The renewal of the National Cervical Screening Program

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Australia has a good record in reducing cervical cancer rates — but strategies must change with new knowledge

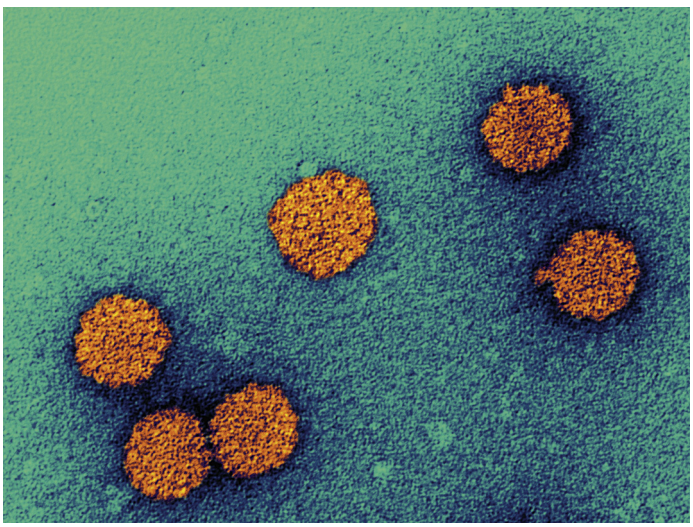
It is an unfortunate fact that cervical cancer remains common and deadly throughout the world. It is estimated that each year 500 000 women develop cervical cancer, and that 250 000 women die of the disease.[1] In Australia, cervical cancer also continues to be deadly, but the numbers of affected women are substantially lower than overseas, primarily as the result of an integrated and coordinated national screening strategy.[2]

Before 1991, Australian women underwent opportunistic screening for cervical cancer, usually annually. From 1991, a national, coordinated approach was implemented, the National Cervical Screening Program (NCSP), which included Pap tests (cervical smears) for women aged 18–70 years every 2 years. This approach has resulted in a significant reduction — nearly 50% — in the incidence of cervical cancer as a direct consequence of the diagnosis and treatment of pre-invasive cervical disease.[3]

Despite this success, the sensitivity and specificity of the Pap test are relatively low, each being estimated at 60–70%.[4] Alternative strategies that either supplement or replace the Pap test have therefore been evaluated, including liquid-based cytology, computer-assisted smear analysis, and testing for the human papillomavirus (HPV).

Persistent infection with a high risk or oncogenic HPV is necessary (although not sufficient) for developing cervical cancer. Almost all women with cervical cancer test positive for HPV DNA, and the cervical cancer risk attributable to HPV is greater than that of smoking for lung cancer.[2] More than 100 HPV genotypes have been identified, of which 40 infect the moist environment of the lower genital tract. Fifteen are regarded as high risk or oncogenic types, and infections with HPV types 16 and 18 account for 70% of invasive cervical cancers.[5] The virus is transmitted by skin-to-skin or mucosa-to-mucosa contact; while the most common mode of transfer is penetrative vaginal intercourse, HPV can also be transmitted to the cervix following infection of the introitus or lower genital tract, and oral and anal sex may also facilitate transmission.[5]

Lower genital tract HPV infection is very common in sexually active young adults. During intercourse, micro-abrasions of the lower genital tract epithelium allow the virus to be deposited onto the basement membrane, from where it is internalised, in a complicated process, by the host keratinocyte. Such infections are largely hidden from the infected person's immune system, and the innate immune system is not activated. Unlike most other infections, there are no constitutional symptoms, local signs or regional adenopathy that signify that an infection has occurred. Amplification and replication of the virus in the maturing keratinocyte leads to a productive infection when the keratinocyte is shed. In a persistent infection, the circular, double-stranded HPV DNA is more likely to be integrated into the host cell genome. During the process of integration, disruption of the E2 open reading frame (ORF) triggers deregulation of the E6 and E7 ORFs. The E6 oncoprotein binds and degrades the p53 protein, and the E7 protein inactivates the retinoblastoma gene; the result is genetic instability, inhibition of apoptosis, and uncontrolled cellular proliferation.[6]



With the advent of recombinant DNA technology, two prophylactic vaccines, one bivalent (against HPV 16 and 18) and the other quadrivalent (for HPV types 6, 11, 16 and 18) became commercially available. In Australia, this allowed the vaccination of young girls (from 2007) and boys (from 2013) under the National HPV Vaccination Program, and has resulted in a dramatic reduction in the incidence of HPV infections.[7] In the United States, the Food and Drug Administration has recently approved a 9-valent vaccine with even broader coverage that may prevent as many as 90% of cervical cancers.[8]

While the NCSP has been very successful, the significant false negative rates associated with the Pap test, our greater understanding of the aetiology and natural history of cervical cancer and its precursors, and the ability to detect HPV in clinical samples has motivated a "renewal" of the NCSP. The Australian Medical Services Advisory Committee has made several recommendations for this renewal,[7] including:

- HPV testing to be performed every 5 years;
- liquid-based cytology triage of HPV-positive patients;
- screening to commence at age 25;
- an exit test for women aged 70–74 years.

Change can sometimes be difficult to accept, but the public and clinicians can be reassured that the data underpinning the

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renewed NCSP are evidence-based, and that the changes (together with widespread HPV vaccination) will further reduce the number of cervical cancers, by at least 15%.[9] An HPV test every 5 years is more effective and as safe as a Pap test every 2 years, but will save more lives and require fewer tests. Raising the age for the first screening test to 25 years and increasing the time interval between screens is already recognised as safe and cost-effective. The approach of the renewed NCSP is further supported by the analysis by Smith and Canfell of the incidence of cervical cancer in Australia during 1982–2010, published in this issue of the *MJA*.[10]

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