

FEATURES

HPV: THE GOOD NEWS

IMPROVEMENTS IN SCREENING COMBINED WITH A NEW AUSTRALIAN-DEVELOPED VACCINE COULD ULTIMATELY ELIMINATE THE SECOND MOST COMMON CANCER TO STRIKE WOMEN, WRITES MATT JOHNSON.

PHOTOGRAPHER: EAMON GALLAGHER

In Australia, cervical cancer is the 11th most common cancer in women, with 800 cases being diagnosed annually. In 2001, more than 250 Australian women died of the disease.

Worldwide, cervical cancer ranks second only to breast cancer in frequency among women, but because it strikes at a younger age, it is often considered the most devastating of female malignancies.

Nearly half a million cases were diagnosed around the world in 2000, resulting in 235,000 deaths. Women in the developing world are hardest hit.

In Australia, cervical cancer is the 11th most common cancer in women, with 800 cases being diagnosed annually. In 2001, more than 250 Australian women died of the disease.

Because of the extended pre-malignancy state the cells of the cervix progress through before becoming cancerous, cervical cancer has long been considered preventable, with doctors since the 1920s relying on patients to undergo regular Pap smears.

With cells examined under a microscope to detect changes in their structure and catch the disease before it becomes established, the test has proved indispensable but not infallible: abnormal cells are not always identified, and not all cells deemed abnormal are likely to become cancerous.

It wasn't until the 1970s, when a German researcher proposed a link between a viral infection and cervical cancer, that the opportunity to develop better tests, ultimately a treatment and possibly even a vaccine became conceivable.

The vaccine is soon to be released onto the market, but for Australian women already exposed to the virus, the new generation of tests spawned by the viral link remain contentious, with access to the tests limited and often costly.

Of the more than 100 types of Human Papillomaviruses (HPVs), only a few cause abnormal cell growths on the skin, usually in the form of warts on the hands or feet. A further 30 or so types of HPV can be spread by sexual contact but only a few result in genital warts.

In fact, despite HPV being considered the most common sexually transmitted viral infection, with estimates that up to 75 per cent of people will become infected at some time in their life, it is so rarely symptomatic most people will never know they have the virus.

German researcher Harald Zur Hausen discovered that although HPV infection was common and in most cases regressed spontaneously, some infections persisted over a longer period. Hausen found that if these persistent infections were caused by one of the high-risk types of HPV, a small percentage of infected women would develop precancerous and, ultimately, invasive cervical lesions.

Working with his team, Hausen identified two types of HPV linked to

cervical cancer. His discovery prompted a number of molecular, epidemiological and clinical observational studies that by 1995 had proved conclusive: certain HPV types are carcinogenic to humans.

At the same time as Zur Hausen was researching a casual link between HPV and cervical cancer, researchers in



Dr Sepehr Tabrizi at the Royal Women's Hospital in Melbourne suggests the results of HPV tests need to be interpreted with caution.

Australia were working on a vaccine to help HIV/AIDS patients suffering from the virus. Led by Queensland University's Professor Ian Frazer and his team (see boxed text), Zur Hausen's discovery of a casual link between HPV and cervical cancer further inspired Frazer and his team to create a vaccine for the disease.

Viral sequencing and comparison of viral genomes identified 10 types of HPV that, although found in low-grade lesions including warts, were almost never present in cervical cancer.

These were designated low-risk HPV types. Studies also identified 13 HPV genotypes that, in a stunning causative relationship, were evident in almost 100 per cent of cervical cancers. In fact, just four of these are found in up to 80 per cent of cervical cancers.

Confirmation of the relationship between high-risk HPV and cervical cancer led the World Health Organisation to declare cervical cancer the first cancer to be entirely caused by infection, but with the virus so widespread, relatively contagious and mostly asymptomatic, normal methods of infection control were of limited use.

The infectious nature of the disease did, however, open the possibility of developing a less subjective test than the Pap smear.

Last year Michael Quinn, director of oncology/dysplasia at Melbourne's Royal Women's Hospital and an associate professor in Melbourne University's Department of Obstetrics and Gynaecology, proposed that while the Pap smear remained a useful tool, its false

THE FACTS:

- 75 per cent of people are infected with HPV at some time.
- Cervical cancer is the second most common cancer in women worldwide.
- 100 per cent of cervical cancers contain HPV DNA.

THE CONTROVERSY:

- Testing for HPV is not routinely available
- Testing for HPV is not currently publicly funded.

THE HOPE:

- To improve testing to identify women at risk.
- To vaccinate all women not already exposed to HPV.
- To be the first cancer eradicated.

negative rate of anywhere from 40 to 70 per cent was too high to ignore.

Professor Quinn and other health professionals had looked at results such as those of the 1999/2000 national pap screening program and had come to a similar conclusion. In that period 63 per cent of Australian women aged 20-69 were screened, (this rate should be higher and women are encouraged to have

regular Pat Smears) with about 200,000 low-grade lesions detected, 14,000 high-grade lesions, and 99 cases of micro-invasive cervical cancer.

But during this period 646 cases of invasive cancer and 249 cervical cancer deaths were documented. Over a similar period in Britain 47 per cent of invasive cancers were detected in women who had been adequately screened.

Factors limiting the effectiveness of Pap smears include lack of exfoliation of abnormal cells, insufficient sampling of cells, inadequate preparation of specimens or failure to correctly interpret cellular changes.

Professor Quinn proposed introducing two new screening tests to detect cells that might become pre-cancerous. Monolayer testing (using liquid-based cytology, or LBC) and HPV testing were both rejected in 2002 as standardised screenings in Australia and so are not eligible for Medicare rebates. Professor Quinn, along with many others, is asking if new research on their effectiveness is sufficient for a rethink.

Monolayer testing does not test for HPV and is probably best described as “a technologically improved Pap smear”. Because a Pap smear relies on preparing cells for viewing, increasing the number of cells collected and the quality of their presentation can increase the accuracy of results.

Using liquid-based cytology, the instruments used to collect the cells are rinsed in a liquid that is also sent to the laboratory. The liquid is filtered, removing

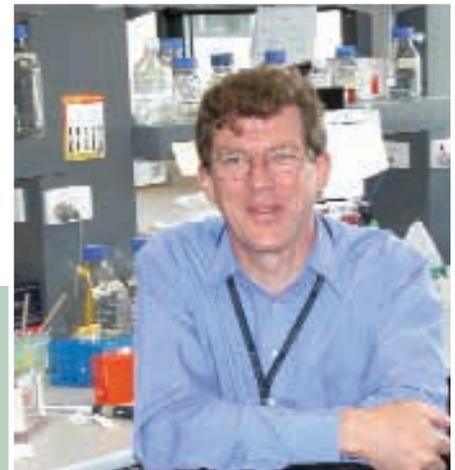
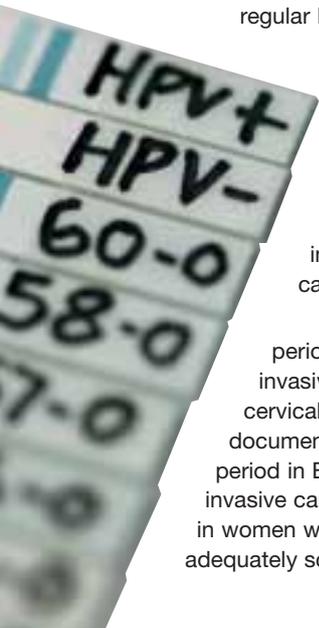
blood, bacteria and other matter, leaving just the cells to be deposited as a single layer onto a slide.

According to studies presented by Professor Quinn, LBC has shown an 84 per cent increase in the pick-up rate of high-grade abnormalities and a 76 per cent reduction in unsatisfactory and borderline smears – results impressive enough for its uniform introduction in Scotland and other parts of Britain.

But it's the correlation between high-risk types of HPV and cervical cancer that has had many asking why public funding has not been approved for HPV testing.

Dr Sepehr Tabrizi is the molecular biologist in charge of molecular testing at the Royal Women's Hospital in Melbourne.

While he agrees that the relationship between high-risk forms of HPV and



Professor Ian Frazer has been working on the preventative HPV vaccine for 20 years.

While the discovery of the link between HPV and cervical cancer has led to debate over what screening tests should be publicly funded and readily available, that same discovery may also, given time, make the argument over testing irrelevant.

Almost 20 years ago in a Brisbane laboratory, two Australian scientists, Dr Jian Zhou and Professor Ian Frazer and Immunopathologist, took the discovery of a viral origin to cervical cancer and started working on a vaccine to prevent HPV infection.

In early 2006 Gardasil, a preventive HPV vaccine, will be released onto the market. About the same time, a second (as yet unnamed) therapeutic vaccine will enter phase one clinical trials in Australia and China.

It is in both human and scientific terms an incredible achievement. More than a quarter of a million women die each year from cervical cancer, but with efficacy rates approaching 100 per cent in phase two trials, Gardasil could effectively end the disease.

The patents developed by Dr Zhou and Professor Frazer have been licensed to pharmaceutical company CSL, which, in conjunction with North American pharmaceutical manufacturer Merck, is about to complete phase three trials in the US and then seek Food and Drug Administration approval.

Once approved, the intent is to distribute the vaccine to all girls in developing countries before they become sexually active.

For Anton Sanker, the business manager for the University of Queensland Centre for Immunology and Cancer Research, where Professor Frazer heads the team that developed the vaccine, the implications are almost overwhelming.

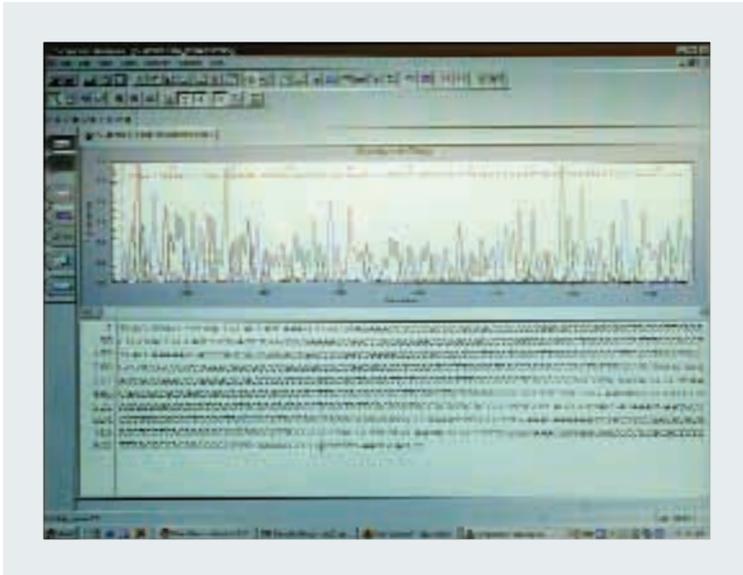
“We plan that every girl in the world aged 12 will receive this vaccine,” he says. “It is potentially the largest vaccination ever, it involves half the world's population. It's the biggest cancer cure of our lifetime.”

Gardasil will be available in Australia next year as a course of three injections over six months, and discussions are

already under way with the Federal Government to include the vaccine on the immunisation schedule for every Australian girl.

Complementing Gardasil will be the trial of the therapeutic vaccine developed by Professor Frazer's team for women already exposed to HPV. Unlike Gardasil, which works like most vaccines and uses a harmless manufactured form of the virus to “trick” the body's immune system into creating antibodies and preventing future infection, the second vaccine treats existing infections.

Professor Frazer and his team say developing this vaccine has proved much more complex, which is why it is only just entering early stage clinical trials, at the Princess Alexandra Hospital in Brisbane and Wenzhou Medical College in China. The Wenzhou College was chosen as a trial site in tribute to Dr Jian Zhou, who died in 1999 and had trained at the college.



cervical cancer is obligatory and now established beyond doubt, the presence of HPV in cervical cells, even high-risk types, does not indicate those cells will definitely become malignant.

“Results of HPV tests need to be interpreted with caution,” warns Dr Tabrizi. “As more than 30 per cent of the population are infected at any one time, the presence of an HPV infection does not reflect the risk of developing cancer.

“Especially for women less than 30, the likelihood is that these infections are transient and will probably not cause abnormalities. Remember, it usually takes over 10 years to develop cervical cancer.”

But Dr Tabrizi is confident HPV testing will eventually be used to identify more-established infections in women over 30, as an adjunct to improve the sensitivity of Pap smears where cell changes are unclear. Whether it will ever be used to screen women over 30 to ensure they are HPV negative is still uncertain.

At present, using the test to screen for changes is only available at the request of a doctor who may be seeking to clarify a borderline lesion, but there is no Medicare rebate. The test is, however, approved as a “test of cure” for women who have undergone treatment for abnormal cells, to ensure they remain clear of HPV and to monitor the effectiveness of treatment and is planned to be on the Medicare schedule later this year.

For Professor Peter Russell, of Mayne Health Laverty Pathology and the Department of Anatomical Pathology at the Royal Prince Alfred Hospital in NSW, the transition from cell-based screening to HPV DNA testing may not be smooth but is inevitable.

Professor Russell and his colleagues recently published a study on one particular form of HPV testing – staining for a marker known as p16INK4a – that seeks to increase the accuracy of separating high-risk and low-risk HPV infections.

Despite promising results, Professor Russell doubts that even the p16INK4a test will influence the short-term debate over the pre-eminence of HPV testing in cervical cancer screening programs.

For him the test is “a very useful adjunct to the existing procedures and should reduce the subjectivity and observer errors inherent in cervical biopsies,” but it should not be considered a replacement for biopsies.

Professor Russell says testing for HPV and the use of p16INK4a are not

revolutionary and, alone, will not replace existing tests. “It’s just a practical approach of good basic research to help pathologists make an accurate diagnosis. The right answer means the right treatment.” 🔥

Pap test results can often be confusing and frightening, with results described in terms that are specific to doctors, but are open to a wide range of interpretation by patients. The current terms include:

Unsatisfactory sample

This means a sample could not be assessed properly. The slide may have broken, there may not have been enough cells, or the pathologist may have noted some minor abnormalities that could have been caused by contamination by blood or mucus.

Atypia/ Non-specific minor changes

The cells examined were not normal, but the changes were very slight and could have been caused by inflammation or an infection such as thrush. There is not normally any need to have a second Pap test.

Mild dysplasia/Cervical Intraepithelial Neoplasia Grade 1 (CIN1)

Two interchangeable terms that refer to minor abnormal cell changes. Women with this finding will be monitored with more frequent Pap tests, and in 60 per cent of cases the changes will resolve without treatment. In the remaining cases the changes may remain static or progress to a higher grade abnormality. Patients’ doctors will discuss with them the options of monitoring the changes or removing the cells.

Higher-grade abnormalities (CIN2 and CIN3)

As the cervical cells become more abnormal, they progress through a series of classes before being described as cancer. Moderate dysplasia/Cervical Intraepithelial Neoplasia Grade 2 (CIN2) and Severe dysplasia/Cervical Intraepithelial Neoplasia grade 3 (CIN3) are the two stages that typically precede cancer of the cervix.

