

National Cancer Prevention Policy

2007–09



Immunisation

Human papilloma virus

H u m a n p a p i l l o m a v i r u s

Prophylactic vaccination against human papilloma virus (HPV) 16/18 has the potential to prevent up to 70% of cervical cancers. The National Cervical Screening Program has been effective at reducing cervical cancer incidence and mortality, and the vaccine offers the potential to further decrease the incidence of and mortality from this disease.

HPV

Species specific papilloma viruses infect a range of animals including humans. Over 100 different types of HPV have been identified. The majority of HPV types infect only epithelial cells of the skin and mucosa. Most produce no evident disease. Some HPV types have been associated with anogenital and aerodigestive diseases (Baseman & Koutsky 2005). Some produce proliferative lesions (warts) of skin and genital skin, and these tend to be grouped as low and high risk based on their potential to cause malignancy.

There are in excess of 40 anogenital HPV types, about 15 of which are oncogenic (high risk) (Schiffman & Kjaer 2003). Anogenital HPVs are the most common sexually transmitted infections.

Transmission

Genital HPVs are primarily transmitted through sexual contact (genital-genital or genital anal), though this need not include penetrative sexual intercourse. Other modes of transmission, including perinatal, digital, oral and autoinoculation, are less common (IARC 1995). HPV infections are thought to be established in the basal epithelium through abrasion or microtrauma of the superficial epithelium (Lowy & Schiller 2006). In sexually active adults acquisition of HPV is common. Prevalence among sexually active young women is high at around 20% to 25% (Ho et al 1998). Repeated testing of teenagers over a three-year period has documented a cumulative prevalence rate of 44% (95% CI, 40 to 48) (Woodman et al 2001). Infection may be with one or more HPV subtypes and these may change over time (NHMRC 2005).

The link between HPV infection and cancer

HPV infections can induce the development of either benign or malignant lesions. Benign lesions include non-genital and anogenital skin warts, oral and laryngeal papillomas and anogenital mucosal condylomata (Lowy & Schiller 2006). Persistent infection with high-risk HPVs are generally subclinical, but can result in the development of a range of anogenital tumours including cancers of the cervix, anus, penis, vulva and vagina (Lowy & Schiller 2006). It has been estimated that HPV infections are present in over 80% of anal cancers (Frisch et al. 1999, Daling et al. 2004), 40% of penile cancers, 40% of vulval and vaginal cancers, and nearly 100% of cervical cancers (Parkin 2006). An association of HPV infection with squamous cell carcinomas of the head and neck has been established and HPV infection is thought to contribute to 3% and 12% of cancers of the mouth and oro-pharynx respectively (Parkin 2006). The role of HPV infection in the development of

epithelial carcinomas of the bladder, oesophagus and lung is being studied (Persing & Prendergast 1999).

The role of HPV infection in the aetiology of a range of anogenital and other cancers has been demonstrated. However, the HPV vaccines currently available have principally been tested for and aimed at reducing cervical cancer incidence. The following summary will focus on HPV infection and cervical cancer.

HPV and cervical cancer

The association between HPV and cervical cancer was not determined until the 1970s, and it wasn't until the mid-1990s that the primary role of HPV in the development of cervical cancer was definitely confirmed (Eurogin 2003). Research has now distinguished between high-risk (oncogenic) and low-risk (non-oncogenic) types of HPV, and persistent infection with high-risk types of HPV is now recognised to be a necessary precursor to the development of cervical cancer (Nobbenhuis et al. 1999).

Oncogenic and non-oncogenic HPVs cause low-grade squamous intraepithelial lesions (LSIL) of the cervix (Baseman & Koutsky 2005). It was believed that the development of cervical cancer involved progression from low to moderate to high-grade intraepithelial lesions (HSIL). However, natural history studies suggest that low and high-grade cervical lesions are distinct HPV processes (Baseman & Koutsky 2005). LSIL represent the transient appearance of viral infection where the HPV-infected epithelium undergoes differentiation and maturation and displays minor cellular abnormalities (Baseman & Koutsky 2005). Longitudinal studies were conducted in Brazil (Schlecht et al. 2003) and the Netherlands (Nobbenhuis et al. 2001) to examine the natural history of low grade cervical neoplasia. Schlecht et al. (2003) reported that, in the absence of intervention, only a minority of LSIL progressed to HSIL (mean progression time 86.4 months, 95% CI, 81.9 to 90.9), with the majority (78%) of LSIL regressing in less than one year (mean regression time 10.5 months, 95% CI, 8.1 to 12.9). The regression rates reported by the Dutch (Nobbenhuis et al. 2001) were slightly lower, 37.2% (95% CI, 24.8 to 49.6) at 12 months, and 54.9% (95% CI, 41.9 to 67.9) at 24 months, which probably reflects their stricter definition of regression (two negative follow-up Pap tests).

HSIL occurs when HPV infects immature cells and prevents maturation and differentiation, resulting in the replication of immature cells and the accrual of genetic changes that can lead to cervical cancer (Baseman & Koutsky 2005). Cervical screening data shows the incidence of HSIL is 0.7% (VCCR 2005) and is most commonly found amongst women in their twenties, declining rapidly with age (NHMRC 2005). In an unscreened population, it is estimated that between one third and two thirds of women will develop cervical cancer after HSIL, although the time to development of cancer is variable. (Schiffman & Kjaer 2003) The world age standardised incidence rate of cervical cancer is 26.9 per 100,000, peaking at age 54 years (Gustafsson et al. 1997).

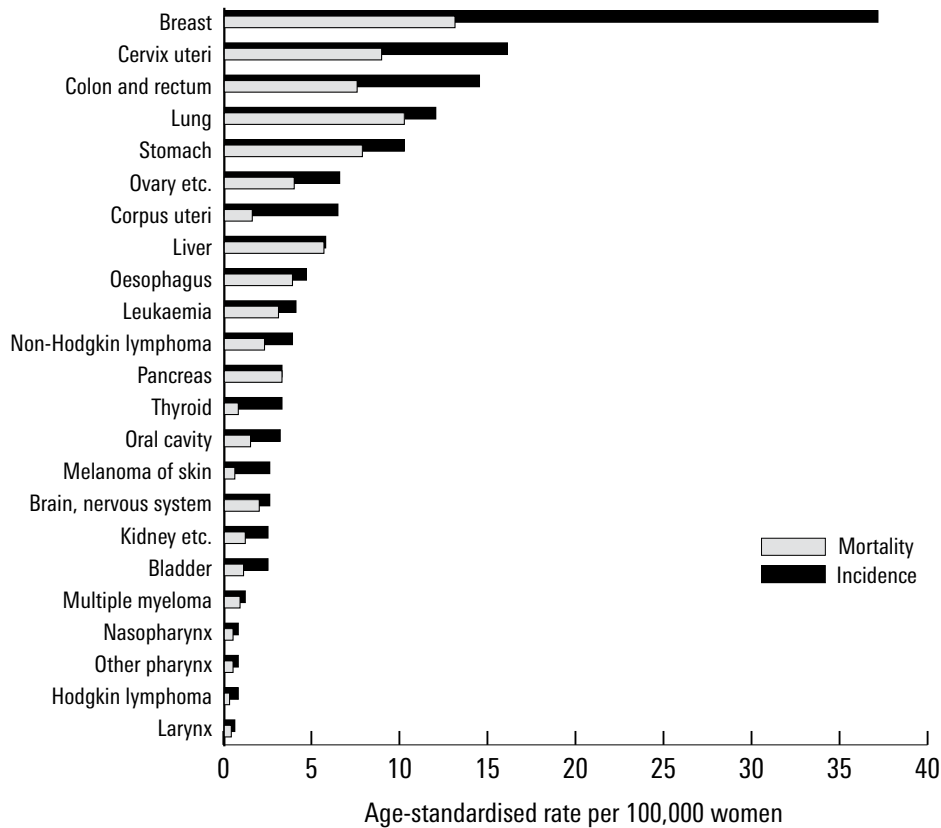
It is estimated that it takes an average of 10 years from HPV infection to malignant progression (Schiffman & Kjaer 2003). The steps involved in HPV-induced cervical carcinogenesis include HPV infection, HPV persistence, progression to precancer and invasion (Schiffman & Kjaer 2003). Most HPV infections are transient and clearance of HPV infection and regression of precancerous changes can occur (Schiffman & Kjaer 2003). The majority of type-specific HPV infection clears within two years (Richardson et al. 2003). The mean time for regression of precancerous changes is longer in women infected with high-risk HPV types (mean duration of regression 13.8 – 17.1 months) compared to low-risk HPV types (mean duration of regression 7.7 – 8.9 months) (Schlecht et al. 2003). Precancerous changes also persist longer and progress faster in women infected with high-risk HPVs (Schlecht et al. 2003), and those with HIV infection (Ferenczy et al. 2003).

The impact

About 70% of invasive cervical cancers are caused by HPV 16 and 18 (Munoz et al. 2003) and about 90% of genital warts are caused by HPV 6 or 11 (Von Krogh 2001).

Cervical cancer is the second most common cancer, and the third most common cause of cancer deaths in women worldwide (Figure 3.1). Eighty per cent of cervical cancer cases occur in the developing world (Jones 1999).

Figure 3.1 Female cancer incidence and mortality worldwide: leading sites of new cancer and cancer death 2002



Source: Ferlay et al. 2004

In 2005 in Australia, there were 610 estimated cases of cervical cancer (AIHW 2006) and there were 212 deaths in 2004 (AIHW 2005), making cervical cancer the 12th most common cause of cancer in women and 16th most common cause of cancer death (AIHW & AACR 2004). Approximately 80% of cervical cancers occur in less developed countries and this is largely attributable to the absence of organised population-based cervical cancer screening programs (Monsonogo et al. 2004). HPV has been identified in 99.7% of cervical cancer specimens (Walboomers et al. 1999). The estimated lifetime risk for women of one or more genital HPV infection is 75%.

Worldwide there are estimated to be 326 million adult women who are infected with HPV. In comparison, there are approximately 450,000 new cases of cervical cancer worldwide each year (Bosch 2000); thus, HPV is considered necessary but not sufficient for the development of cervical cancers.

The challenge

Stigmatisation of cervical cancer as a sexually transmitted disease

HPV is a sexually transmitted infection and most individuals become infected with HPV within two to five years of initiating sexual activity (Wright et al. 2006). Risk factors for HPV transmission include age at first sexual intercourse, age of the woman and her partner, the number of sexual partners and other surrogate indicators for the likelihood that a sexual partner is infected with HPV (Schlecht et al. 2003). Prophylactic vaccines must be administered to individuals prior to virus exposure. This ideally prevents the establishment of the HPV infection by eliminating the virus at the time of, or shortly after, exposure to HPV. This is achieved by stimulating the immune system to produce neutralising antibodies that bind to certain areas of the virus, preventing it from attaching to the host cell (Devaraj, Gillison & Wu 2003).

Parents may be reluctant to involve their young daughters in a vaccination program that is linked to sexual activity. However, cervical cancer should be considered as a rare complication of oncogenic HPV infection rather than as a sexually transmitted disease. Overall, the impact of the HPV vaccines on cervical cancer will be influenced by uptake of the vaccine by the population. In turn, the uptake of the vaccines will be influenced by perceived benefits and risks. Therefore communication strategies with health professionals, parents, women and adolescents which are sensitive to culture, religion and age are required to support uptake of the HPV vaccine.

Encouraging high levels of uptake in the indigenous community

Immunisation should positively impact on under-screened groups and populations with a higher incidence of cervical cancer. In Australia, Aboriginal women are more than four times more likely to die of cervical cancer than other Australian women (AIHW 2006). This difference is in part due to lower participation of this group in the National Cervical Screening Program. Vaccinating Aboriginal girls and women should reduce the incidence and mortality from cervical cancer but this will require better understanding of their barriers to participation. Targeted efforts are required for this at-risk population.

Confusion about the importance of continuing to screen

Confusion about HPV vaccination and cervical screening may lessen compliance with cervical screening in the vaccinated population. The currently available vaccines target only two or four of the 40 HPV types infecting the anogenital tract, therefore effective communication strategies will be required to ensure women still participate in the National Cervical Screening Program.

The duration and scope of protection provided by the vaccine is unknown

Current level 1 evidence supports the delivery of the vaccine to young women who have not yet commenced sexual activity and have therefore not yet been infected with the virus. The level of protection provided to older, sexually active women or boys is under evaluation in clinical trials (Kahn & Burk 2007). As this information becomes available, changes may need to be made to the delivery of the vaccine and the communication strategy.

Effective interventions

National Cervical Screening Program

Between 1991 and 2002 the incidence of cervical cancer almost halved among women aged 20 to 69 (AIHW 2006) and the mortality from cervical cancer in Australia is among the lowest in the world. The decline in incidence and mortality, in part, is attributable to the success of the National Cervical Screening Program (see pages 138 to 144).

Prophylactic vaccine

Prophylactic vaccination against HPV 16/18 has the potential to prevent up to 70% of cervical cancers. While the National Cervical Screening Program has been effective at reducing cervical cancer incidence and mortality, the vaccine offers the potential to further decrease the incidence of and mortality from this disease. Internationally the greatest impact of the vaccine will be in countries without an organised screening program, in conditions of nutrient deficiency and where HIV is endemic (Gravitt & Shah 2005).

Two HPV L1 VLP vaccines have been developed commercially. Cervarix is a bivalent HPV 16/18 vaccine developed by GlaxoSmithKline. The vaccine is given as an intra-muscular injection in a three-step protocol at zero, one and six month intervals (Stanley, Lowy & Frazer 2006). Gardasil, developed by Merck and Co. Inc., is a quadrivalent HPV 16/18/6/11 L1 VLP vaccine delivered by an intra-muscular injection at zero, two and six month intervals (Stanley, Lowy & Frazer 2006).

Early studies have shown the HPV vaccines to be safe and well tolerated (Giles & Garland 2006). Results demonstrate that both vaccines are effective at protecting against persistent cervical HPV 16/18 infection and associated disease (Stanley, Lowy & Frazer 2006). Trials have shown almost universal seroconversion in vaccinated subjects (Giles & Garland 2006) and 100% efficacy for preventing persistent infection. The quadrivalent vaccine was shown to confer additional protection in women against HPV 6/11-induced mucosal and cutaneous genital disease (Stanley, Lowy & Frazer 2006). The vaccines have been shown to be safe and effective in preventing infection with HPV 16 and 18. The duration of protection conferred by the vaccine beyond five years is under evaluation in clinical trials (Kahn & Burk 2007).

In the short term the impact of the HPV vaccines will be a reduction in cervical dysplasia. The long-term impact is a reduction in the incidence and mortality from cervical cancer. Taken together this translates to a reduction in treatment costs as well as psychological and medical morbidity (Lowy & Schiller 2006).

The impact of the vaccine on other anogenital cancers and aero-digestive cancers is not presently known.

The prophylactic vaccine and the development of therapeutic vaccines together with emerging new technologies in screening present the opportunity to progressively reduce HPV-associated malignancy and in doing so significantly decrease the burden of cervical cancer on the community (Roden & Wu 2003).

Therapeutic vaccine

Worldwide it is estimated that there are 100 million women infected with high-risk HPV types, and five million women have persistent infections which may result in anogenital cancers (Giles & Garland 2006).

The goals of a therapeutic vaccine could include: clearing an existing HPV infection, preventing the development and progression of lesions, and eliminating existing lesions and possibly cancers (Devaraj, Gillison & Wu 2003).

When available, the impact of the therapeutic vaccine will include less invasive and disfiguring treatment options for women with pre-existing HPV lesions (Brinkman et al. 2005), potentially lessening the treatment costs and psychosocial impact on women. However such vaccines are at least 10 years from market.

The policy context

In 2006 the Therapeutics Goods Administration approved the quadrivalent HPV vaccine Gardasil for use in women aged nine to 26 and males aged nine to 15 .

Since April 2007, free HPV vaccination in Australia has been provided through school-based programs to girls aged between 12 and 18. From July 2007 until 30 June 2009, the HPV vaccine will be made available through general practitioners and other immunisation providers for females aged 12 to 18 who did not receive the vaccine through the school-based program. Females aged 18 to 26 are eligible to receive the free vaccine, however, the full course of three doses must be completed before the end of June 2009. Under the National HPV Vaccination Program the HPV vaccine is not funded for males and is not available as a PBS product.

In 2007 the TGA approved the bivalent vaccine Cervarix for use in women aged 12 to 45 – this vaccine is not available as part of the free vaccination program and is not available as a PBS product.

Aims

As the prophylactic HPV vaccine is made available in Australia there are a number of public health challenges which need to be addressed.

What needs to be achieved	How The Cancer Council Australia and its members (the state and territory cancer councils) will do this
Maximised uptake of the prophylactic vaccine and effective communication	<p>Promote uptake of the vaccine and compliance with the vaccination schedule among adolescent girls and young women</p> <p>Devise a clear and culturally and age-sensitive communication strategy</p> <p>Communicate information about HPV in a way which meets the information needs of the public and health professionals</p> <p>Provide information in a culturally sensitive manner</p>
Immunisation of populations with higher incidences and poorer outcomes	<p>Focus on strategies to facilitate vaccination among Aboriginal women, who have a higher incidence of and mortality from cervical cancer than the rest of the Australian population, and recent immigrants from high prevalence countries.</p>

What needs to be achieved	How The Cancer Council Australia and its members (the state and territory cancer councils) will do this
Ensure that the National Cervical Screening Program continues to have high participation by relevant women	<p>Communicate clearly about the role of cervical screening in vaccinated women, to limit confusion and prevent reduced compliance with screening</p> <p>Devise approaches to managing different screening schedules, if changes in the frequency of screening are indicated for vaccinated women</p>
Monitor and evaluate the program	<p>Set up data processes to capture and monitor vaccination data</p> <p>Match vaccination data with screening program data and state cancer registries</p>
Research on therapeutic vaccine	Advocate for continued research on the application and effect of therapeutic vaccines on regression of lesions and cancers. Studies on the acceptability of a vaccine as treatment also need to be undertaken
Further research	<p>Advocate for further research in:</p> <ul style="list-style-type: none"> • vaccine efficacy and booster requirements • two versus three doses • epidemiology and vaccination of boys – issue of herd immunity • infant vaccination efficacy • adult vaccination efficacy • uptake and acceptability of the vaccine in non-English speaking communities • barriers to screening • most effective way of screening for cervical cancer in a vaccinated population • genotype replacement over time

References

Australian Institute of Health and Welfare (AIHW) 2006. *Cervical screening in Australia 2003–2004*. AIHW cat. no. 28; Cancer Series no. 33. Canberra: AIHW.

— — — 2005. Cancer: cervical screening. At www.aihw.gov.au/cancer/screening/cervical/cervical.cfm viewed 5 September 2007.

Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2004. *Cancer in Australia 2001*. AIHW cat. no. 23; AIHW Cancer Series no. 28. Canberra: AIHW.

Baseman JG & Koutsky LA 2005. The epidemiology of human papillomavirus infections. *J Clin Virol* 32 (1 Suppl): S16–24.

Bosch F 2000. Clinical cancer and HPV: a worldwide perspective. In *Proceedings of the Fourth International Multidisciplinary Congress: Eurogin 2000*. Bologna, Italy.

- Brinkman JA, Caffrey AS, Muderspach LI, Roman LD & Kast WM 2005. The impact of anti HPV vaccination on cervical cancer incidence and HPV induced cervical lesions: consequences for clinical management. *Eur J Gynaecol Oncol* 26(2): 129–42.
- Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, Carter JJ, Porter PL, Galloway DA & McDougall JK 2004. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 101(2): 270-280.
- Devaraj K, Gillison ML & Wu TC 2003. Development of HPV vaccines for HPV-associated head and neck squamous cell carcinoma. *Crit Rev Oral Biol Med* 14(5): 345–62.
- Eurogin 2003. *Conclusions: cervical cancer control, priorities and new directions. International charter.* 1–22.
- Ferenczy A, Coutlee F, Franco E & Hankins C 2003. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. *CMAJ* 169(5): 431-434.
- Ferlay J, Bray F, Pisani P & Parkin P 2004. Globocan 2002. Cancer incidence, mortality and prevalence worldwide. [IARC CancerBase No. 5, version 2.0]. Lyon, IARC Press.
- Frazer IH 2004. Prevention of cervical cancer through papillomavirus vaccination. *Nat Rev Immunol* 4(1): 46–54.
- Frisch M, Fenger C, van den Brule AJ, Sorensen P, Meijer CJ, Walboomers JM, Adami HO, Melbye M & Glimelius B 1999. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. *Cancer Res* 59(3): 753-757.
- Garcia-Hernandez E, Gonzalez-Sanchez JL, Andrade-Manzano A, Contreras ML, Padilla S, Guzman CC, Jimenez R, Reyes L, Morosoli G, Verde ML & Rosales R 2006. Regression of papilloma high-grade lesions (CIN 2 and CIN 3) is stimulated by therapeutic vaccination with MVA E2 recombinant vaccine. *Cancer Gene Ther* 13(6): 592–7.
- Giles M & Garland S 2006. Human papillomavirus infection: an old disease, a new vaccine. *Aust N Z J Obstet Gynaecol* 46(3): 180–5.
- Gravitt PE & Shah KV 2005. A virus-based vaccine may prevent cervical cancer. *Curr Infect Dis Rep* 7(2): 125–31.
- Gustafsson L, Ponten J, Bergstrom R & Adami HO 1997. International incidence rates of invasive cervical cancer before cytological screening. *Int J Cancer* 71(2): 159-165.
- Ho GY, Bierman R, Beardsley L, Chang CJ and Burk RD 1998. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 338(7):423–428.
- International Agency for Research on Cancer (IARC) 1995. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 64. Human papillomaviruses: summary of data reported and evaluation. Lyon, France: IARC.
- Jones SB 1999. Cancer in the developing world: a call to action. *BMJ* 319: 505–8.
- Kahn JA & Burk RD 30-6-2007. Papillomavirus vaccines in perspective. *Lancet* 369(9580): 2135-2137.
- Lowy DR & Schiller JT 2006. Prophylactic human papillomavirus vaccines. *J Clin Invest* 116(5): 1167–73.

- Mahdavi A & Monk BJ 2005. Vaccines against human papillomavirus and cervical cancer: promises and challenges. *Oncologist* 10(7): 528–38.
- Monsonego J, Bosch FX, Coursaget P, Cox JT, Franco E, Frazer I, Sankaranarayanan R, Schiller J, Singer A, Wright TC Jr, Kinney W, Meijer CJ, Linder J, McGoogan E, Meijer C 2004. Cervical cancer control, priorities and new directions. *Int J Cancer* 108(3): 329–333.
- Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ & Meijer CJ 2003. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348(6): 518–527.
- National Health and Medical Research Council 2005. *Screening to prevent cervical cancer: guidelines for management of asymptomatic women with screen detected abnormalities*. Canberra: NHMRC.
- Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Bezemer PD, Verheijen RH & Meijer CJ 2001. Cytological regression and clearance of high-risk human papillomavirus in women with an abnormal cervical smear. *Lancet* 358(9295): 1782–1783.
- Nobbenhuis MA, Walboomers JM, Helmerhorst TJ, Rozendaal L, Remmink AJ, Risse EK, van der Linden HC, Voorhorst FJ, Kenemans P & Meijer 1999. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 354(9172): 20–5.
- Parkin DM 2006. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118(12): 3030–44.
- Persing DH & Prendergast FG 1999. Infection, immunity, and cancer. *Arch Pathol Lab Med* 123(11): 1015–22.
- Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, Coutlee F & Franco EL 2003. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev* 12(6): 485–90.
- Roden R & Wu TC 2003. Preventative and therapeutic vaccines for cervical cancer. *Expert Rev Vaccines* 2(4): 495–516.
- Rous P & Kidd JG 1938. The carcinogenic effect of a papilloma virus on the tarred skin of rabbits: description of the phenomenon. *J Exp Med* 67: 399–428.
- Schiffman M & Kjaer SK 2003. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr* (31): 14–19.
- Schlecht NF, Platt RW, Duarte-Franco E, Costa MC, Sobrinho JP, Prado JC, Ferenczy A, Rohan TE, Villa LL & Franco EL 2003. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst* 95(17): 1336–43.
- Shope R & Weston Husrt E 1933. Infectious papillomatosis of rabbits. *J Exp Med* 58: 607–24.
- Stanley M, Lowy DR & Frazer I 2006. Chapter 12: Prophylactic HPV vaccines: underlying mechanisms. *Vaccine* 24 (3 Suppl): S106–13.
- Von Krogh G 2001. Management of anogenital warts (condylomata acuminata). *Eur J Dermatol* 11(6): 598–604

Victorian Cervical Cytology Registry 2006. *Statistical report 2005*. Melbourne: Victorian Cervical Cytology Registry.

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJF, Peto J, Meijer CJLM & Munoz N 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12–19.

Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, Yates M, Rollason TP & Young LS 2001. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 357(9271):1831–1836.

Wright TC, Bosch FX, Franco EL, Cuzick J, Schiller JT, Garnett GP & Meheus A 2006. HPV vaccines and screening in the prevention of cervical cancer; conclusions from a 2006 workshop of international experts. *Vaccine* 24 (3 Suppl): S51–61.