Cervical cancer prevention in the HPV era

As understanding of the role of HPV in the development of cervical cancer increases, we are entering a new era in disease prevention.

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Cervical cancer screening with the Pap test has been the most successful cancer prevention strategy in medical history. Since organised screening in Australia began, the incidence and attributable mortality have been halved.[1] Australia now has the lowest mortality and the second lowest incidence of cervical cancer in the developed world.[1]

Following recognition of the fact that infection with a high risk human papilloma virus (HPV) is necessary for the development of cervical cancer, the field of disease prevention has evolved rapidly. GPs need to be aware of two major changes, both of which recognise the pivotal role of HPV in cervical cancer:

- the updated NHMRC management guidelines, *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities* (2005)[1]
- the introduction of the first cancer prevention vaccine for clinical use.

Natural history of HPV infection and cervical neoplasia

The causal role of HPV in all cancers of the cervix has been firmly established biologically and epidemiologically.[2] There are more than 100 types of HPV and at least 40 types are identified as being related to genital tract infections. These are divided into:

- low risk types (such as HPV types 6 and 11), which are associated with genital warts and almost never found in cancers
- high risk (oncogenic) types (such as HPV types 16, 18, 31 and 45).

The high risk HPV types are found in varying proportions around the world, but types 16 and 18 are associated with more than 70% of cancers in all regions.

Infection with high risk HPV is almost always sexually transmitted. Natural history studies of young women have indicated that after sexual

IN SUMMARY

- **The causal role of HPV in all cancers of the cervix has been firmly established. However, although infection with HPV is very common, cervical cancer is a rare outcome from HPV infection.**
- **Most HPV infections clear spontaneously. Persistent infection with a high risk type is necessary to establish malignant transformation of the cervix.**
- **Clinical trials of Gardasil – the HPV vaccine now licensed for clinical use in Australia – have shown it to be highly effective at preventing infection with two high risk types of HPV and at preventing the precursor cervical lesions associated with persistent HPV infection.**
- **The development of clinical management protocols matched to the natural history of cervical cancer and the availability of a vaccine are key features in a new era of disease prevention.**
- **Women treated for high grade lesions of the cervix are at increased risk of further high grade disease and cancer. HPV testing is now incorporated into the follow up of such women.**
- **Women with clinical symptoms of cervical cancer should be referred for investigation regardless of their Pap test result.**

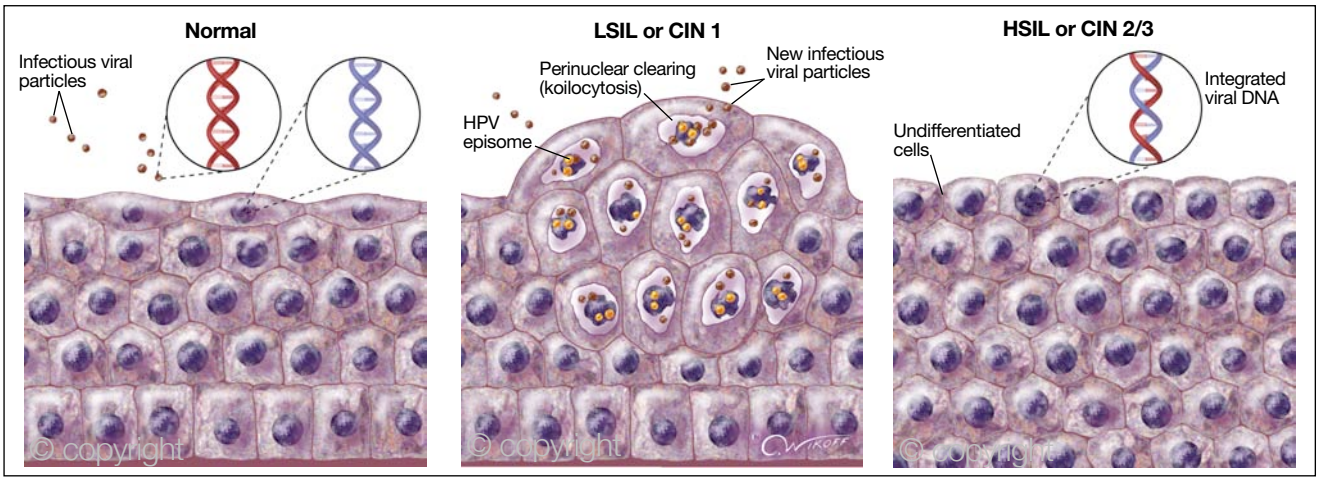


Figure 1. Changes in cervical squamous epithelium associated with HPV infection. a (left). Normal cervical squamous epithelium. b (centre). Low grade squamous epithelial lesion (LSIL). When HPV infection occurs, the virus exists in the cell as a circular episome that can replicate to form new infectious virus particles. Perinuclear clearing (koilocytosis) indicates this stage of infection. c (right). High grade squamous epithelial lesion (HSIL). In some cases, viral DNA transforms host DNA. The episome breaks into a linear strand before integration into the host DNA. As well as loss of genes needed to form a complete virus, the break disrupts a regulatory region that controls viral induced cell proliferation, leading to excessive undifferentiated cell growth and neoplasm formation.

Adapted from: Goodman A, Wilbur D. N Engl J Med 2003; 349: 1555-1564.

intercourse with a partner who has a productive anogenital HPV infection, the probability of transmission is greater than 50%.[3] Detailed detection methods have shown that the peak incidence of genital HPV infection occurs within the first five years after commencing sexual activity, and the cumulative prevalence is approximately 60% in men and women over this period. The median duration of infection is usually more than eight months. Most HPV infections clear spontaneously.

HPV particles, which contain double stranded DNA, are adapted to their natural host tissue (epithelial cells of skin or mucosa). The virus enters the body through microabrasions of the anogenital skin and replicates within the nucleus of basal epithelial cells. Large numbers of virions are manufactured, and cells with this acute infection demonstrate the characteristic morphological changes identified as low grade squamous intraepithelial abnormalities or koilocytic atypia. Desquamation of mature epithelial cells releases into the genital tract large numbers of infective virions that can then be transmitted to a new sexual partner.

Women who have persistent infection with an oncogenic HPV are at risk of developing a high grade abnormality. The protein products of two viral genes bind to proteins that have tumour suppressor functions, thus preventing the usual arrest of cell division. During uncontrolled cellular proliferation, an infected cell acquires the cytological appearance of a high grade squamous lesion. Exposure to further carcinogens increases the risk of acquiring additional genetic errors and developing a fully malignant genotype that may potentially lead to invasive cervical cancer. The spectrum of changes in cervical squamous epithelium associated with HPV infection are shown in Figure 1.

Cytological sampling of the cervix produces characteristic appearances for the four clinical states that may manifest:

- normal (uninfected) state
- acute viral infection or low grade changes
- high grade intraepithelial lesions
- frankly invasive cancer.

A Pap smear taken from an individual woman will show the features of a particular state, and this should be reflected in management. Examples of Pap smear cytology are shown in Figures 2 to 5. The period for progression from the normal state to cervical cancer is at least 10 years, and it is recognised that both high and low grade precursor lesions may regress.

New terminology

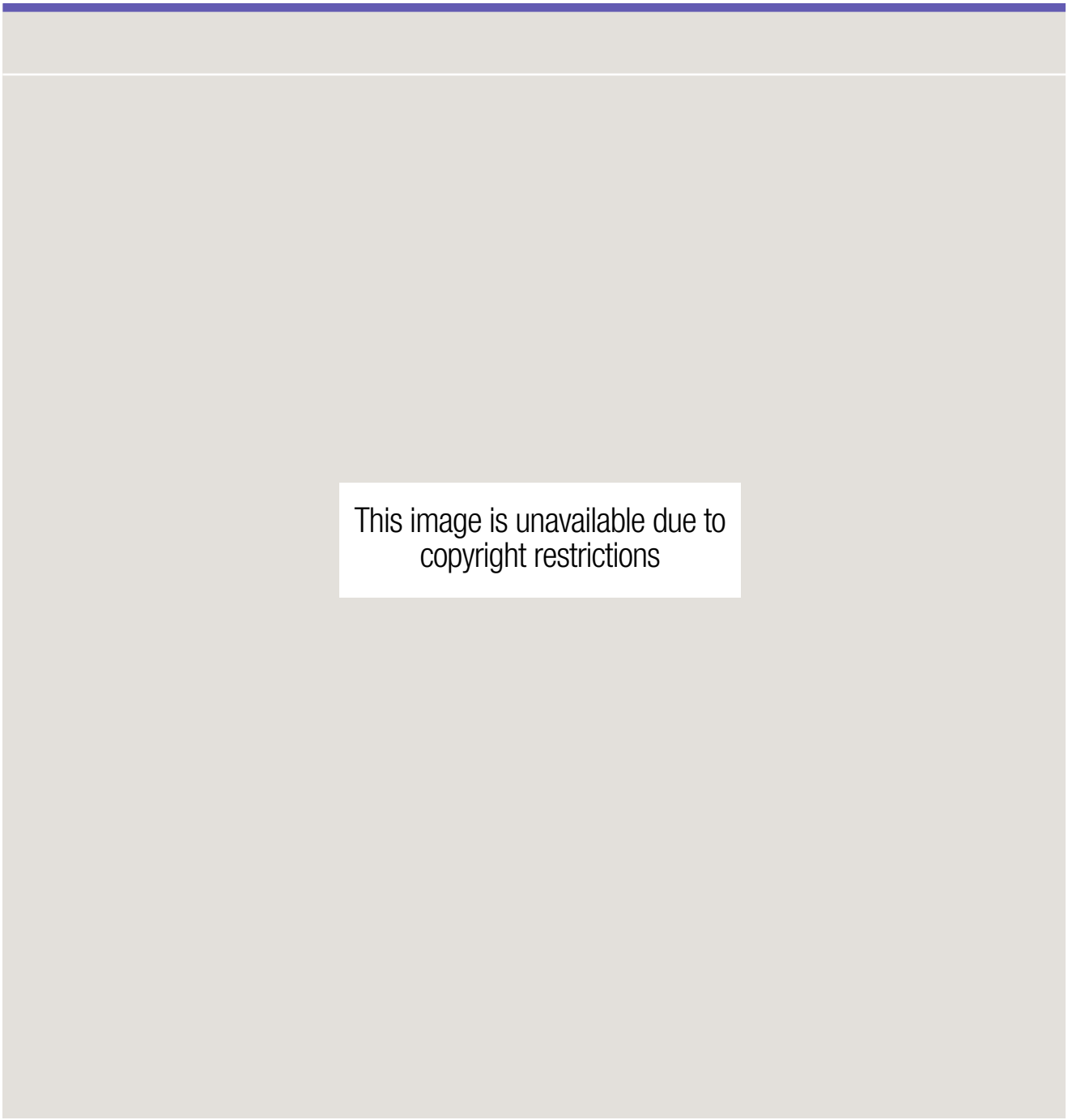
The previously mentioned 2005 NHMRC *Guidelines*[1] introduce terminology known as the Australian Modified Bethesda System (AMBS 2004) that should be applied to cytological abnormalities noted on Pap smears. It represents a change from previous Australian NHMRC-endorsed terminology, introduced in 1994, which contained a number of clinically irrelevant distinctions with poor reproducibility. The Table presents a comparison of the AMBS 2004 terminology with the previous Australian terminology and the Bethesda System 2001 terminology (on which the new Australian terminology is based).

The AMBS 2004 terminology for cytological squamous abnormalities reflects the different phases of HPV infection of the cervix. The low grade squamous intraepithelial lesion (LSIL) is the morphological correlate of productive viral infection and incorporates the previous designations of HPV effect and CIN 1. When the cell changes are thought to represent an underlying LSIL but are not thought to be sufficiently obvious to justify a 'definite' diagnosis, the term 'possible LSIL' is applied. When the characteristic changes of a true preneoplastic lesion are seen, reflecting integrated HPV, the lesion is described as a high grade squamous intraepithelial lesion (HSIL). This category encompasses the cell changes previously described

as CIN 2 and CIN 3. When the changes are insufficient to justify a confident diagnosis, the term 'possible HSIL' is applied.

The morphological changes observed in glandular cells encompass a broad spectrum and do not so easily reflect the cytological changes seen in squamous cells infected with HPV. Consequently, various descriptive categories are applied with the new terminology, which depend on the degree of cytological abnormality and confidence regarding the underlying lesion.

It is important to note that the AMBS 2004 terminology described here relates only to cervical cytology. Terminology for reporting histological specimens remains



unchanged, and thus cervical biopsies will be described as showing changes consistent with a firm diagnosis of the relevant grade of CIN.

Management

Low grade squamous lesions

HPV infections of the cervix are common and usually self-limited in nature. Consequently, low grade cytological abnormalities are frequently reported. It is estimated that approximately 100,000 Australian women receive a report of a low grade abnormality on a Pap test in a year, most of which reflect acute HPV infection.[4] Management must reflect the fact that most of these abnormalities are benign and self-limited, but it must also maintain and incorporate the capacity to detect those that demonstrate persistent viral infection with genuine neoplastic potential.

As part of the review of the *Guidelines*, the outcomes of all women with low grade cytological abnormalities detected in 1999 (n=90,566) were assessed after 24 months by the results reported to the various Australian Pap test registries.[4] The most common subsequent outcome was either a normal Pap test or a further low grade smear; however, 41 women developed cervical cancer during the two-year period, and 10 of these had microinvasive cervical cancer. Although the Pap test registers do not record symptoms, it is likely that some of these women with cancer were symptomatic, and it is emphasised that the recommended management outlined in the *Guidelines* should be applied strictly to asymptomatic women. Women with clinical symptoms of cervical cancer should be referred for investigation regardless of their Pap test result.

The recommended management of a woman with a screen detected low grade squamous abnormality is summarised in

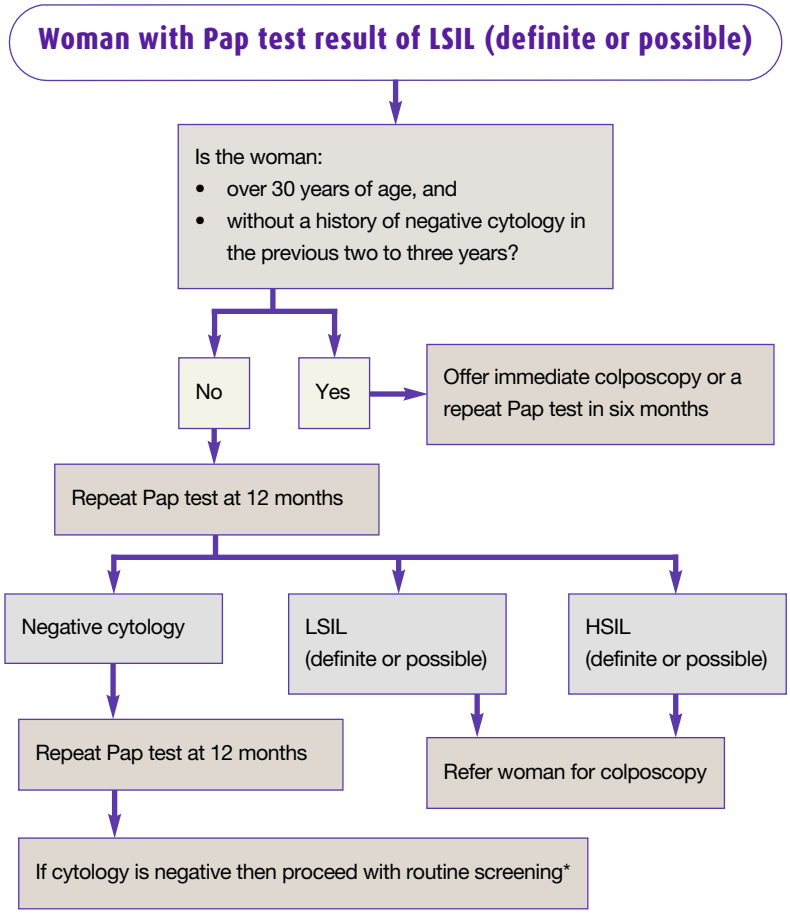
Table. Pap smear reporting: a comparison of the AMBS 2004 terminology with other terminologies

AMBS 2004*†	Australian NHMRC-endorsed terminology 1994	The Bethesda System 2001	Incorporates
Squamous abnormalities			
Possible low grade squamous intraepithelial lesion	Low grade epithelial abnormality	Atypical squamous cells, undetermined significance	Nonspecific minor squamous cell changes; changes that suggest, but fall short of, HPV/CIN 1
Low grade squamous intraepithelial lesion	Low grade epithelial abnormality	Low grade squamous intraepithelial lesion	HPV effect, CIN 1
Possible high grade squamous lesion	Inconclusive, possible high grade squamous abnormality	Atypical squamous cells, possible high grade lesion	Changes that suggest, but fall short of, CIN 2, CIN 3 or squamous cell carcinoma
High grade squamous intraepithelial lesion	High grade epithelial abnormality	High grade squamous intraepithelial lesion	CIN 2, CIN 3
Squamous cell carcinoma	High grade epithelial abnormality	Squamous cell carcinoma	Squamous cell carcinoma
Glandular abnormalities			
Atypical endocervical cells of undetermined significance	Low grade epithelial abnormality	Atypical endocervical cells, undetermined significance	Nonspecific minor cell changes in endocervical cells
Atypical glandular cells of undetermined significance	Low grade epithelial abnormality	Atypical glandular cells, undetermined significance	Nonspecific minor cell changes in glandular cells
Possible high grade glandular lesion	Inconclusive, possible high grade glandular abnormality	Atypical endocervical cells, possibly neoplastic	Changes that suggest, but fall short of, adenocarcinoma *in situ* or adenocarcinoma
Endocervical adenocarcinoma *in situ*	High grade epithelial abnormality	Endocervical adenocarcinoma *in situ*	Adenocarcinoma *in situ*
Adenocarcinoma	High grade epithelial abnormality	Adenocarcinoma	Adenocarcinoma

Reproduced from: NHMRC's *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities* (2005).
 * AMBS 2004 = Australian Modified Bethesda System 2004. † Terminology introduced in the 2005 *Guidelines*.

continued

Managing cytological prediction of possible or definite LSIL



* See Section 6.7 of the *Guidelines* (reference 1) for information about fluctuating abnormalities.
Abbreviations: LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion.
Reproduced from: NHMRC's *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities* (2005). © Commonwealth of Australia, reproduced by permission.

the flowchart above. After a smear report of a definite or possible LSIL, a woman should be offered a repeat smear in 12 months. An exception to this recommendation relates to the woman over 30 years of age with no history of negative smears in the preceding two to three years – in the absence of a good screening history, she is potentially demonstrating evidence of HPV infection that may have been present for a longer period and she should be offered either an immediate colposcopy or an earlier repeat smear, within six months, depending on the clinical circumstances.

Subsequent management will depend on the results of the 12-month test and is included in the flowchart. Under the updated *Guidelines* (unlike the previous version), if the final histological diagnosis is a low grade squamous lesion then it is strongly recommended that an observational approach be undertaken and no treatment instituted. This avoids the side effects associated with unnecessary treatment.[5]

The *Guidelines* do not support the use of HPV testing as part of the triage of low grade lesions because there is insufficient evidence to support this approach. HPV testing in women under the age of 30 years is particularly problematic because the incidence of infection in this age group is very high and a positive result is both very likely and clinically unhelpful.

High grade squamous lesions

The recommended management of women with screen detected high grade squamous lesions has not changed in the updated *Guidelines*. Such women are best assessed with colposcopy, which allows a magnified view of the cervix. The characteristic features of the lesion should be identified and a biopsy of the most suspicious area performed to confirm the diagnosis. When a high grade squamous lesion is confirmed on biopsy, either ablative or excisional treatment is recommended. There are well recognised side effects from treatment – especially related to subsequent pregnancies[5] – so all management decisions need to be considered carefully.

HPV as 'test-of-cure'

Results from several studies have suggested that women treated for high grade lesions of the cervix are at increased risk of further high grade disease and cancer.[6,7] Under the previous NHMRC management guidelines, these women were advised to undergo annual cytological surveillance for the rest of their lives. Recurrence may be the result of inadequately treated disease or further development of CIN.

HPV testing has been shown to be a sensitive predictor of recurrent disease and is now incorporated into the follow up of women treated for high grade lesions.[8,9] Under the updated *Guidelines*, it is recommended that a woman treated for HSIL undergo colposcopy and cervical cytology between four and six months after treatment. Cervical cytology and HPV typing should be carried out 12 months after treatment and annually thereafter until she has tested negative by both tests on two consecutive occasions. At this point,

screening should be continued according to the recommendation for the average population.

Glandular abnormalities

Cervical cytology suggesting a glandular abnormality is rare, constituting well under 1% of all reports. Screening is less effective at preventing cervical adenocarcinoma than preventing squamous cell carcinoma, and the incidence of cervical adenocarcinoma has remained stable in spite of the organised screening program. Cervical adenocarcinomas now account for a higher proportion of cervical cancers. This probably relates to a less predictable and well defined natural history, the anatomical situation of glandular abnormalities, greater potential for poor sampling of the endocervix, and difficulties with cytological recognition of glandular abnormalities.

A review of outcomes of women with glandular cytological abnormalities has suggested that there is a high incidence of underlying significant histological abnormality regardless of the extent of the cytological prediction (see appendix 8 of the *Guidelines*). Colposcopic assessment of glandular lesions is widely regarded as difficult and fraught with diagnostic uncertainty. Consequently, a woman with a Pap test result suggesting any glandular abnormality should be referred to a gynaecologist with expertise in the management of gynaecological malignancies or to a gynaecological oncologist.

The HPV vaccine

A highly effective HPV vaccine, Gardasil, is now licensed for clinical use in Australia. Gardasil is manufactured by Merck and marketed in Australia by CSL Ltd. The vaccine contains HPV structural proteins that form virus-like particles which mimic the outer shell of the naturally occurring oncogenic types 16 and 18 – which are associated with approximately 50% of cervical abnormalities and 70% of cervical cancers – as well as the low risk types 6 and 11. Clinical trials have shown the vaccine to be highly effective at preventing infection with these strains of HPV and at preventing the precursor cervical lesions associated with persistent HPV infection.[10] A second vaccine, Cervarix (manufactured by GlaxoSmithKline), is targeted against HPV types 16 and 18 only and is expected to be licensed in Australia in mid-2007. Cervical cancer vaccination offers the potential for the addition of a primary prevention strategy to the existing secondary protection program, and will likely lead to a further reduction in the incidence of cervical cancer.

Communicating with patients

The thinking about cervical cancer prevention is changing. There is a substantial difference between the view that the Pap test is a 'cancer test' and the sophisticated concept of 'cytologic surveillance of a chronic and potentially serious viral infection of the cervix' that can be largely prevented by vaccination. This message needs to be communicated carefully. The frequency of HPV infection in the community needs to be appreciated and the whole situation destigmatised. Explanations bridging the associations between HPV, sexual activity, viral transmission and persistence, and cervical neoplasia need to be given patiently to women who may be reluctant to accept the connotations of a sexually transmitted infection and its relevance to themselves. However, there is evidence to suggest that women accept clear, detailed explanation about HPV infection and are empowered in their understanding and management of the situation. Effective educational resources have been developed by the Australian Government (www.cervicalscreen.health.gov.au/internet/screening/publishing.nsf/Content/pubs2) and by CSL (www.i-can.net.au).

Conclusion

Appreciation of the role of HPV in the development of cervical cancer offers the potential for major changes in disease prevention. The development of clinical management protocols matched to the natural history of the disease and the availability of a vaccine against two high risk HPV types suggest that we are now in a new era of prevention. MT

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DECLARATION OF INTEREST: Dr Wain was Chair of the Low-Grade Working Party of the NHMRC Guidelines Review Group. He is also Chair of CSL's advisory board for Gardasil and has been involved in some of the Merck clinical trials for the vaccine.