrc.gov.au).[18]

NATURAL HISTORY OF HPV INFECTION

Infection with genital HPV is almost always sexually transmitted. Approximately 40 types of HPV affect the genital tract of which 15 are high-risk types associated with 99% of all invasive cervical cancers.[19]

HPV infection is common, with 80% of women infected with at least one genital type of HPV in their lifetime. Rates of infection are highest in young women, peaking soon after the age at which most women become sexually active.[19] First infection with high-risk genital HPV usually occurs between the ages of 15 and 25 years.[18] Low-grade squamous intraepithelial lesions represent an acute HPV infection and most women will clear the virus over about 10 months with no lasting effect.[18] Only a few women will progress to a high-grade squamous intraepithelial lesion with a mean time of 86.4 months.[20] As HPV incidence and prevalence falls quickly with age and is comparatively low over the age of 30 years, older HPV-positive women are more likely to be persistent HPV carriers.

For these reasons, women less than 30 years of age, with a single low-grade lesion of the cervix are offered a repeat Pap test 12 months later to ensure that the virus has been cleared. By contrast, women aged 30 years and older with a low-grade lesion and no history of a negative Pap test in the preceding two or three years should be offered either immediate colposcopy or a repeat Pap test within six months (see the flowchart on page 49).[18]

Persistence of a high-risk HPV infection can result in HPV DNA integrating into the host cell genome of the cervix, interfering with normal cervical cell growth and repair. This can result in a high-grade cervical lesion and a small proportion of these will progress to invasive squamous cell carcinoma.[18] Statistical models have estimated that the average duration between high-grade cervical lesions and cancer is between 10 and 15 years.[18]

HPV DNA TESTING

What is the role of HPV DNA testing?

One of the most commonly used HPV DNA tests detects 13 types of high-risk HPV DNA in cervical specimens. Although HPV DNA testing is likely to play an increasingly significant role in

cervical screening worldwide, it has no current role in the Australian screening program and does not attract a Medicare rebate for this purpose. As there are no current Australian guidelines for the management of HPV DNA testing as an adjunct to cervical cytology screening, performing the test has potential for anxiety and should be avoided.

Well women who have an HPV DNA test outside the recommended guidelines should continue to have regular Pap tests irrespective of the HPV DNA test result.

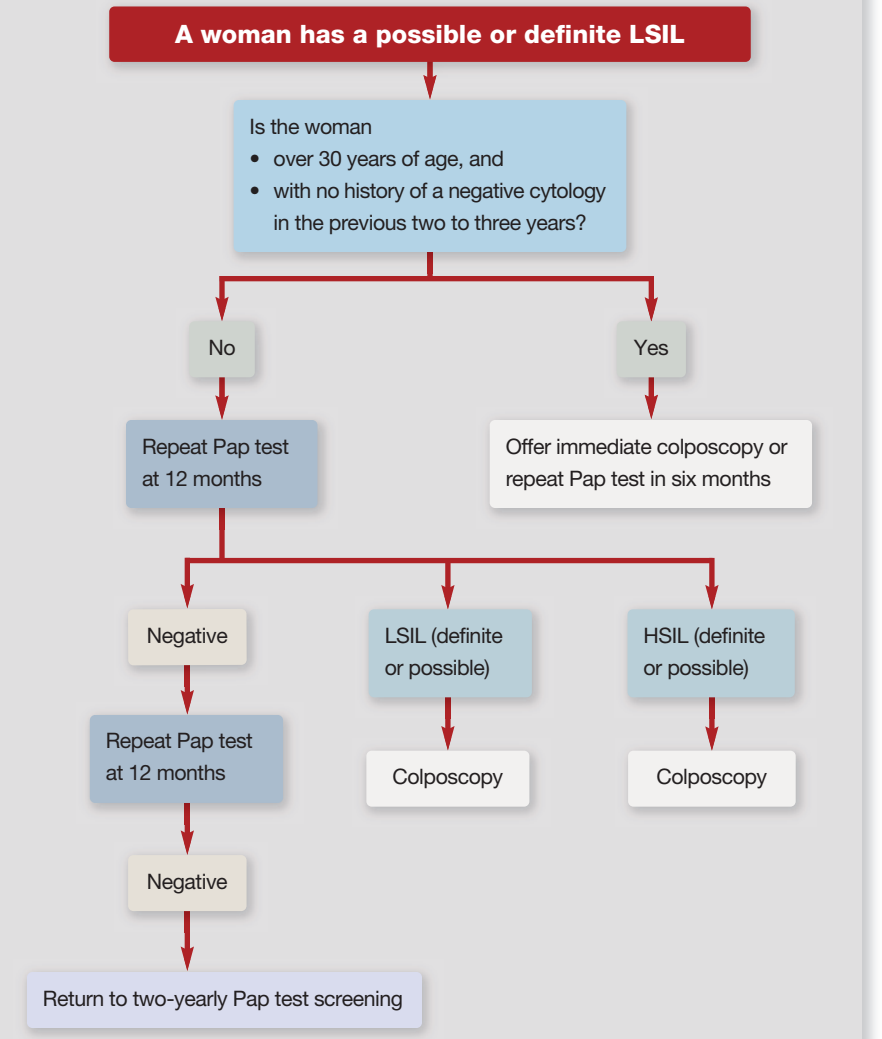
HPV DNA testing does, however, have an important current role in the follow up of women who have been treated for a high-grade cervical abnormality because it is used as a test of clearance of HPV.

HPV DNA testing following treatment for high-grade abnormalities

The role of HPV DNA testing following treatment for high-grade abnormalities is described below.

- The high-risk HPV DNA test is listed on the Medicare Benefits Schedule for monitoring, as a 'test of cure', following treatment for high-grade intraepithelial lesions of the cervix.
- Post-treatment HPV DNA testing is carried out at 12 months and 24 months at the same time as follow-up Pap tests. HPV DNA and Pap testing should be continued annually until both tests are negative on two consecutive occasions. The woman can then return to routine two-yearly Pap test screening.
- A woman previously advised to have annual cytological review for a high-grade lesion treated in the past (prior to use of HPV DNA testing) can now also be offered both cervical cytology and HPV DNA testing as described above. Once she has tested negative on both Pap and HPV DNA testing on two consecutive occasions over 24 months she can also return to routine two-yearly Pap test screening.[18]
- A Medicare rebate will be paid for a maximum of two occasions of HPV DNA testing in a 24-month period for a woman who has had treatment for high-grade changes. No Medicare rebate is currently available for any other HPV DNA testing.

MANAGEMENT FOR POSSIBLE OR DEFINITE LSIL[18]



ABBREVIATIONS: HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

Printed with permission from NHMRC. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities (2005). © Commonwealth of Australia.[18]

HPV DNA testing in the future

HPV DNA tests have a higher sensitivity than that of cervical cytology for detection of high-grade squamous intraepithelial lesions and cervical cancer.[21] HPV DNA testing will almost certainly play an important role in the cervical screening program in the future. The challenge is to work out exactly what role this should be.

RESOURCES ON CERVICAL CANCER IN AUSTRALIA

- **New South Wales**
  www.csp.nsw.gov.au
- **Australian Capital Territory**
  www.health.act.gov.au/c/health?a=sp&pid=1075768380
- **Northern Territory**
  www.health.nt.gov.au/Womens_Health/Well_Womens_Cancer_Screening/index.aspx
- **Queensland**
  www.health.qld.gov.au/cervicalscreening/resources/default.asp
- **South Australia**
  www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Health+information/Health+information+for+the+clinician/Cervical+screening/cervical+screening
- **Tasmania**
  www.dhhs.tas.gov.au/cancerscreening/cervical_screening_register
- **Victoria**
  www.vcs.org.au/women/index.html
- **Western Australia**
  www.health.wa.gov.au/cervical/home

The role of HPV DNA testing is likely to vary with age. It may have a limited role as a screening test in women under the age of 30 years because as many as 25% in this age group will test positive for oncogenic viruses.[22] Most of these younger women will clear the virus naturally so they would be better screened first by cytology, with follow-up HPV DNA testing used to determine which women with definite or possible low-grade squamous intraepithelial lesions require referral for colposcopy.

In women over 30 years of age who have a lower incidence and prevalence of HPV infection, HPV DNA testing could potentially be used as a primary screening test.[23]

HPV DNA testing may allow for the extension of the screening interval beyond the current two years for some groups of women as we know that women with a negative HPV test have a low risk of developing cervical cancer in the five years following the test.[21]

HPV VACCINATION

The development of vaccines to prevent HPV infection has provided a primary prevention tool against cervical and other HPV-related cancers, such as anal and throat cancers. Epidemiological evidence indicates that HPV types 16 and 18 are responsible, for 50% and 20% respectively, of cervical cancers worldwide, and that vaccines targeting these HPV types can be expected to prevent up to 70% of cervical cancers and a significant number of cervical cancer precursors.[24] Vaccination ideally occurs before sexual debut and Australia led the world in 2007 with its free school-based national HPV immunisation program for girls aged 12 to 13 years. There was also a subsidised catch-up HPV vaccination program for women aged 13 to 26 years between 2007 and December 2009.

Currently, the quadrivalent HPV vaccine, which offers protection against HPV types 16, 18, 6 and 11, is licensed for use in women aged 9 to 45 years and males aged 9 to 26 years, whereas the bivalent vaccine protecting against HPV types 16 and 18 is licensed for use in females aged 10 to 45 years. Women outside the school-based program need to pay for their HPV vaccines, which is costly at approximately $450 for the full course of three doses.

At a population level the cost effectiveness of the HPV vaccine in older sexually-experienced women will be lower than HPV-naïve women.[25] Providing advice to older women about the benefits of HPV vaccination needs to include a discussion of possible future exposure to new HPV types.[25]

The exact benefit of the vaccine in an older woman is difficult to assess.[25] It will depend on her past sexual history, the likelihood of new sexual partners in the future as well as the sexual behaviour of her sexual partner(s). Although some women may be deterred by the cost, it is important to still raise the possibility of benefit with unvaccinated women at the time of their Pap test.

CERVICAL SCREENING AFTER HPV VACCINATION

It is essential to continue Pap tests according to the recommended screening guidelines regardless of a woman's HPV vaccine history. This is because HPV vaccination will not protect women against all the possible HPV types that can potentially lead to cervical cancer and will have no effect on HPV 16 and 18 infections that occurred prior to completing the course of HPV vaccinations.

As the incidence of cervical abnormalities decreases over time due to the vaccination program and there is an eventual decline of the positive predictive value of the test, it is possible that the Pap test may be replaced by HPV DNA testing as the primary screening tool. The world will watch Australia with interest as we see the impact of our comprehensive vaccination program on cervical pathology.

CONCLUSION

New knowledge about the role of HPV in the development of cervical cancer has led to the development of the first effective 'cancer vaccine' and Australia leads the way in determining the impact of the vaccine on the natural history of HPV disease. Emerging evidence for the effectiveness, as well as the cost effectiveness, of new cervical screening technologies including LBC and HPV DNA testing will almost certainly lead to changes to the current screening program.

Despite these advances, the Pap test remains the cornerstone for the detection of premalignant HPV-related changes in the cervix, yet almost 40% of women in Australia remain unscreened. Most

women diagnosed with squamous cell cancer of the cervix have either never been screened or have been under-screened.[26] As primary healthcare practitioners, we need to constantly review how we can increase participation of under- or never-screened women in the program. Opportunistically asking women of a screening age the simple question: 'When was your last Pap test?' is a good place to start. Online resources on cervical cancer from different states and territories in Australia are shown in the box on page 50. MT

ACKNOWLEDGEMENT

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FURTHER READING

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