Cervical cancer screening in Australia: Past, present and future
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Australia has had a highly successful cervical screening program for more than 20 years, with a significant reduction in the incidence and mortality from cervical cancer.\(^1\)

The success of the program has been due to an organised approach recognising that each aspect of the cervical screening pathway has to be undertaken at the highest possible standard.\(^2\)

Pap test registers were set up in each state and territory of Australia as a fail-safe mechanism for following-up women with abnormalities, and to help monitor outcomes. They also provide information for laboratory quality assurance and patient management.\(^3\) Pap test registers have been essential to the success of the program.
HPV infection and lower anogenital tract disease

Extensive research has led to major breakthroughs in our understanding of the pathogenesis of this disease. Not only has HPV been shown to be a necessary (but not sufficient) cause for the development of cervical cancer, it is also the causative agent in disease of other areas of the lower anogenital tract in both men and women. There are more than 150 different subtypes of HPV and just over 40 of these have been shown to be oncogenic. They are further divided into low and high risk types for the development of neoplasia.

HPV testing in Australia

The HPV virus cannot be easily cultured and serological (blood) tests are not available. However, reliable HPV tests for high-risk HPV types became available in the late 1990s, using a direct sample from the cervix. The first commercially available test used hybrid capture for direct identification of viral particles. Newer and more specific molecular tests have been subsequently developed.

HPV testing was introduced on the Medicare schedule in 2006 in the NHMRC guidelines for management of screen-detected abnormalities. It is to be used for follow-up of women with histologically proven high-grade squamous abnormalities as part of a test-of-cure regime. A recent study reported a surprisingly low uptake of this management strategy.

HPV testing can be performed at the request of the clinician in any circumstance, but the cost of the test will not be covered by Medicare. There remains a low level of understanding of HPV and HPV testing in the medical community.

Numerous studies have shown that HPV testing has a higher sensitivity for detection of high-grade lesions than conventional cytology. This is at the expense of specificity.

Further, in many of these international studies, the standard of conventional cytology reporting is rarely discussed and is arguably much lower than the very high standards of Australian cytology reporting.

In assessing the efficacy of HPV testing as a primary screen, consideration must be given to the test’s performance in a population-based screening program, which may be different to a test used in a diagnostic setting. The test, obviously, must be reliable.

HPV tests may be inhibited in certain circumstances and concerns have been raised over collection media in some systems.

Internal controls become highly relevant in a population-screening program.

False negatives do occur in HPV testing; just as in cervical cytology and as in cervical cytology, these need to be monitored and minimised.

A large trial comparing primary HPV testing to cytology is underway in Victoria. The so-called Compass trial should answer many of these questions.

Australia’s HPV vaccination program

In 2007, Australia introduced a free HPV vaccine program for schoolgirls and a catch-up program for women up to the age of 26 using the quadrivalent vaccine for HPV types 16, 18, 6 and 11. The HPV
vaccine is now offered to both boys and girls in their first year of high school.

The uptake of the HPV vaccine has been high in Australia, with a three-dose coverage rate of 71% among young women turning 15 years in 2013. The delivery of the vaccine has also been much more evenly distributed than our National Cervical Cancer Screening Program (NCSP), with only a 4.1% difference in rates of full vaccination between young women in high and low socioeconomic groups.

The high coverage achieved to date has already led to significant reductions in the prevalence of vaccine-preventable HPV types in the Australian community. This has occurred in vaccinated and unvaccinated women, suggesting a herd immunity effect.

Further, there have been some reductions in the prevalence of genotypes not targeted by the vaccine but related to vaccine targeted types (31, 33 and 45), suggesting partial cross-protection.

The number of high-grade abnormalities being reported in routine laboratories is now falling. This was initially seen in the youngest cohorts of screened women, but is now seen in older age groups as the vaccinated cohorts move into the screening program.

The need for change

Although Australia’s cervical screening program has been a success, two major factors are driving the need for change: the development of new testing technologies (molecular testing for high-risk HPV and liquid-based cytology) and the success of the vaccination program as described above.

In anticipation of these major changes, Australia has undertaken a major review of its screening program.

In April 2014, the Medical Services Advisory Committee considered the information from the evidence review. They recommended that following:

- A screening program be established based on five-yearly testing with an HPV test (with partial genotyping) and reflex liquid-based cytology triage.
- It is to be offered to HPV-vaccinated and unvaccinated women aged 25-69, with an additional exit test for women aged up to 74.
- The establishment of an invitation and call/recall register system to support the new program.
- Self-collection of an HPV sample, facilitated by a medical or nurse practitioner, be offered to women who are underscreened or never screened.
- This program is purely for screening. If a woman presents with any abnormal signs or symptoms, at any age or at any time she will need to be investigated outside the screening program.

In September 2014 the Australian health ministers endorsed these recommendations. It is now planned that the new program will be rolled out on the 1st May, 2017.

Implementation

The Australian Government has recently started the implementation of this new program.

This is an opportunity to not only introduce new technology, but also to correct recognised deficiencies in the current screening program. One of the main projects will be establishing a National Cancer...
Screening Register, which will cross state and territory boundaries, and will allow all women and doctors access across Australia. The register will be crucial to recruitment strategies, as well as ensuring women present at 25 years of age, and continue to screen. New standards will be set for HPV testing and for cytology. The nature of gynaecological cytology will necessarily change. It will now be a diagnostic test rather than a screening test. The nature of colposcopy will also change. Colposcopy findings will need to be recorded in the register and appropriate standards set. Part of the implementation is also to develop new guidelines for management of screen-detected abnormalities and this process is also underway.

**In the interim**

This period of implementation before the new program starts needs special consideration. Women must continue to screen as normal. It is important to remember that the current screening program is a very good one. Reminders will continue to be sent by the current Pap test registers.

Women may have heard of the impending changes and ask their GP for advice. Questions may be raised as to introducing HPV testing now. HPV testing will not have a Medicare rebate until May 2017, but is available if the patient is willing to pay for it. However, interpretation of results may be difficult and confusing.

New guidelines for management of screen-detected abnormalities are still being developed as part of the implementation process. Laboratories have major changes to face, both in their workforce and testing regimen. Because of the profound impact of these changes on the number of cytologists, ensuring scientists continue to report cervical cytology may be difficult. Laboratories will be under considerable strain in making changes and continuing to provide a high-quality screening service. These changes are significant. The effect of these changes will be far-reaching, and Australia is conscious that the eyes of the world will be watching as this implementation is rolled out.

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CASE STUDY 1

A 22-year-old woman presents to your surgery for the first time, requesting contraceptive advice and asking for a Pap smear. She thinks she had the HPV vaccine at school, but is not sure and can’t remember how many “injections” she had. On further questioning, she does admit to intermenstrual bleeding. On examination she is relatively fit and well.

You decide to take a Pap smear and she is happy to pay for a ThinPrep as well. At the time of taking the Pap smear, you note that there is a moderate degree of contact bleeding and the cervix appears slightly reddened.

The Pap smear report comes back as atypical endocervical cells of uncertain significance with a normal squamous component, and a colposcopy is recommended.

Your surgery recalls the patient. At this next appointment you explain to her the nature of the abnormality and arrange a referral to a gynaecologist.

Six weeks later you receive a letter from the gynaecologist saying that she a colposcopy showed minor abnormalities, but a subsequent large loop excision of the transformation zone (LLETZ) procedure showed the presence of adenocarcinoma in-situ.

The patient returns to you some six months later. She has not returned to the gynaecologist, but requests you to do a follow-up smear to check whether everything is alright.

You take a Pap and ThinPrep at the time. The cervix appears still red and mildly distorted. The Pap smear result comes back as adenocarcinoma in-situ. The patient then returns to the gynaecologist for a LLETZ procedure, which does show residual adenocarcinoma in-situ but with clear excision margins.

A subsequent cytology and HPV test 12 months later are negative.

Comment

In the current screening program there is no question as to this patient, symptomatic or not, being offered a cervical cytology test. Adenocarcinoma in-situ of the cervix is not uncommon and can occur at a young age. It is associated with human papillomavirus infection especially types 16 and 18.

In the new screening program, this patient can also be offered investigation based on both the clinical history of intermenstrual bleeding and also abnormal appearances seen at the time of taking the sample. It will become even more important in the new program to question patients carefully about symptoms or signs, and to record these results on the request form for cervical testing. It will also be important to check the vaccination status of the patient as this may also influence the way the patients are managed at the time.

In the new program, this patient would not have received a request from the cervical screening program.
She has had two cervical biopsies and a LLETZ procedure, however both showed only chronic inflammation.

for screening but every opportunity should be given, as in this case where a patient is requesting contraceptive advice, to check the clinical history and use this as a general sexual health check.

**CASE STUDY 2**

A 32-year-old woman presents seeking help on suspected infertility. She has been married for a year and is keen to have children. You ask her for her previous gynaecological history including Pap smear results. She gives a history of many abnormal Pap smears over the past couple of years with investigations and she thinks some procedures, but says she has been told “everything is alright”. She is otherwise well and asymptomatic.

You decide to do a Pap smear as her last Pap smear was just under two years ago and she is not sure of the result.

The Pap smear comes back as high-grade squamous intraepithelial lesion (HSIL), CIN 3. You contact the Pap Test Register for this woman’s history and learn she has had a number of Pap smears, all showing high grade squamous intraepithelial lesions.

You refer her to a gynaecologist, noting the current abnormal Pap smear, but also alerting the gynaecologist to this history of previous abnormal Pap smears and investigations.

The gynaecologist contacts the laboratory to check on previous results and finds that she has had three Pap smears showing high-grade squamous intraepithelial lesions and an HPV test, which is positive for HPV 16.

She has had two cervical biopsies and a LLETZ procedure, however both showed only chronic inflammation.

The gynaecologist does a thorough colposcopy and
is able to detect a lesion in the vaginal fornix. A biopsy shows high-grade squamous intraepithelial lesion, which is treated with laser therapy.

Comment

This case introduces the important concept of lower anogenital squamous lesions. Increased knowledge shows that HPV can infect not just the cervix, but the vagina, vulva, perineum and anus. In a patient such as this, with a history of mismatched cytology, colposcopy and biopsy results, clinical review is needed.

In this patient in particular, a positive HPV 16 test is also significant in alerting you to the seriousness of these findings, and the importance of locating the lesion. In the new program, a patient such as this will be most likely offered both HPV testing and cervical cytology. The exact details of patient management is still to be determined as part of the renewal program, but this patient was HPV 16 positive, which is a known high-risk infection and she would have been managed with appropriate colposcopy.

Colposcopists are aware that the whole of the lower anogenital tract needs to be examined to find such lesions.

CASE STUDY 3

A 41-year-old woman makes an appointment for her routine Pap smear. She originally had a high-grade lesion diagnosed 15 years ago that was treated with a LLETZ procedure at the time. She has been attending your surgery regularly and following that procedure had annual Pap smears up until 2006.

At that time, the test of cure was introduced and your patient was offered cytology and an HPV test, which were both negative. She then reverted to having two-yearly cytology tests, which have all subsequently been normal.

On this occasion, given the current discussions about HPV testing, you’ve decided to offer her both cytology and an HPV test, and the patient was happy to have this at the time. The HPV test came back as negative but the cytology came back as possible high-grade intraepithelial lesion. The patient was referred for a colposcopy, at which time a biopsy was taken. The biopsy confirmed high-grade squamous intraepithelial lesion. A LLETZ procedure was undertaken, which showed high-grade squamous intraepithelial lesion but with complete removal.

Comment

This case illustrates the importance of understanding that false negatives can occur with HPV testing. False negatives can occur for a number of reasons, ranging from poor sampling to inhibition of the test by blood or mucus. There are many different types of HPV tests and all of these have individual limitations as well. This particular case illustrates the importance of investigating abnormal cytology, even when the HPV test is negative.

In the new program, exact follow-up details are still to be decided, but it is important to remember that just as in any testing procedure, false negatives can occur and patients need to be apprised of these difficulties. Appropriate management will entail checking all test results and clinical history.

References available on request